(1-AZINONE) -SUBSTITUTED PYRIDOINDOLES AS MCH ANTAGONISTS

Cross-Reference to Related Application

This application claims the benefit of priority from U.S. Provisional Application Serial No. 61/020,530, filed January 11, 2008, and U.S. Provisional Application Serial No. 61/048,677, filed April 29, 2008, the disclosures of which are incorporated herein by reference.

Field of the Invention

The invention relates to human melanin-concentrating hormone (MCH_1) receptor-selective antagonists substituted pyridoindoles that are useful for treating obesity, to pharmaceutical compositions comprising these compounds, and to methods for the treatment of obesity, anxiety, depression, and psychiatric disorders in a mammal.

Background of the Invention

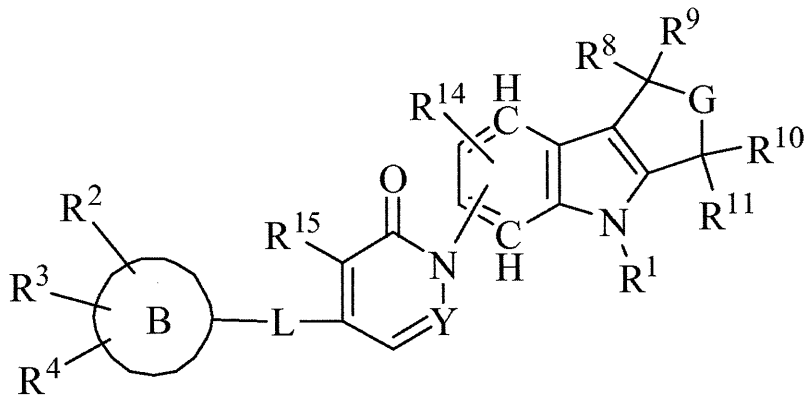
Obesity and the multitude of co-morbidities associated with obesity such as diabetes, dyslipidemia, coronary heart disease, and certain cancers are a major concern for public health. The currently available pharmaceutical therapies for the treatment of obesity have limited efficacy and side effects that limit their use. Thus, there is a significant medical need for better pharmacotherapy for obesity.

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, A. 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, L. L. 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, M. D. Recent advances in the discovery of melanin-concentrating hormone receptor antagonists Curr. Opin. Drug Disc. & Dev. 9(4), 496, 2006).

Summary of the Invention

In accordance the present invention, there is provided a compound of formula **(I)**



(I)

wherein

R^1 is H or optionally substituted alkyl;

R^2, R^3, R^4 are each independently selected from H, -O-alkyl, -S-alkyl, alkyl, halo, $-CF_3$, and –CN;

G is $-CR^{12}R^{13}-NR^5-$ or $-NR^5-CR^{12}R^{13}$;

R^5 is H, optionally substituted alkyl, optionally substituted heterocycle, $-C(=O)-R^6$, $-C(=O)-O-R^7$, or $-C(=O)-NR^{19}R^{20}$;

R^6 and R^7 are each optionally substituted alkyl or optionally substituted heterocycle;

R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{19} and R^{20} are each independently selected from H or optionally substituted alkyl;

R^{14} and R^{15} are each independently H or halogen;

Y is CH or N;

L is $-CH_2-O-$, $-CH_2CH_2-$, -CH=CH- or a bond; and

B is aryl or heteroaryl or cycloalkyl;

with the proviso that, when L is a direct bond, B cannot be unsubstituted heteroaryl or heteroaryl monosubstituted with fluorine.

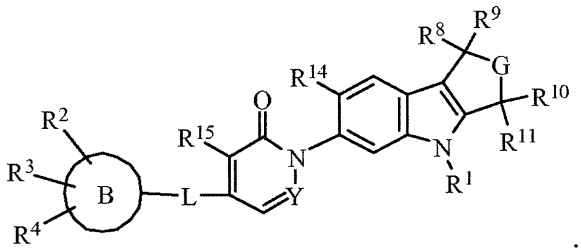
Detailed Description of the Invention

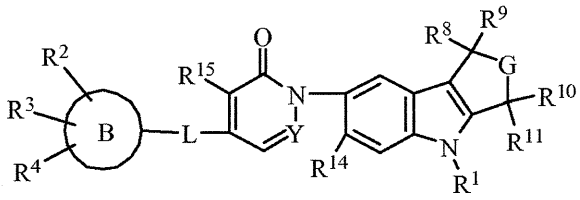
In accordance with the present invention, compounds represented by formula **(I)** above may be substituted derivatives either of tetrahydro-β-carboline, where G is $-CR^{12}R^{13}-NR^5-$, or of tetrahydro-γ-carboline, where G is $-NR^5-CR^{12}R^{13}-$. In some embodiments of the invention, G is $-CH_2-NR^5-$; in other embodiments, G is $-NR^5-CH_2-$. In accordance with some embodiments of the invention, R^1 is H.

In accordance with other embodiments of the invention, R^1 is alkyl, for example, methyl or ethyl.

In accordance with some embodiments of the invention, R^5 is H. In other embodiments, R^5 is optionally substituted alkyl. In some embodiments, R^5 is selected from methyl, ethyl, 2-propyl, 2-hydroxyethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 2-oxo-2-(pyrrolidin-1-yl)ethyl, 2-(pyrrolidin-1-yl)ethyl and (*S*)-pyrrolidin-2-ylmethyl. In other embodiments, R^5 is optionally substituted heterocycle. In some embodiments, R^5 is selected from piperidin-4-yl and 1-methylpiperidin-4-yl. In other embodiments, R^5 is $-C(=O)-R^6$. In other embodiments, R^5 is $-C(=O)-O-R^7$.

In some embodiments, R^6 and R^7 are each optionally substituted alkyl, for example, methyl, 2-propyl, 2-(pyrrolidin-1-yl)-ethyl, pyrrolidin-1-ylmethyl, and dimethylaminomethyl. In some embodiments, R^6 is optionally substituted heterocycle, for example, pyrrolidin-3-yl, (*R*)-pyrrolidin-2-yl, (*S*)-pyrrolidin-2-yl, 1-methylpyrrolidin-3-yl, (*R*)-1-methylpyrrolidin-2-yl and (*S*)-1-methylpyrrolidin-2-yl.

In accordance with some embodiments of the invention, the compound has the structure  .

In accordance with other embodiments of the invention, the compound has the structure  .

In accordance with some embodiments of the invention, the L is a bond. In accordance with other embodiments of the invention, L is $-CH_2-O-$. In accordance with some embodiments of the invention, L is $-CH_2CH_2-$. In accordance with other embodiments of the invention, L is -CH=CH-.

In accordance with some embodiments of the invention, B is aryl, for example, phenyl. In accordance with other embodiments of the invention, B is heteroaryl, for example, pyridinyl. In some embodiments, B is pyridin-2-yl or pyridin-3-yl. In other embodiments, B is pyridazinyl, for example, pyridazin-3-yl. In some other embodiments, B is pyrimidinyl, for example, pyrimidin-5-yl or pyrimidin-2-yl. In accordance with other embodiments of the invention, B is cycloalkyl, for example, cyclohexyl.

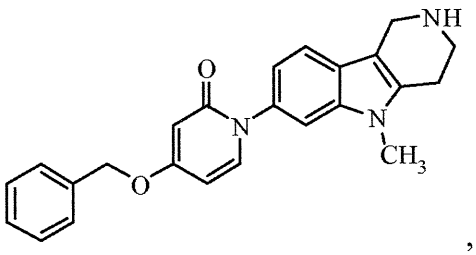
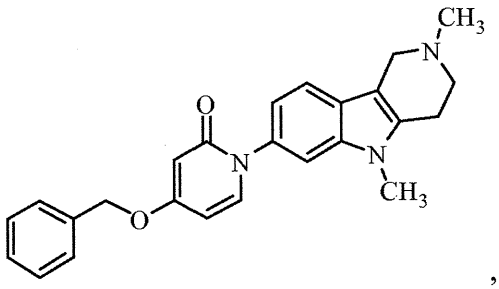
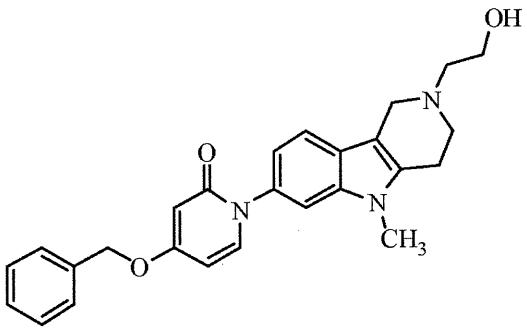
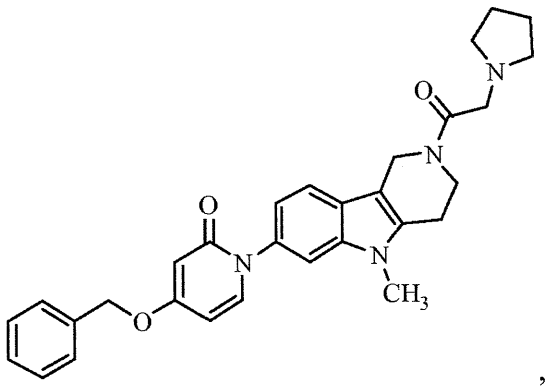
In accordance with some embodiments of the invention, R^2, R^3 and R^4 are each H. In accordance with other embodiments of the invention, two of R^2, R^3 and R^4 are H, and the other of R^2, R^3 and R^4 is selected from trifluoromethyl, chloro, fluoro, methyl, methoxy and methanethio.

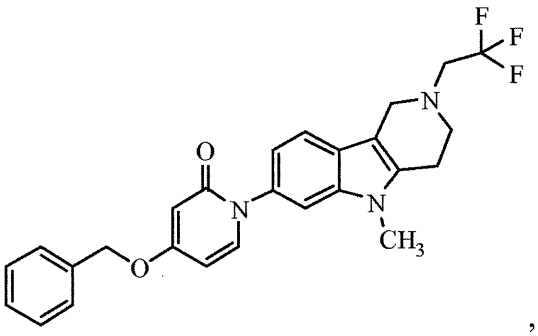
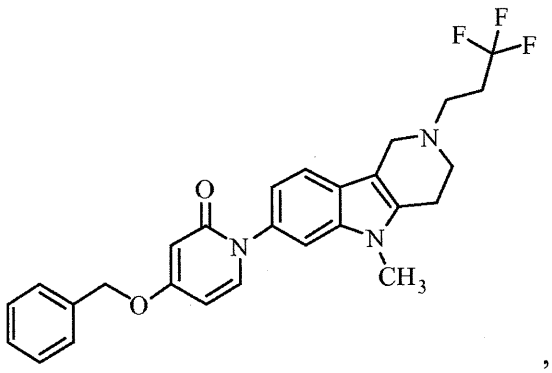
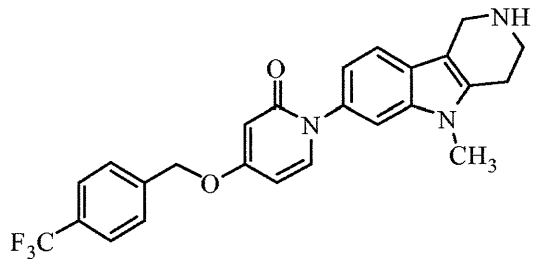
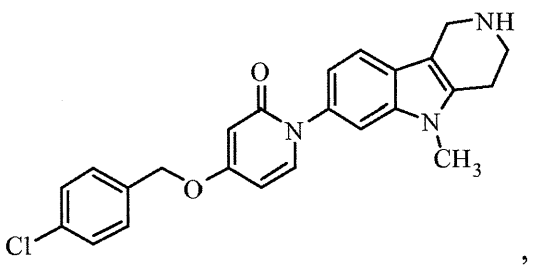
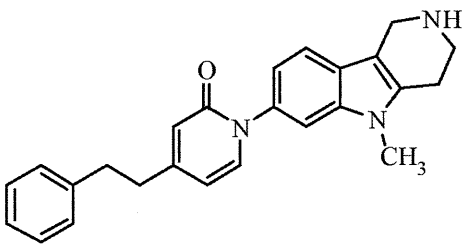
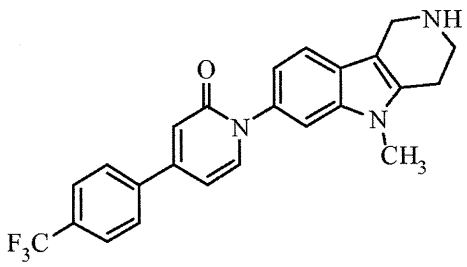
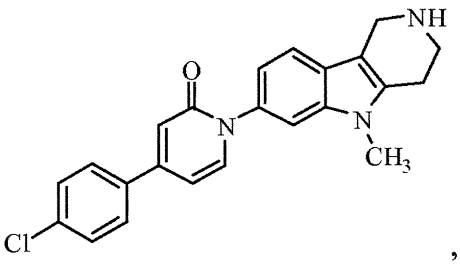
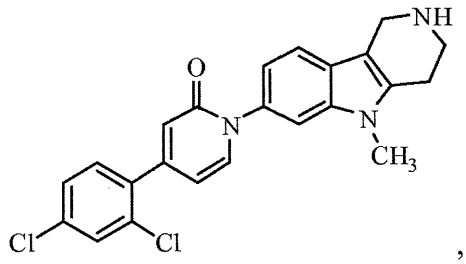
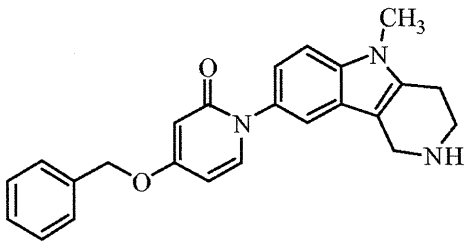
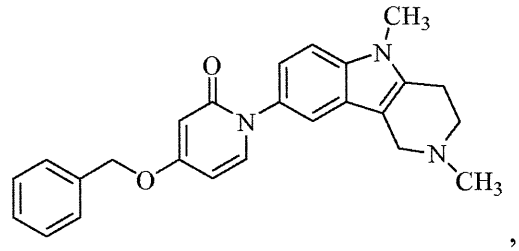
In accordance with other embodiments of the invention, one of R^2, R^3 and R^4 is H, another of R^2, R^3 and R^4 is Cl, and the third of R^2, R^3 and R^4 is F, Cl or methoxy. In accordance with other embodiments of the invention, one of R^2, R^3 and R^4 is H, another of R^2, R^3 and R^4 is F, and the third of R^2, R^3 and R^4 is methoxy. In accordance with other

embodiments of the invention, one of R^2, R^3 and R^4 is H, another of R^2, R^3 and R^4 is methoxy, and the third of R^2, R^3 and R^4 is methyl.

In accordance with some embodiments of the invention, B, together with R^2, R^3 and R^4, is selected from phenyl, 4-trifluoromethylphenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 4-fluorophenyl, 4-chloro-2-fluorophenyl, 2-fluoro-4-methoxyphenyl, pyridin-2-yl, 5-chloropyridin-2-yl, 5-(trifluoromethyl)pyridin-2-yl, 5-fluoropyridin-2-yl, 6-(trifluoromethyl)pyridazin-3-yl, 6-methylpyridazin-3-yl, 4-fluoro-2-methoxyphenyl, 6-(trifluoromethyl)pyridin-3-yl, 2-(trifluoromethyl)pyrimidin-5-yl, 5-(trifluoromethyl)pyrimidin-2-yl, 5-methylpyridin-2-yl, 6-methylpyridin-3-yl, cyclohexyl, 4-chloro-2-methoxyphenyl, pyrimidin-2-yl, imidazo[1,2-*a*]pyridin-6-yl, imidazo[1,2-*a*]pyridin-2-yl, 4-methoxyphenyl, 4-methanethiophenyl and 4-methoxy-2-methylphenyl.

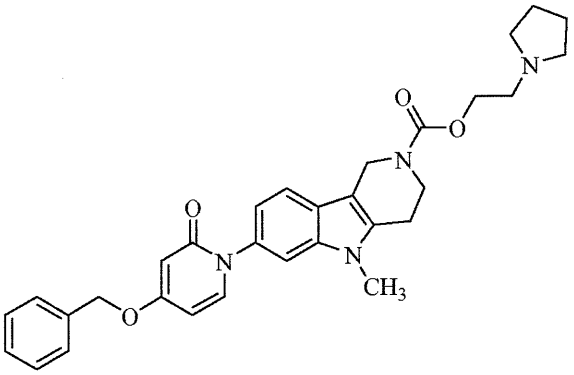
In accordance with some embodiments of the invention, at least one of R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{19} and R^{20} is H. In other embodiments, at least one of R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{19} and R^{20} is optionally substituted alkyl, for example, methyl, ethyl, or hydroxymethyl.

In accordance with some embodiments of the invention, the compound is selected from  ,  ,  ,  ,

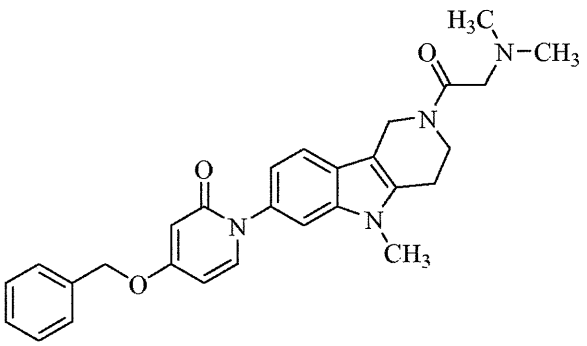

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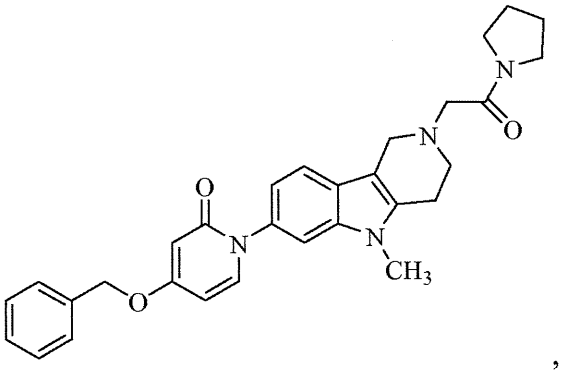
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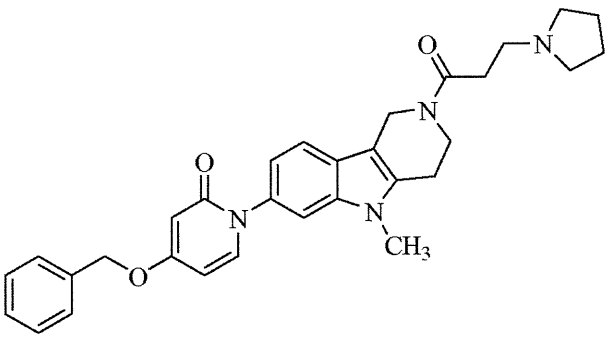
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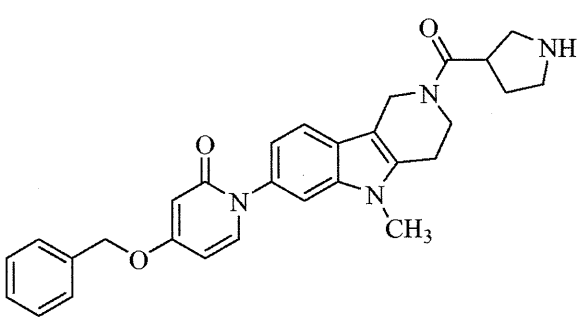
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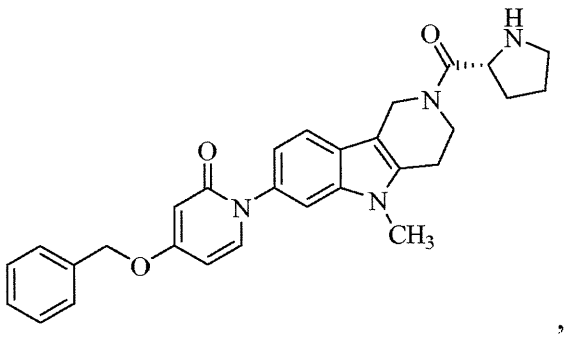
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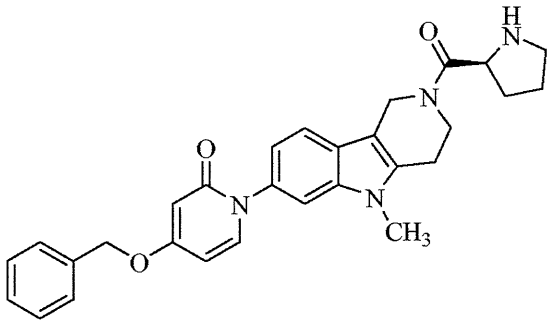
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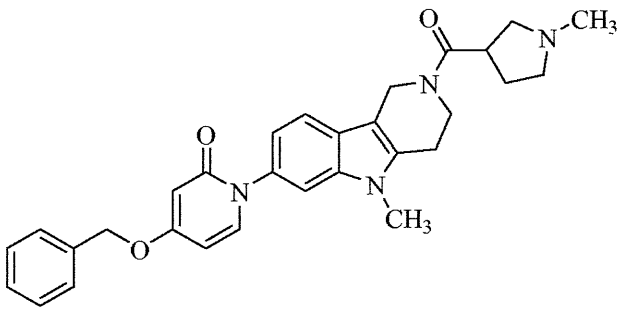
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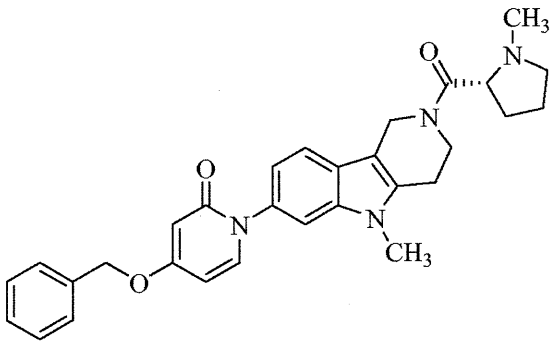
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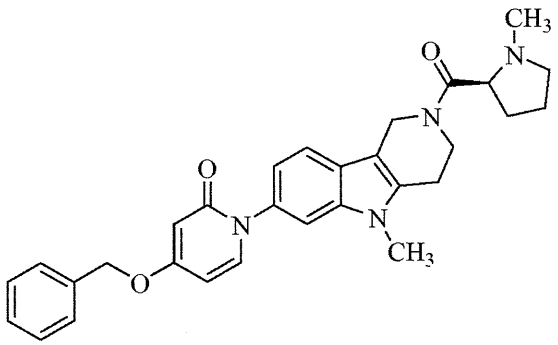
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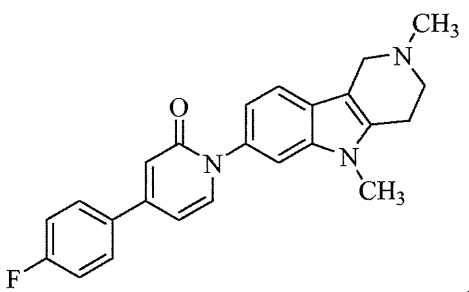
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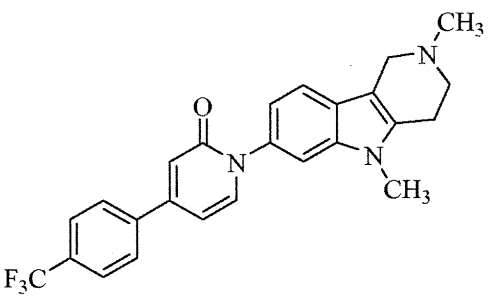
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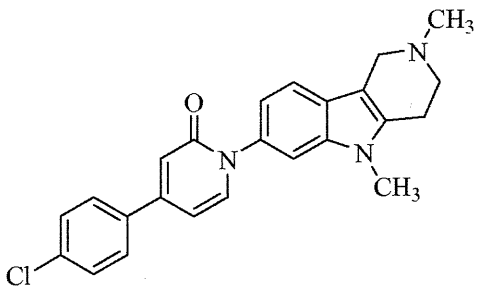
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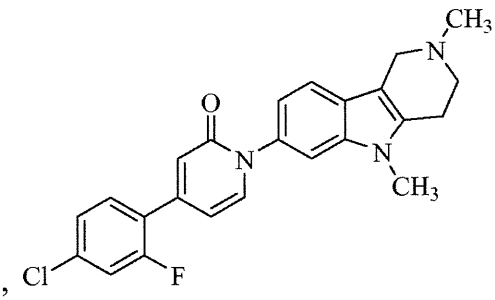
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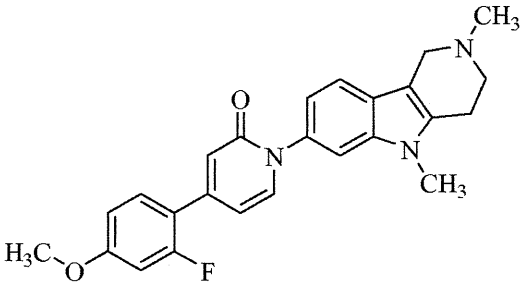
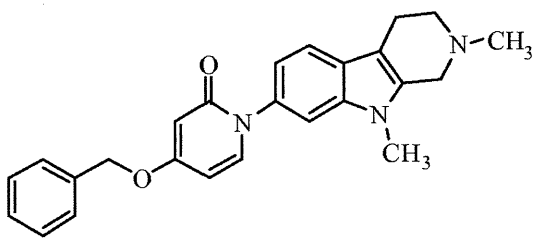
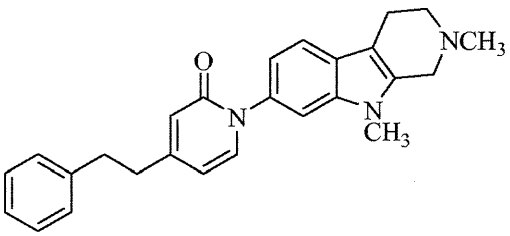
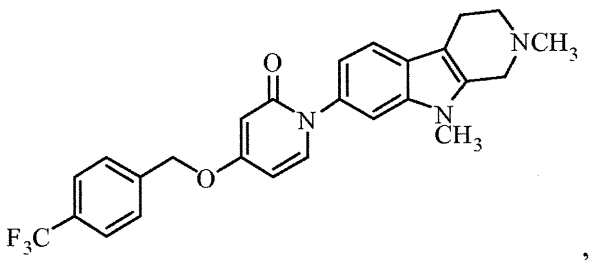
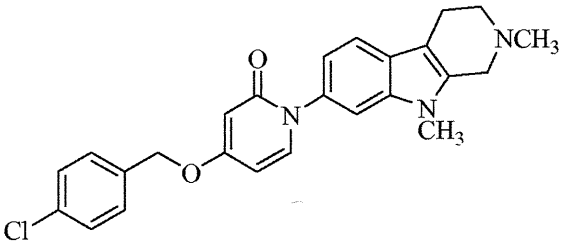
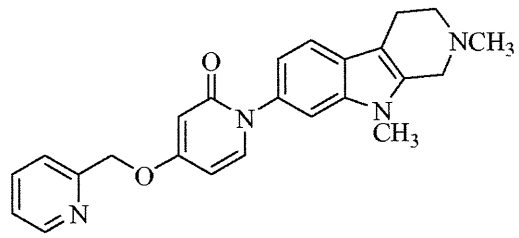
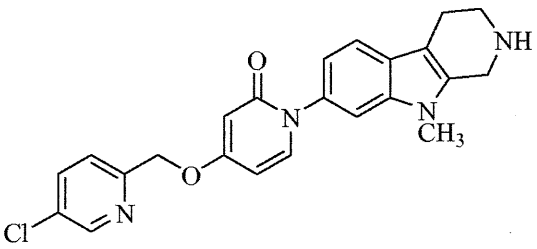
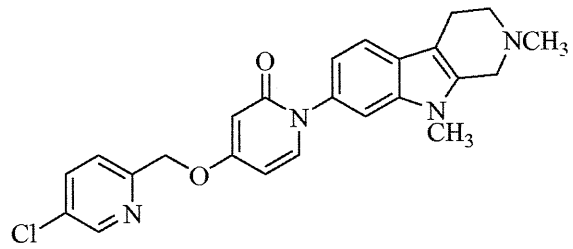
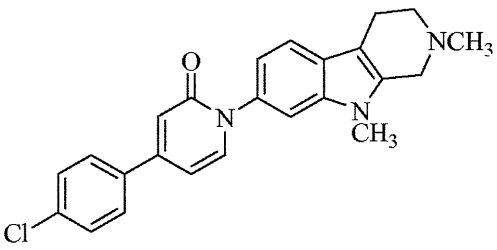
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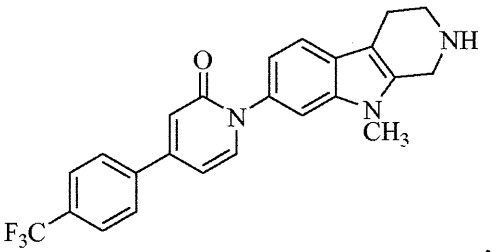
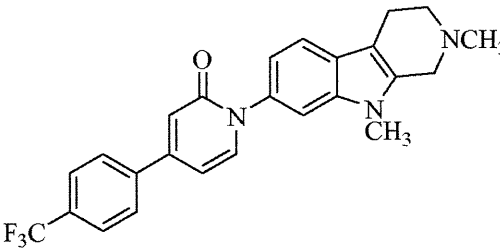
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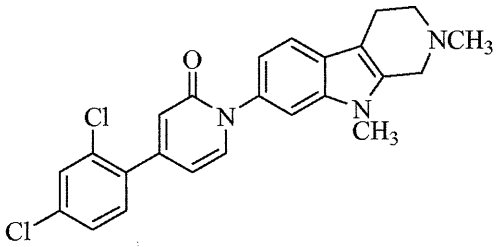
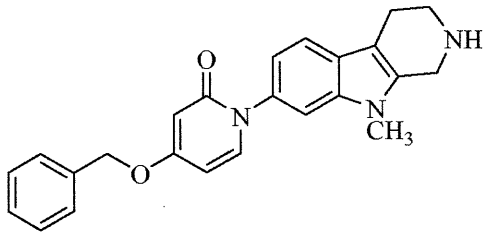
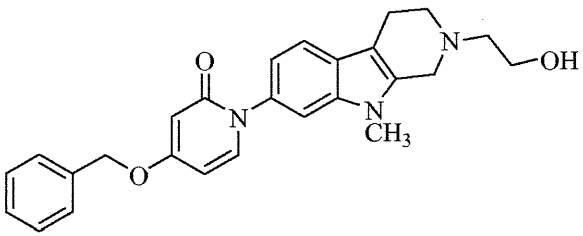
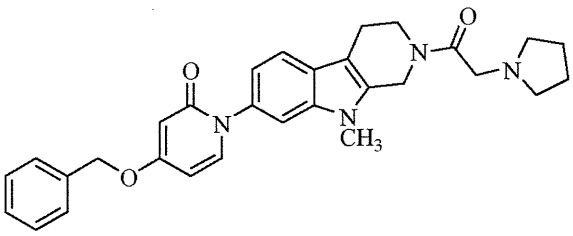
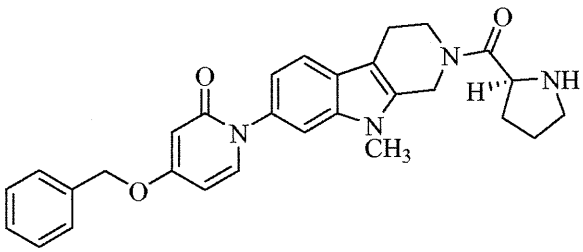
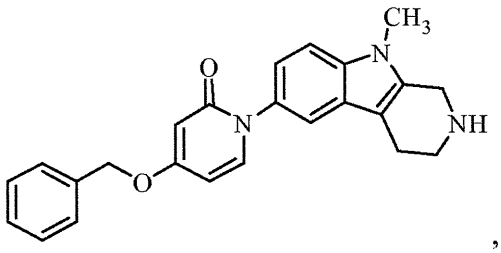
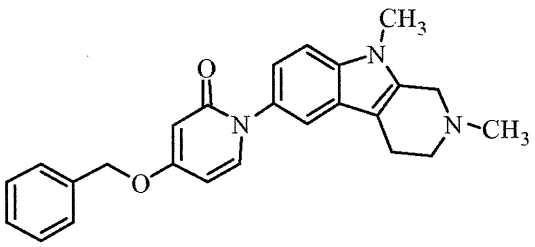
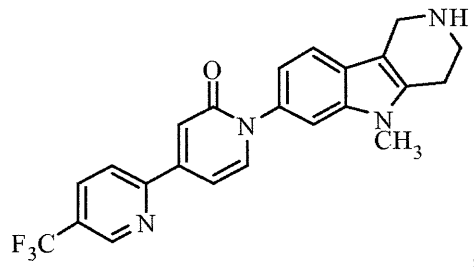
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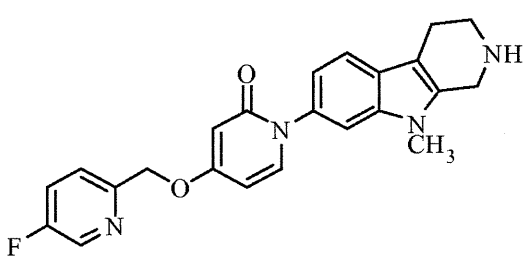
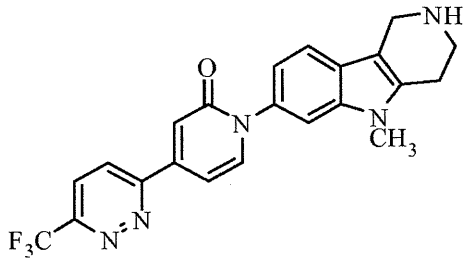
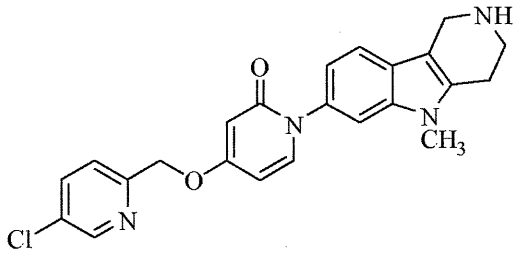
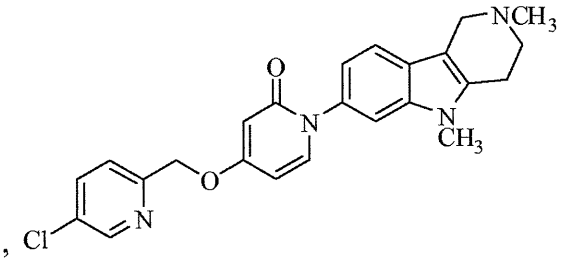
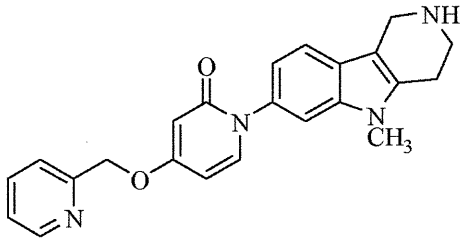
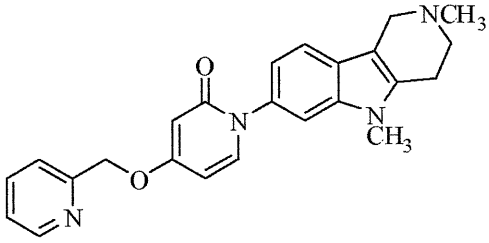
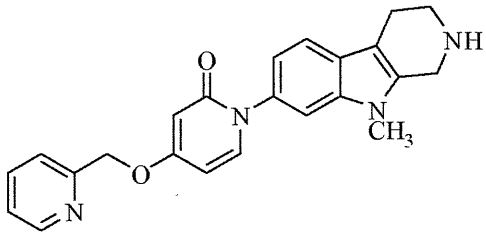
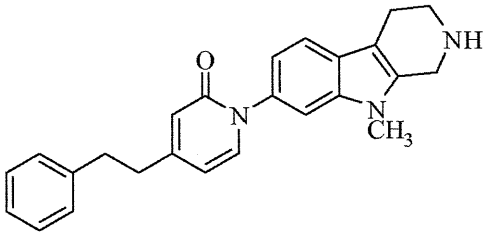
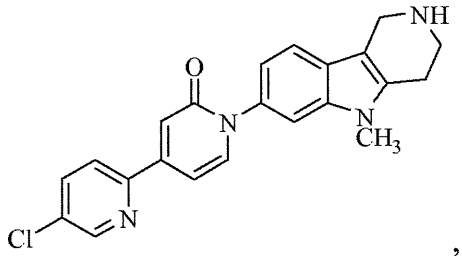
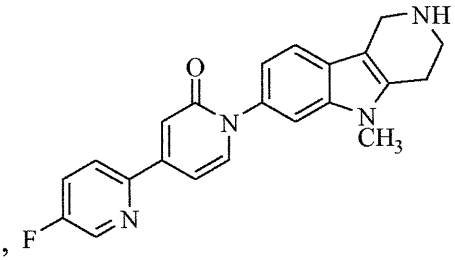
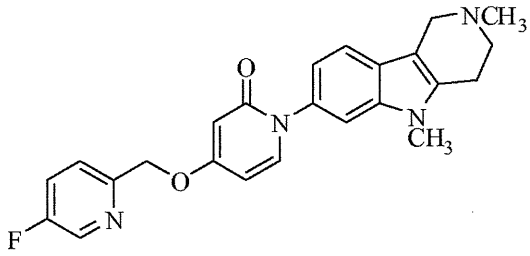
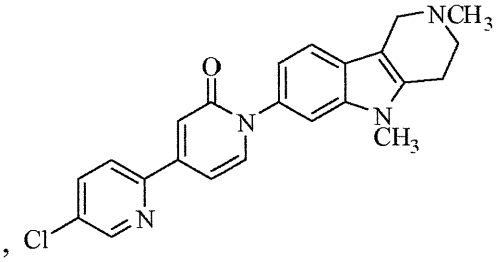
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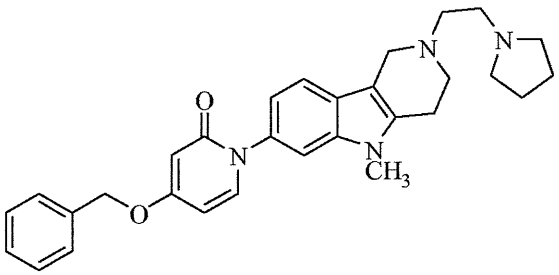
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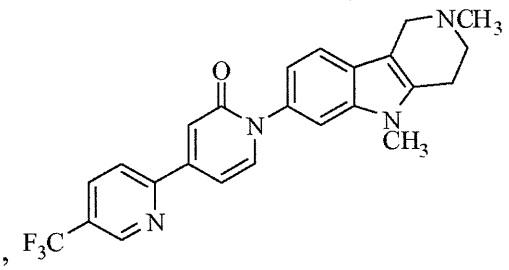

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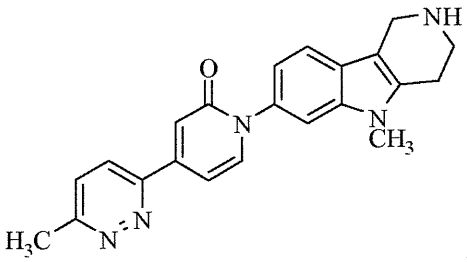

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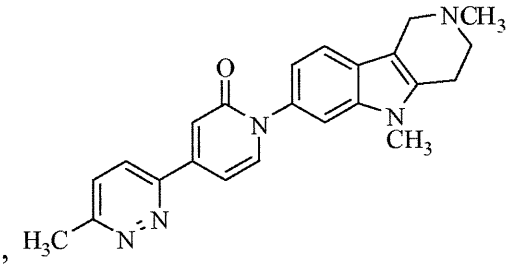
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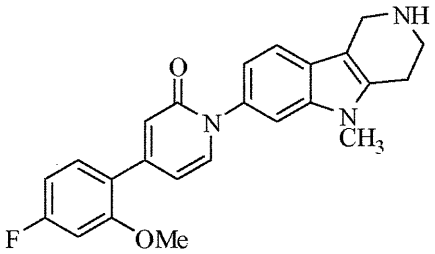
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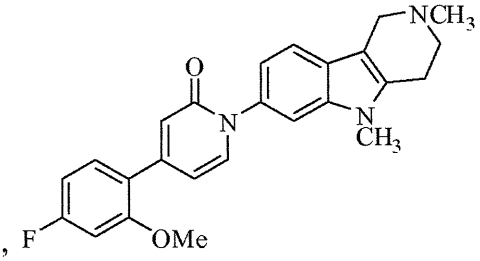


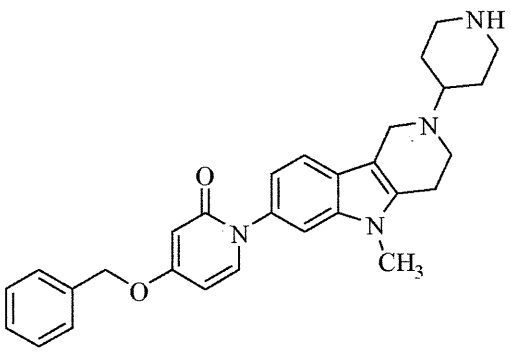


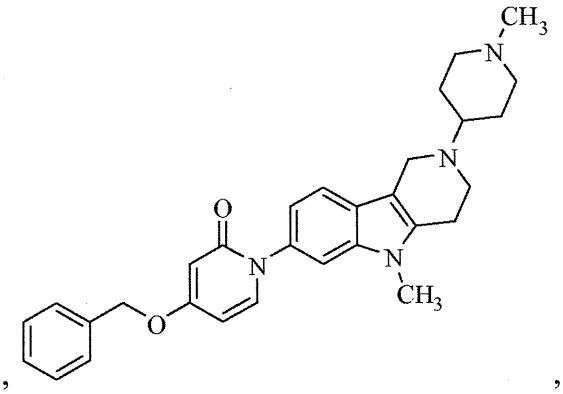


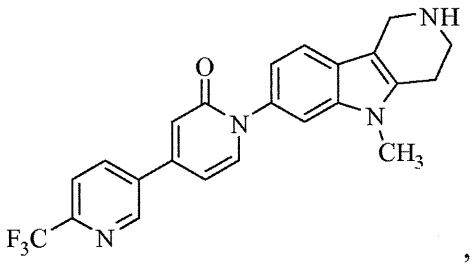


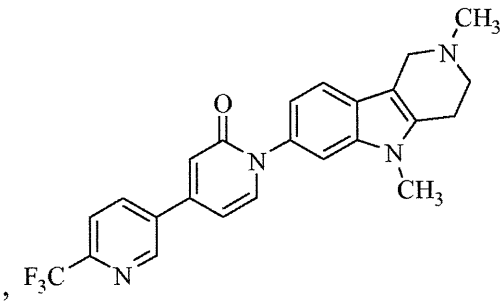


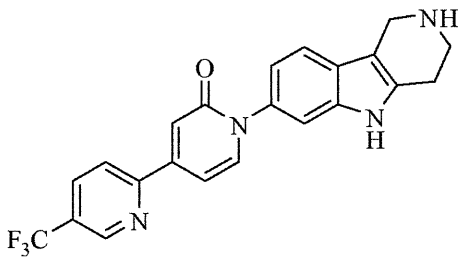
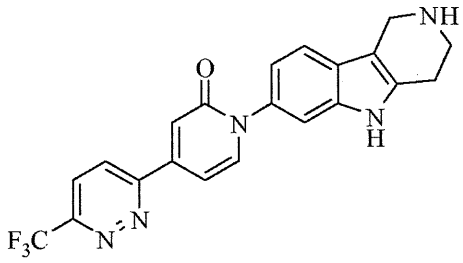
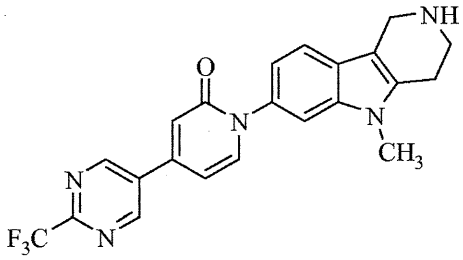
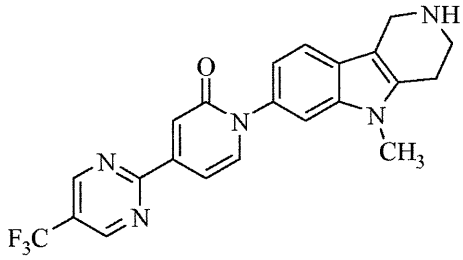
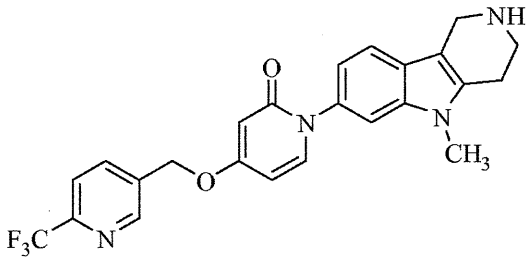
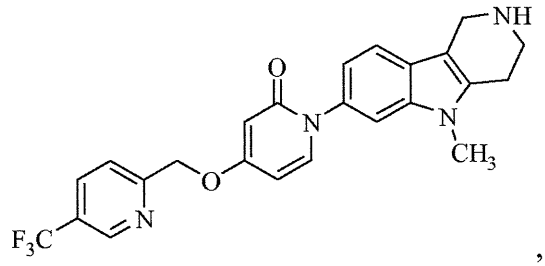
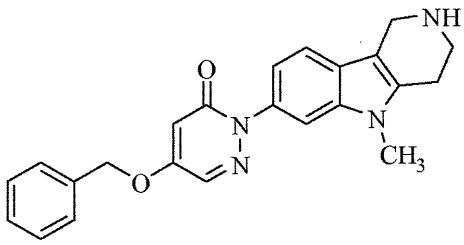
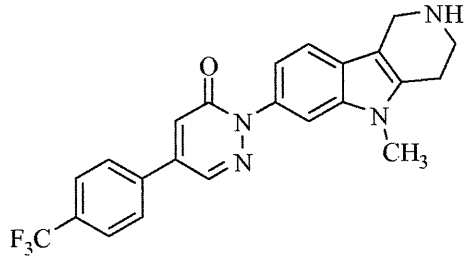
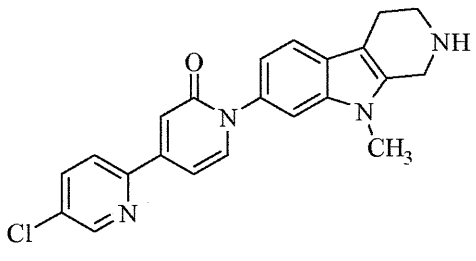
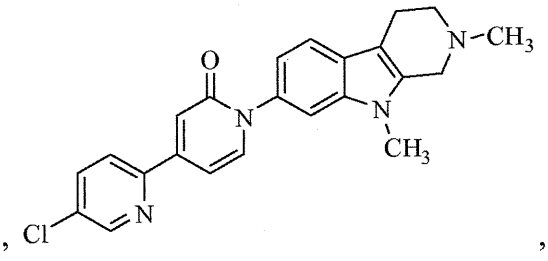
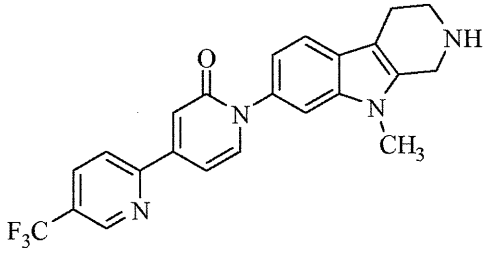
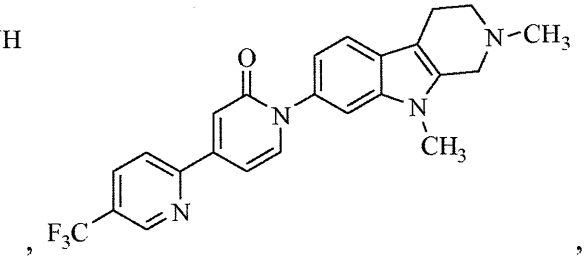


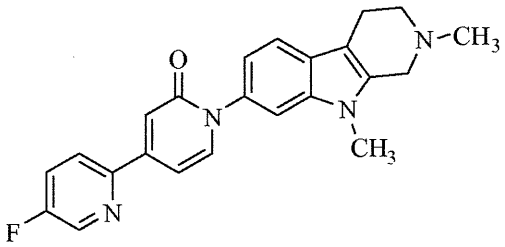
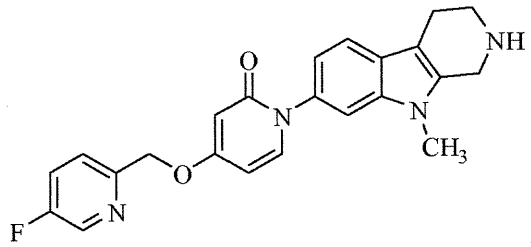
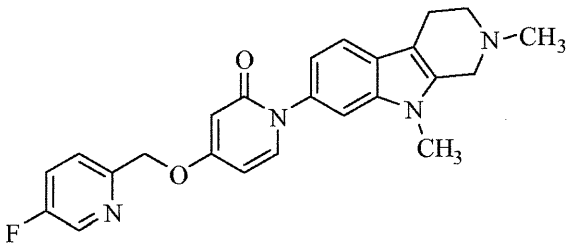
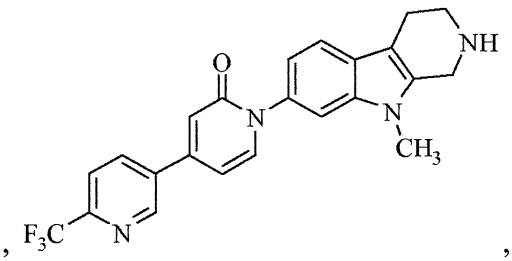
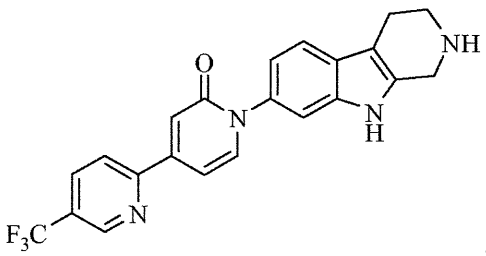
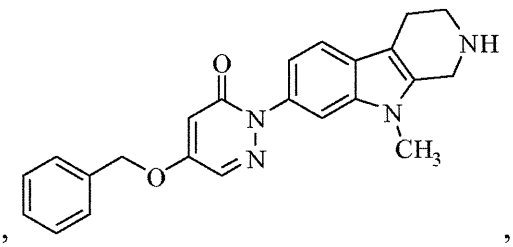
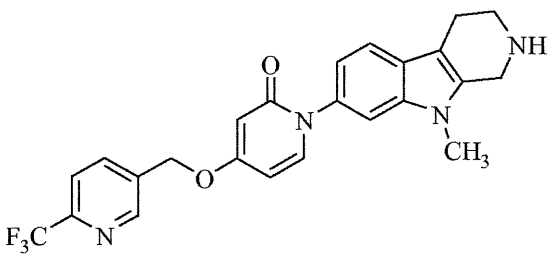
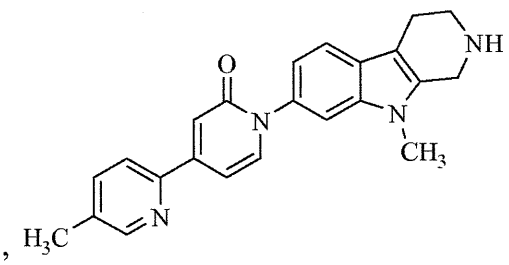
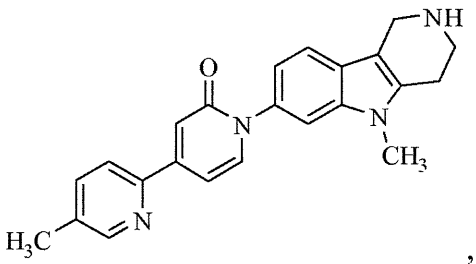
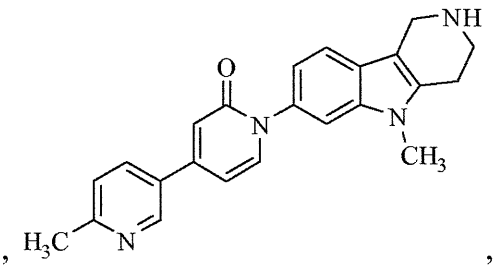
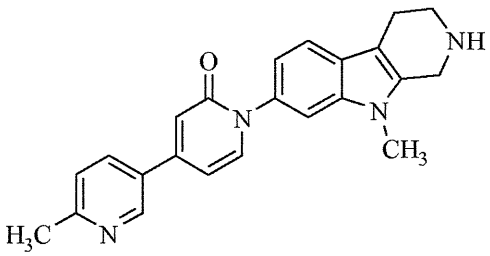
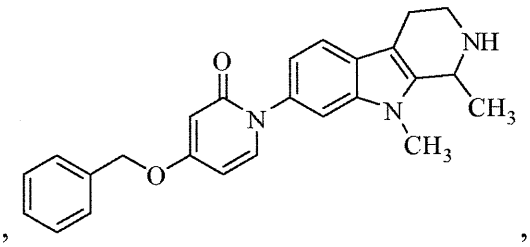


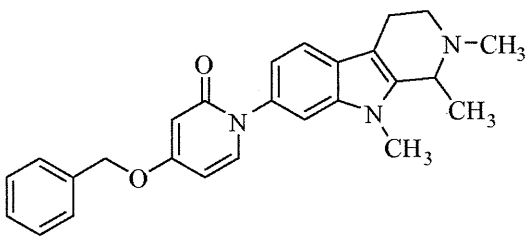
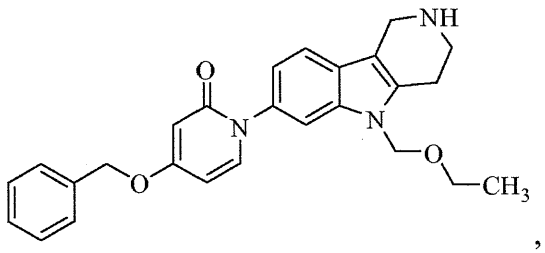
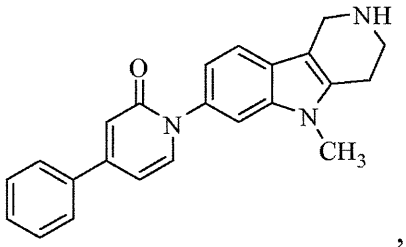
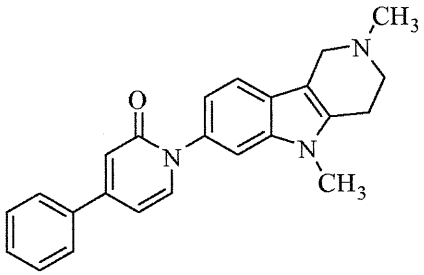
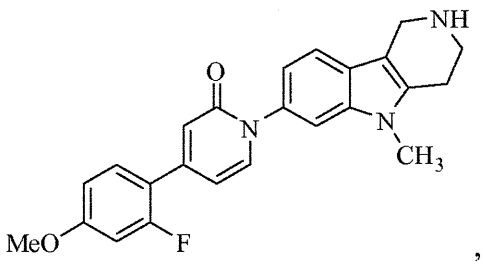
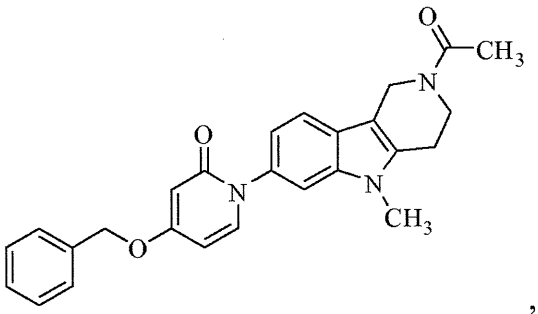
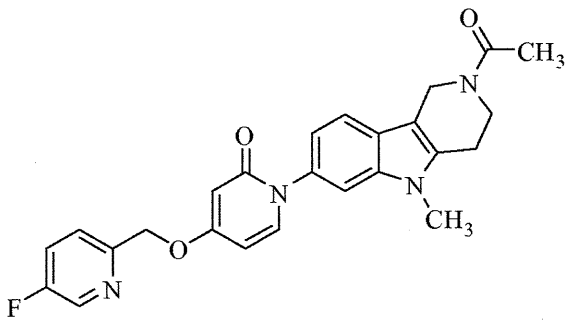
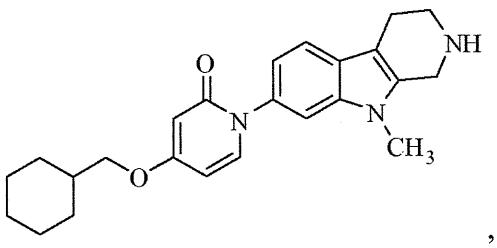
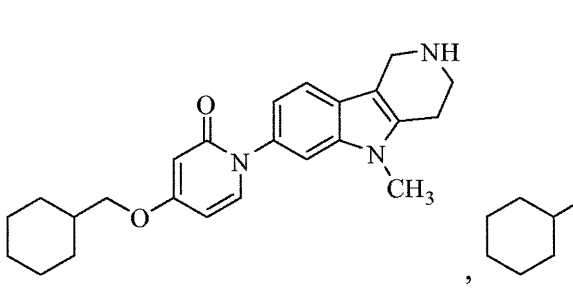
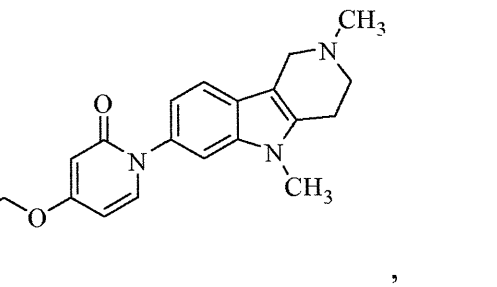






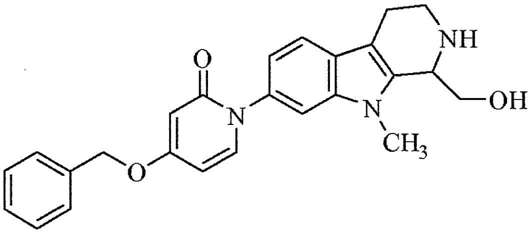
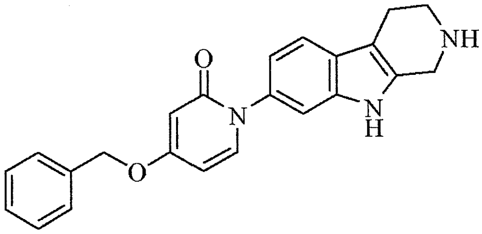
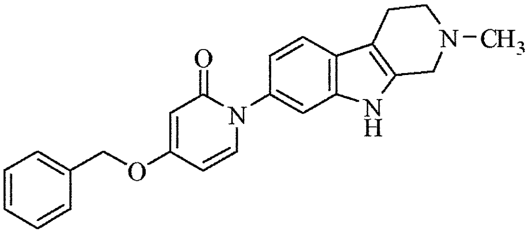
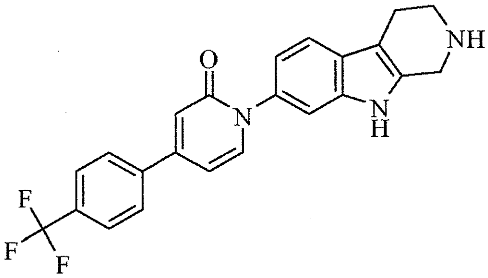
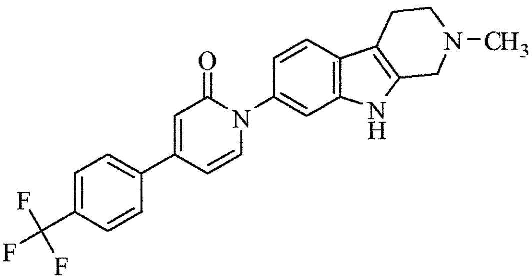
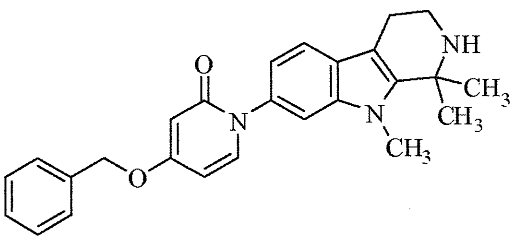
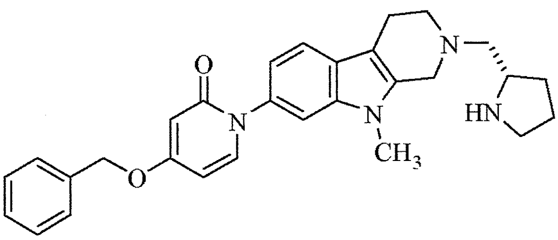
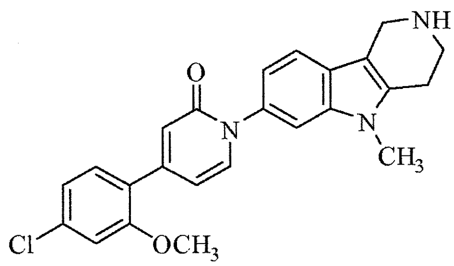
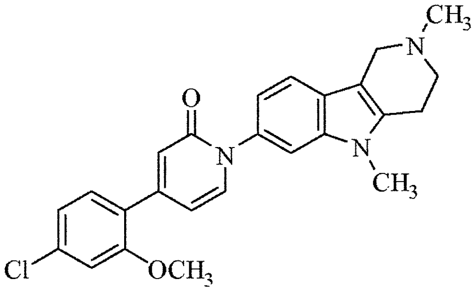
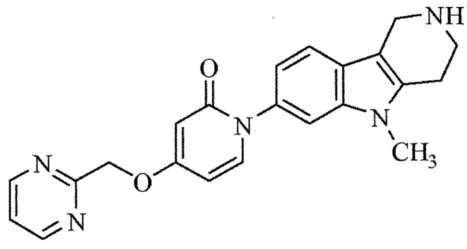

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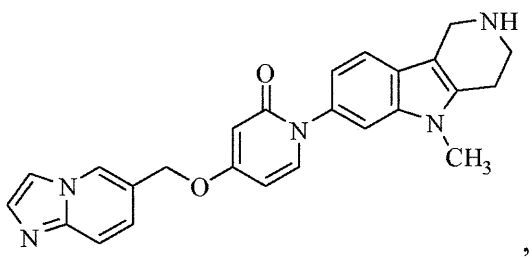
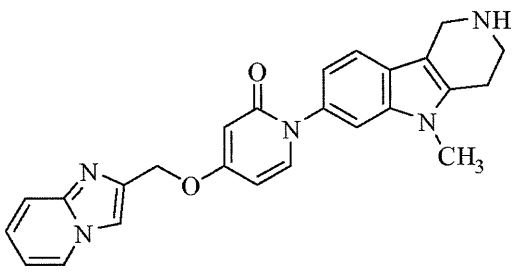
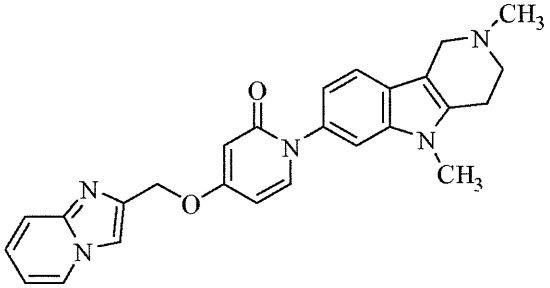
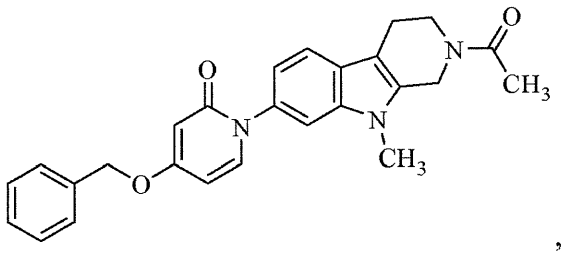
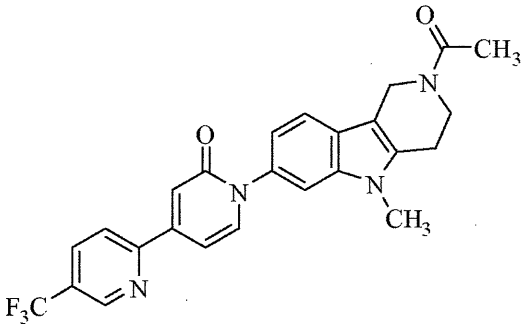
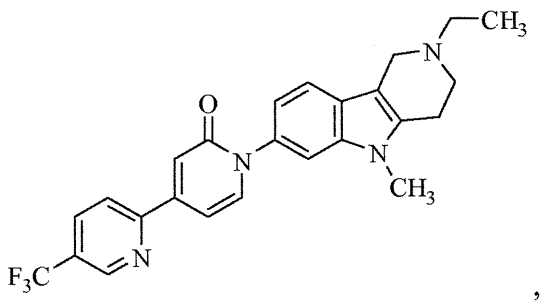
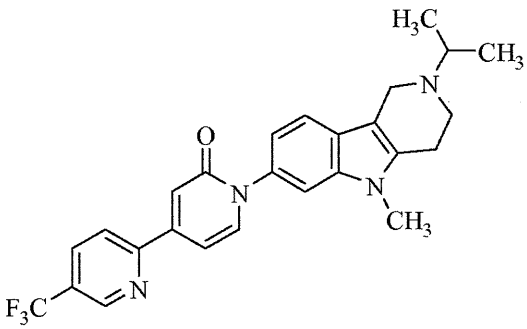
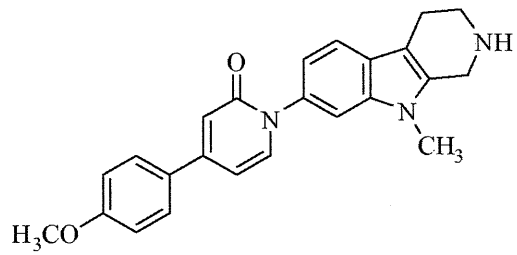
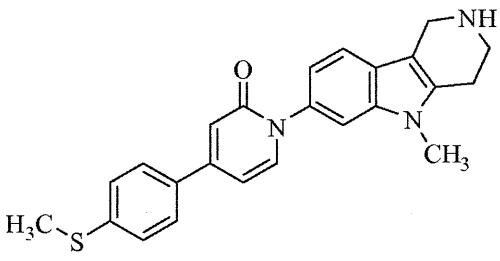
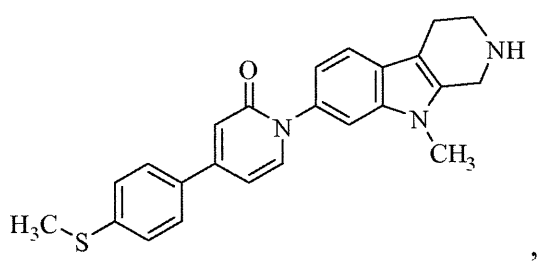

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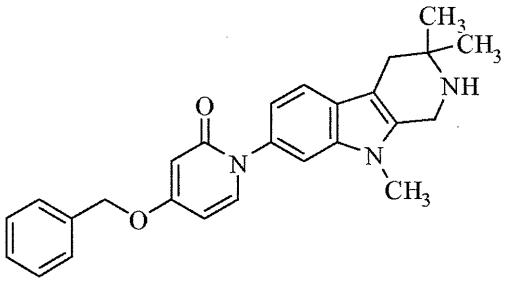
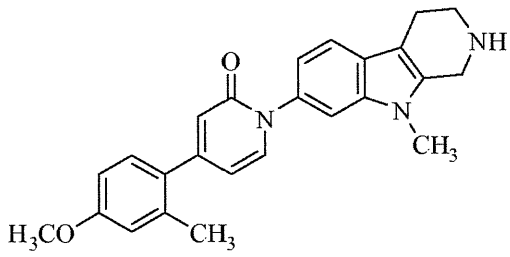
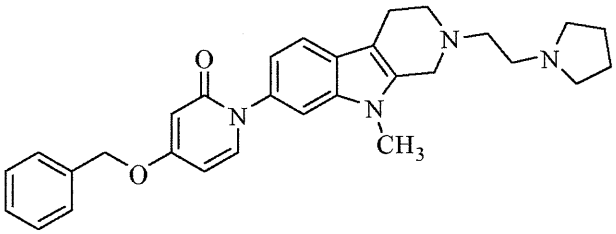
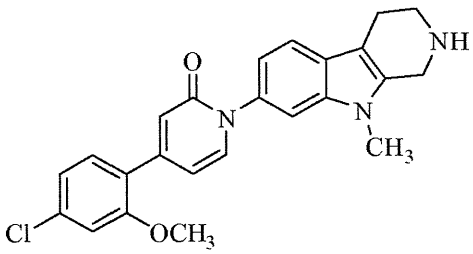
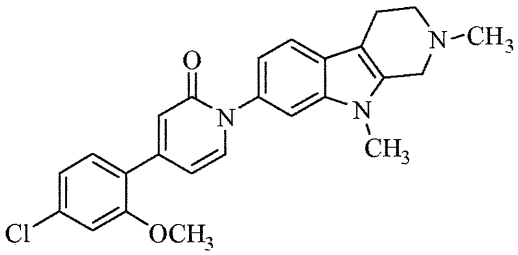
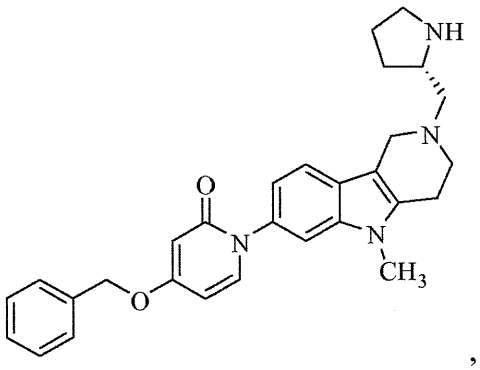
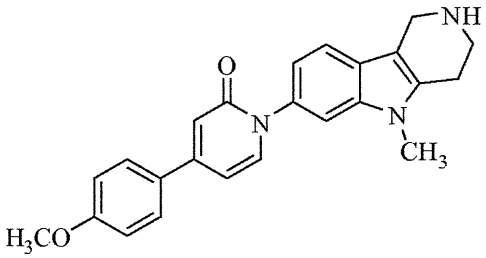
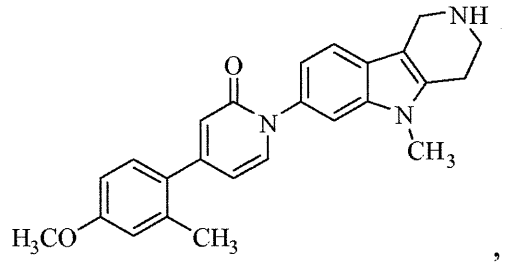
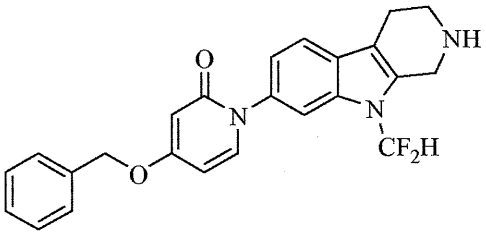
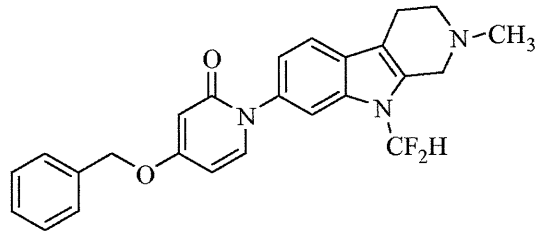

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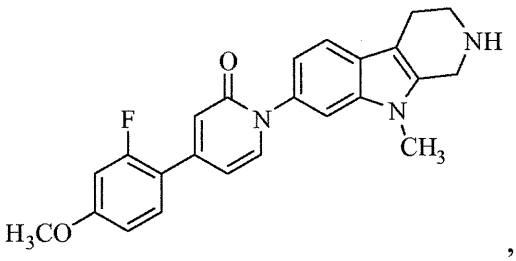
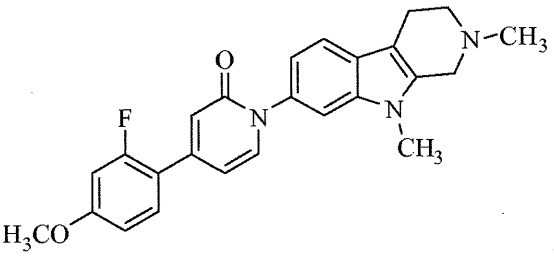
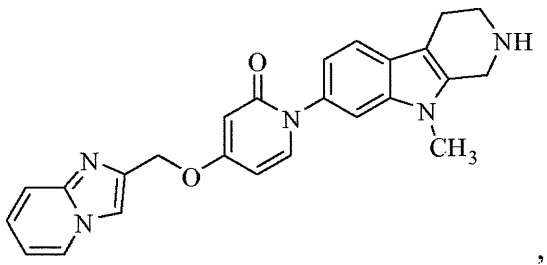
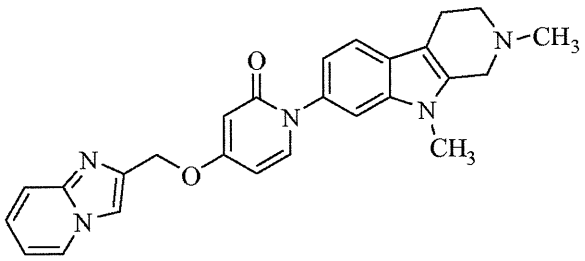
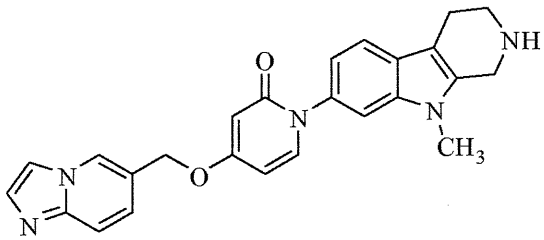
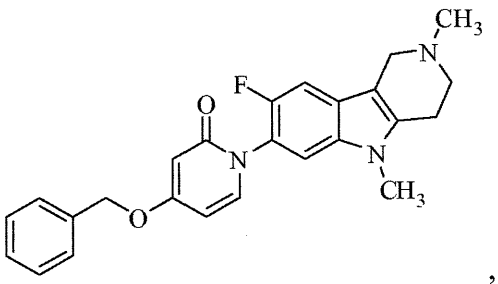
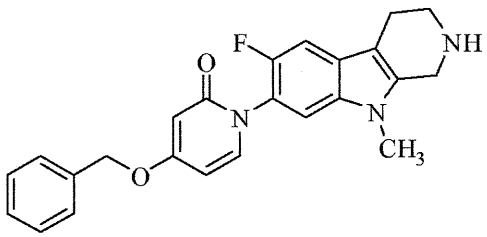
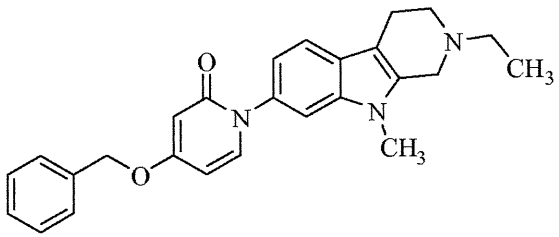
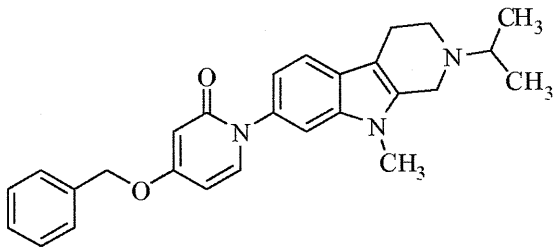
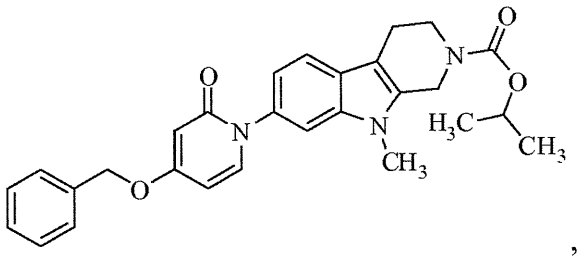
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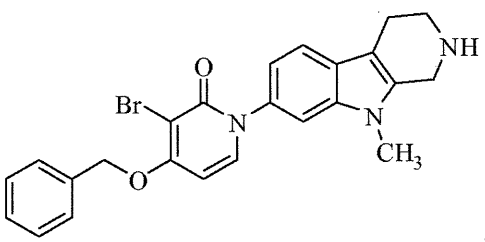
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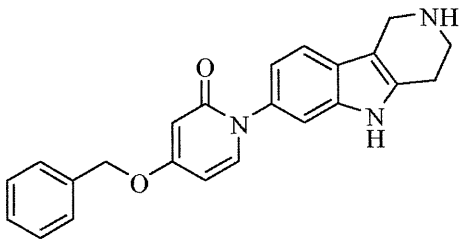

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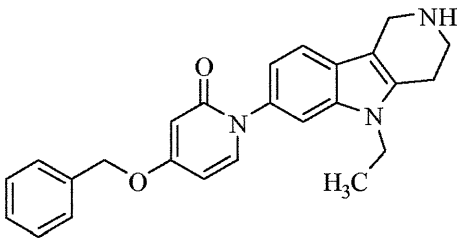

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In accordance with some embodiments of the invention, the compound is a pharmaceutically acceptable salt thereof. In some embodiments, the salt is an HCl salt. There is also provided, in accordance with embodiments of the invention, a pharmaceutical composition comprising a compound as described herein, and a pharmaceutically acceptable carrier, excipient or diluent therefore.

There is also provided, in accordance with embodiments of the invention, a method of treating obesity, comprising administering to a patient in need of obesity reduction an obesity-reducing effective amount of a compound as described herein.

There is also provided, in accordance with embodiments of the invention, a method of treating anxiety, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound as described herein.

There is also provided, in accordance with embodiments of the invention, a method of treating depression, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound as described herein.

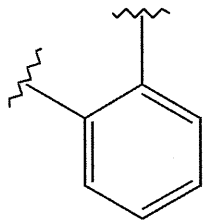
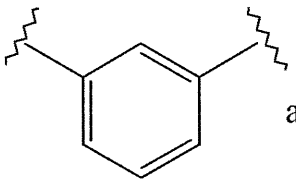
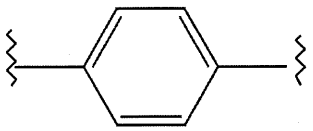
There is also provided, in accordance with embodiments of the invention, a method of treating non-alcoholic fatty liver disease, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound as described herein.

There is also provided, in accordance with embodiments of the invention, a method of treating a disease or condition which is susceptible to treatment with an MCH_1 receptor modulator, comprising administering to a patient in need thereof a therapeutically effective amount of a compound as described herein.

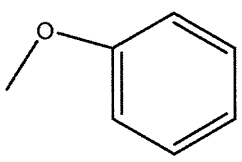
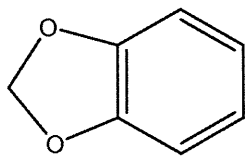
Definitions

Throughout this specification the terms and substituents retain their definitions. Alkyl is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof. When not otherwise restricted, the term refers to alkyl of 20 or fewer carbons. Lower alkyl refers to alkyl groups of 1, 2, 3, 4, 5 and 6 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s-and t-butyl and the like. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of 3, 4, 5, 6, 7, and 8 carbon atoms. Examples of cycloalkyl groups include c-propyl, c-butyl, c-pentyl, norbornyl, adamantyl and the like.

C_1 to C_{20} Hydrocarbon (e.g. C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20}) includes alkyl, cycloalkyl, alkenyl, alkynyl, aryl and combinations thereof. Examples include benzyl, phenethyl, cyclohexylmethyl, camphoryl and naphthylethyl. The term "phenylene" refers to ortho, meta or para residues of the formulae:



and


Alkoxy or alkoxyl refers to groups of 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of a straight, branched, 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,


or

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Oxaalkyl refers to alkyl residues in which one or more carbons (and their associated hydrogens) have been replaced by oxygen. Examples include methoxypropoxy, 3,6,9-trioxadecyl and the like. The term oxaalkyl is intended as it is understood in the art [see Naming and Indexing of Chemical Substances for Chemical Abstracts, published by the American Chemical Society, ¶196, but without the restriction of ¶127(a)], i.e. it refers to compounds in which the oxygen is bonded via a single bond to its adjacent atoms (forming ether bonds). Similarly, thiaalkyl and azaalkyl refer to alkyl residues in which one or more carbons have been replaced by sulfur or nitrogen, respectively. Examples include ethylaminoethyl and methylthiopropyl.

Acyl refers to groups of 1, 2, 3, 4, 5, 6, 7 and 8 carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through a carbonyl functionality. One or more carbons in the acyl residue may be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include formyl, acetyl, propionyl, isobutyryl, t-butoxycarbonyl, benzoyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to four carbons.

Aryl and heteroaryl refer to aromatic or heteroaromatic rings, respectively, as substituents. Heteroaryl contains one, two or three heteroatoms selected from O, N, or S. Both refer to monocyclic 5- or 6-membered aromatic or heteroaromatic rings, bicyclic 9- or 10-membered aromatic or heteroaromatic rings and tricyclic 13- or 14-membered aromatic or heteroaromatic rings. Aromatic 6, 7, 8, 9, 10, 11, 12, 13 and 14-membered carbocyclic rings include, e.g., benzene, naphthalene, indane, tetralin, and fluorene and the 5, 6, 7, 8, 9 and 10-membered aromatic heterocyclic rings include, e.g., imidazole, pyridine, indole, thiophene, benzopyranone, thiazole, furan, benzimidazole, quinoline, isoquinoline, quinoxaline, pyrimidine, pyrazine, tetrazole and pyrazole.

Arylalkyl means an alkyl residue attached to an aryl ring. Examples are benzyl, phenethyl and the like.

Substituted alkyl, aryl, cycloalkyl, heterocyclyl etc. refer to alkyl, aryl, cycloalkyl, or heterocyclyl wherein 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.

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

The term "prodrug" refers to a compound that is made more active in vivo. 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.

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.

It will be recognized that the compounds of this invention can exist in radiolabeled form, i.e., the compounds may contain one or more atoms containing an atomic mass or mass number different from the atomic mass or mass number usually found in nature. 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.

The terms "methods of treating or preventing" mean amelioration, prevention or relief from the symptoms and/or effects associated with lipid disorders. The term "preventing" as used herein refers to administering a medicament beforehand to forestall or obtund an acute episode or, in the case of a chronic condition to diminish the likelihood or seriousness of the condition. The person of ordinary skill in the medical art (to which the

present method claims are directed) recognizes that the term "prevent" is not an absolute term. In the medical art it is understood to refer to the prophylactic administration of a drug to substantially diminish the likelihood or seriousness of a condition, and this is the sense intended in applicants' claims. As used herein, reference to "treatment" of a patient is intended to include prophylaxis.

Throughout this application, various references are referred to. Each of the patents, patent applications, patent publications, and references mentioned herein is hereby incorporated by reference in its entirety.

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.

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. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration; thus a carbon-carbon double bond depicted arbitrarily herein as E may be Z, E, or a mixture of the two in any proportion. Likewise, all tautomeric forms are also intended to be included.

As used herein, and as would be understood by the person of skill in the art, the recitation of "a compound" is intended to include salts, solvates and inclusion complexes of that compound as well as any stereoisomeric form, or a mixture of any such forms of that compound in any ratio. 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. In accordance with some embodiments of the invention, the salt is a hydrochloride salt.

The term "enantiomeric excess" is well known in the art and is defined for a resolution of ab into a + b as

$$ee_a = \left(\frac{conc.\ of\ a - conc.\ of\ b}{conc.\ of\ a + conc.\ of\ b} \right) \quad x \quad 100$$

The term "enantiomeric excess" is related to the older term "optical purity" in that both are measures of the same phenomenon. The value of ee will be a number from 0 to 100, zero being racemic and 100 being pure, single enantiomer. A compound which in the past might have been called 98% optically pure is now more precisely described as 96% ee; in other words, a 90% ee reflects the presence of 95% of one enantiomer and 5% of the other in the material in question.

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 Protective Groups in Organic Synthesis by T.W.Greene [John Wiley & Sons, New York, 1991], which is incorporated herein by reference. Particular attention is drawn to the chapters entitled "Protection for the Hydroxyl Group, Including 1,2- and 1,3-Diols" (pages 10-86).

The following abbreviations and terms have the indicated meanings throughout: Ac = acetyl; Bu = butyl; c- = cyclo; DIEA = N,N-diisopropylethyl amine; TEA = triethylamine; HOAc = acetic acid; mesyl = methanesulfonyl; rt = room temperature; sat'd

= saturated; s- = secondary; t- = tertiary; TMS = trimethylsilyl; tosyl = p-toluenesulfonyl; TFA = trifluoroacetic acid; HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*'*N*'-tetramethyluronium hexafluorophosphate. The abbreviations HPLC, THF, DCM and DMSO represent high performance liquid chromatography, tetrahydrofuran, dichloromethane and dimethylsulfoxide, respectively. The abbreviations Me, Et, Ph, Tf, Ts, Boc and Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, toluenesulfonyl, butyloxycarbonyl and methanesulfonyl respectively. The term dppf refers to 1,1'-Bis-(diphosphenylphosphino)ferrocene. A comprehensive list of abbreviations utilized by organic chemists (i.e. persons of ordinary skill in the art) appears in the first issue of each volume of the Journal of Organic Chemistry. The list, which is typically presented in a table entitled "Standard List of Abbreviations" is incorporated herein by reference.

While it may be possible for the compounds of the invention to be administered as the raw chemical, it is preferable to present them as a pharmaceutical composition. In accordance with an embodiment of the present invention there is provided a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Furthermore, notwithstanding the statement above regarding the term "compound" including salts thereof as well, so that independent claims reciting "a compound" will be understood as referring to salts thereof as well, if in an independent claim reference is made 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 in the dependent claim.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal and topical (including dermal, buccal, 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.

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.

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.

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.

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.

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.

The dose range for adult humans is generally from 0.005 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. However, the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity. A dosage unit (e.g. an oral dosage unit) can include from, for example, 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. 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.

For additional information about pharmaceutical compositions and their formulation, see, for example, Remington: The Science and Practice of Pharmacy, 20th Edition, 2000.

The agents 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), intranasaly (including using a cannula), or by other routes. The agents 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. WO 97/11682) via a liposomal formulation (see, e.g., EP 736299,WO 99/59550 and WO 97/13500), via formulations described in WO 03/094886 or in some other form. The agents 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. 2004, Nature Reviews Drug Discovery 3:115)). The agents can be administered locally, for example, at the site of injury to an injured blood vessel. The agents can be coated on a stent. The agents can be administered using high-velocity transdermal particle injection techniques using the hydrogel particle formulation described in U.S. 20020061336. Additional particle formulations are described in WO 00/45792, WO 00/53160, and WO 02/19989. An example of a transdermal formulation containing plaster and the absorption promoter dimethylisosorbide can be found in WO 89/04179. WO 96/11705 provides formulations suitable for transdermal administration.

The agents can be administered in the form a suppository or by other vaginal or rectal means. The agents can be administered in a transmembrane formulation as described in WO 90/07923. The agents can be administered non-invasively via the dehydrated particles described in U.S. 6,485,706. The agent can be administered in an enteric-coated drug formulation as described in WO 02/49621. The agents can be administered intranasaly using the formulation described in U.S. 5,179,079. Formulations suitable for parenteral injection are described in WO 00/62759. The agents can be administered using the casein formulation described in U.S. 20030206939 and WO 00/06108. The agents can be administered using the particulate formulations described in U.S. 20020034536.

The agents, 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.

Pulmonary formulations may also include surfactants which include but are not limited to bile salts and those described in U.S. 6,524,557 and references therein. The surfactants described in U.S. 6,524,557, 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.

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. 6,632,456. WO 02/080884 describes new methods for the surface modification of powders. Aerosol formulations may include U.S. 5,230,884, U.S. 5,292,499, WO 017/8694, WO 01/78696, U.S. 2003019437, U. S. 20030165436, and WO 96/40089 (which includes vegetable oil). Sustained release formulations suitable for inhalation are described in U.S. 20010036481A1, 20030232019A1, and U.S. 20040018243A1 as well as in WO 01/13891, WO 02/067902, WO 03/072080, and WO 03/079885.

Pulmonary formulations containing microparticles are described in WO 03/015750, U.S. 20030008013, and WO 00/00176. Pulmonary formulations containing stable glassy state powder are described in U.S. 20020141945 and U.S. 6,309,671. Other aerosol formulations are described in EP 1338272A1 WO 90/09781, U. S. 5,348,730, U.S. 6,436,367, WO 91/04011, and U.S. 6,294,153 and U.S. 6,290,987 describes a liposomal based formulation that can be administered via aerosol or other means.

Powder formulations for inhalation are described in U.S. 20030053960 and WO 01/60341. The agents can be administered intranasally as described in U.S. 20010038824. 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.

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.

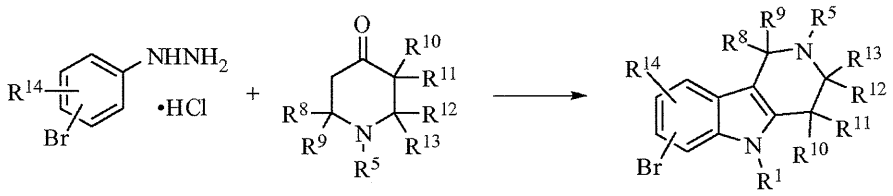
The agent can be incorporated into a liposome to improve half-life. The agent can also be conjugated to polyethylene glycol (PEG) chains. Methods for pegylation and additional formulations containing PEG-conjugates (i.e. PEG-based hydrogels, PEG modified liposomes) can be found in Harris and Chess, Nature Reviews Drug Discovery 2:214-221 and the references therein. The agent can be administered via a nanocochleate or cochleate delivery vehicle (BioDelivery Sciences International). The agents can be delivered transmucosally (i.e. across a mucosal surface such as the vagina, eye or nose) using formulations such as that described in U.S. 5,204,108. The agents can be formulated in microcapsules as described in WO 88/01165. The agent can be administered intra-orally using the formulations described in U.S. 20020055496, WO 00/47203, and U.S. 6,495,120. The agent can be delivered using nanoemulsion formulations described in WO 01/91728A2.

TABLE 1 lists compounds representative of embodiments of the invention. In general, the compounds of the present invention may 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 in themselves known, but are not mentioned here.

Processes for obtaining the compounds of the invention are presented below. Other compounds of the invention may be prepared in analogous fashion to those whose synthesis is exemplified herein. The procedures below illustrate such methods. Furthermore, 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

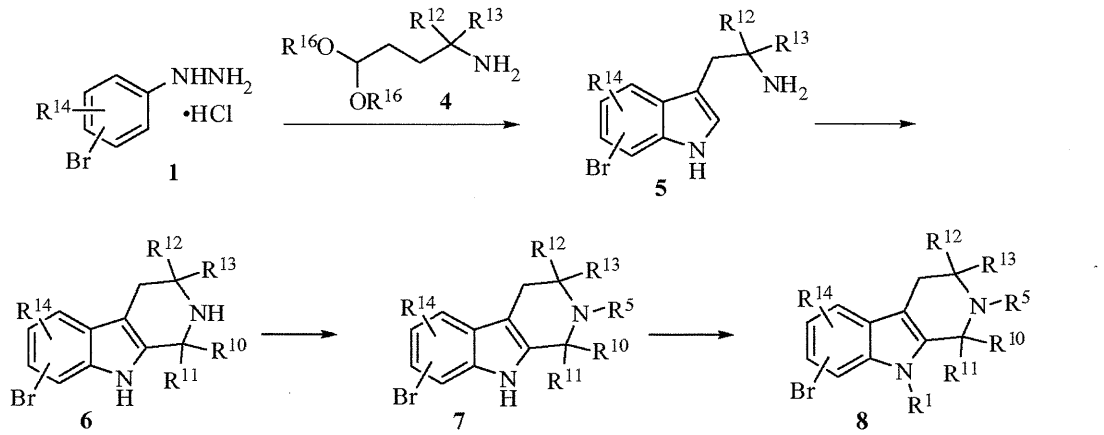


1 **2** **3**

Compounds of formula **3** (wherein R^{14} is H or halogen; R^1 is H; R^5 is a protecting group such as *tert*-butoxycarbonyl or benzyloxycarbonyl; R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are each independently selected from H or optionally substituted alkyl) can be prepared from 3- or 4-bromo phenylhydrazine **1** (or a salt thereof) and piperidinone **2** under heated acidic conditions. Optional N5-alkylation or N5-protection of compound **3** can provide compounds of formula **3** wherein R^1 is alkyl or a protecting group such as *tert*-butoxycarbonyl, benzyloxycarbonyl or *p*-toluenesulfonyl. Optional removal of N2-

protecting group R^5 and reductive amination, alkylation or acylation can provide compounds of formula **3** wherein R^5 is alkyl or acyl.

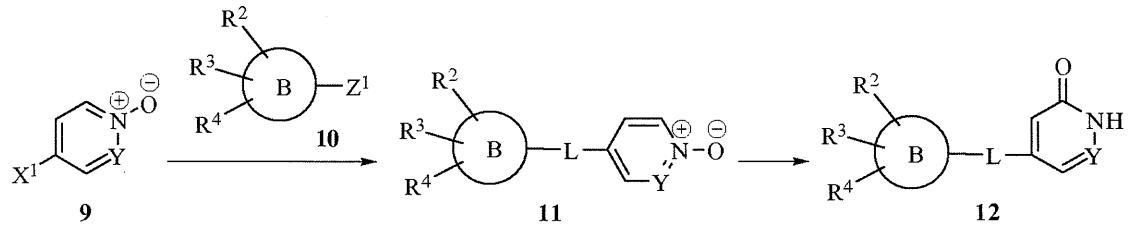
Scheme 2



Compounds of formula **1** (wherein R^{14} is H or halogen) can be treated with compounds of formula **4** (wherein R^{12} and R^{13} are each independently selected from H or optionally substituted alkyl and R^{16} is alkyl) and a Lewis acid such as $ZnCl_2$ under heated conditions to give compounds of formula **5**. Treatment of compounds of formula **5** with ethyl glyoxylate under heated acidic conditions can provide compounds of formula **6** wherein R^{10} and R^{11} are H. Alternatively, compounds of formula **5** can be treated with a ketone under heated acidic conditions to provide compounds of formula **6** wherein R^{10} and R^{11} are optionally substituted alkyl. Compounds of formula **5** also can be treated with an acid chloride under basic conditions, followed by heating with $POCl_3$ and finally by treatment with a reducing agent such as $NaBH_4$ to provide compounds of formula **6** wherein R^{10} is H and R^{11} is optionally substituted alkyl. Protection of the N2-position on the tetrahydrocarboline ring can provide compounds of formula **7** (wherein R^5 is a protecting group such as *tert*-butoxycarbonyl or benzyloxycarbonyl). Protection of the N9-position on the tetrahydrocarboline ring can provide compounds of formula **8** (wherein R^1 is a protecting group such as *tert*-butoxycarbonyl, benzyloxycarbonyl or *p*-toluenesulfonyl). Alternatively, treatment of compound **7** with a base such as sodium hydride and an alkylating agent can provide compounds of formula **8** wherein R^1 is optionally substituted alkyl. Optional removal of N2-protecting group R^5 and reductive

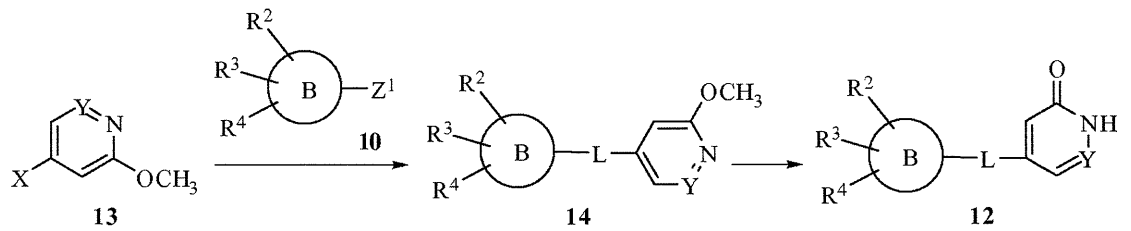
amination, alkylation or acylation can provide compounds of formula **8** wherein R^5 is alkyl or acyl.

Scheme 3



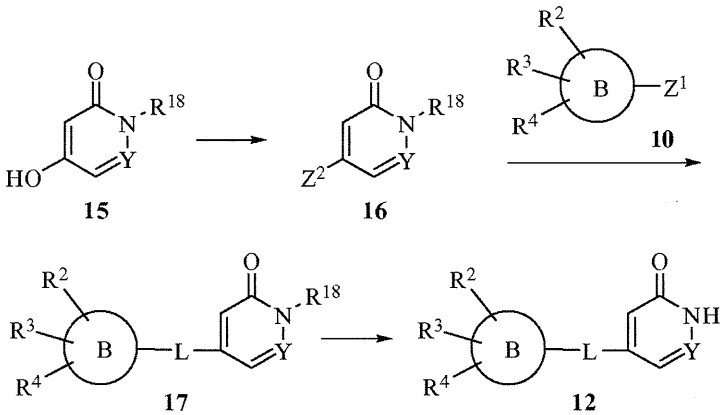
Compounds of formula **12** (wherein B is aryl or heteroaryl; R^2, R^3, R^4 are each independently selected from H, -O-alkyl, S-alkyl, alkyl, halo, $-CF_3$, and –CN; and Y is CH) can be prepared by treating compounds of formula **9** (wherein X^1 is chlorine, bromine or iodine and Y is CH) with compounds of formula **10** (wherein B is aryl or heteroaryl; R^2, R^3, R^4 are each independently selected from H, -O-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 **11**, wherein L is a direct bond. Alternatively, in the case where Z^1 is $-CH_2OH$ and B is aryl, heteroaryl or cycloalkyl, compounds of formula **10** can be treated with a base such as sodium hydride and compounds of formula **9** under heated conditions to give compounds of formula **11**, wherein L is $-CH_2O-$. In turn, compounds of formula **11** 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 **12**, wherein L is $-CH_2O-$ or a direct bond.

Scheme 4



Alternatively, compounds of formula **12** (wherein B is aryl or heteroaryl; R^2, R^3, R^4 are each independently selected from H, -O-alkyl, S-alkyl, alkyl, halo, $-CF_3$, and –CN; and Y is CH) can be prepared by treating compounds of formula **13** (wherein X is chlorine, bromine or iodine and Y is CH) with compounds of formula **10** (wherein Z^1 is -CH=CH-$B(OR^{17})_2$, $B(OR^{17})_2$, $SnR^{17}{}_3$ or the like and R^{17} is H or alkyl), a catalyst such as palladium(0), and a base such as potassium carbonate to give compounds of formula **14**, wherein L is -CH=CH- or a direct bond, in accordance with Z^1. In the case where L is -CH=CH-, compounds of formula **14** can be treated with palladium on carbon under an atmosphere of hydrogen to give compounds of formula **14**, wherein L is $-CH_2CH_2-$. Alternatively, in the case where Z^1 is $-CH_2OH$, compounds of formula **10** can be treated with compounds of formula **13**, 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 **14**, wherein L is $-CH_2O-$. In turn, when L is -CH=CH-, $-CH_2CH_2-$, $-CH_2O-$ or a direct bond, compounds of formula **14** can be heated under acid conditions to provide compounds of formula **12**, wherein L is -CH=CH-, $-CH_2CH_2-$, $-CH_2O-$ or a direct bond, respectively.

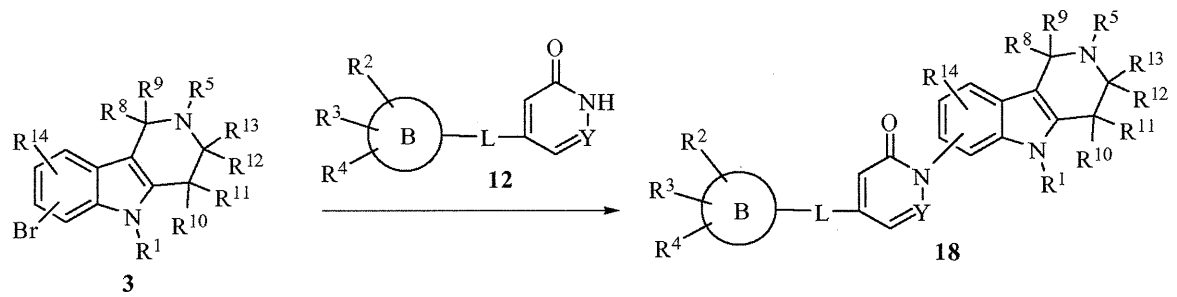
Scheme 5



Alternatively, compounds of formula **12** (wherein B is aryl or heteroaryl; R^2, R^3, R^4 are each independently selected from H, -O-alkyl, S-alkyl, alkyl, halo, $-CF_3$, and –CN; and Y is N) can be prepared from compounds of formula **15** (wherein Y is N and R^{18} is a protecting group such as tetrahydropyran-2-yl). The hydroxyl group on compound **15** can

be converted to an appropriate activating group to give compounds of formula **16**. In the case where Z^2 is triflate, compounds of formula **15** 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 **16**. Treatment of compounds of formula **16** with compounds of formula **10** (wherein B is aryl or heteroaryl; R^2, R^3, R^4 are each independently selected from H, -O-alkyl, S-alkyl, alkyl, halo, $-CF_3$, and -CN; Z^1 = -CH=CH-$B(OR^{17})_2$, $B(OH)_2$, $B(OR^{17})_2$, $SnR^{17}{}_3$ or the like, and R^{17} = alkyl), a catalyst such as palladium(0), and a base such as potassium carbonate under heated conditions can provide compounds of formula **17**, wherein L is -CH=CH- or a direct bond. Removal of the protecting group R^{18} on compound **17** can provide compounds of formula **12**.

Scheme 6



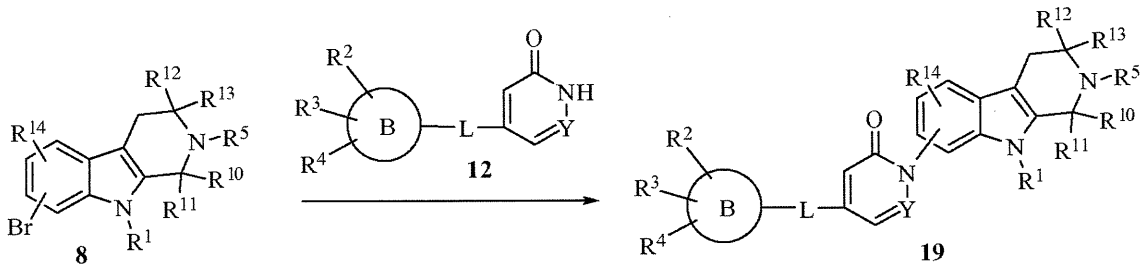
Compounds of formula **18** (wherein B is aryl, heteroaryl or cycloalkyl; R^2, R^3, R^4 are each independently selected from H, -O-alkyl, -S-alkyl, alkyl, halo, $-CF_3$, and -CN; L is $-CH_2$-O-, -CH=CH-, $-CH_2CH_2$-, or a bond; Y is CH or N; R^{14} is H or halogen; R^5 is alkyl, acyl or a protecting group such as *tert*-butoxycarbonyl or benzyloxycarbonyl; R^1 is alkyl or a protecting group such as *tert*-butoxycarbonyl, benzyloxycarbonyl or *p*-toluenesulfonyl; and R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are each independently selected from H or optionally substituted alkyl) can be prepared by treating compounds of formula **3** (wherein R^5 is alkyl, acyl or a protecting group such as *tert*-butoxycarbonyl or benzyloxycarbonyl and R^1 is alkyl or a protecting group such as *tert*-butoxycarbonyl, benzyloxycarbonyl or *p*-toluenesulfonyl) 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 **12**

(wherein B is aryl, heteroaryl or cycloalkyl; R^2, R^3, R^4 are each independently selected from H, -O-alkyl, -S-alkyl, alkyl, halo, $-CF_3$, and -CN; L is $-CH_2-O-$, $-CH=CH-$, $-CH_2CH_2-$, or a bond; and Y is CH or N). Removal of the N2-protecting group R^5 followed by reductive amination or alkylation can provide compounds of formula **18**, wherein R^5 is an optionally substituted alkyl group.

Alternatively, following deprotection, N2 can be acylated to give compounds of formula **18** wherein R^5 is $-C(=O)-R^6$ or $-C(=O)-O-R^7$, and R^6 and R^7 are each optionally substituted alkyl or optionally substituted heterocycle. Additionally, in the case where R^1 is a protecting group, the protecting group can be removed to give compounds of formula **18** wherein R^1 is H.

Alternatively, following removal of the R^1 protecting group, N5 can be alkylated to give compounds of formula **18** wherein R^5 is an optionally substituted alkyl.

Scheme 7



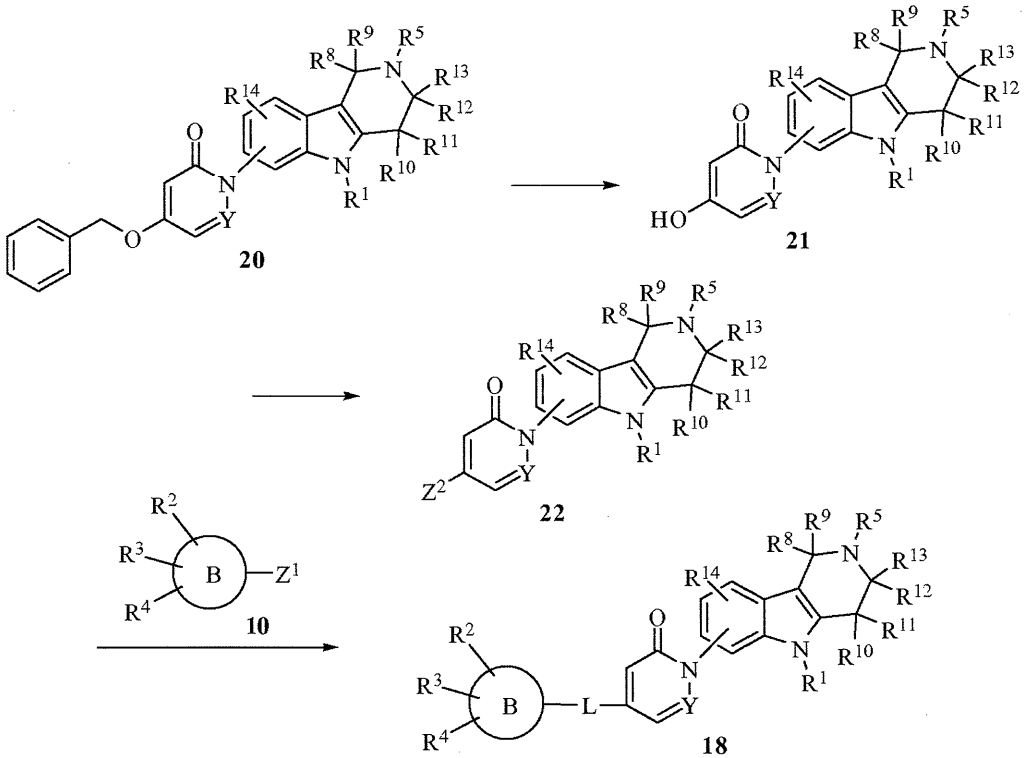
Compounds of formula **19** (wherein B is aryl, heteroaryl or cycloalkyl; R^2, R^3, R^4 are each independently selected from H, -O-alkyl, -S-alkyl, alkyl, halo, $-CF_3$, and -CN; L is $-CH_2-O-$, $-CH=CH-$, $-CH_2CH_2-$, or a bond; Y is CH or N; R^{14} is H or halogen; R^5 is alkyl, acyl or a protecting group such as *tert*-butoxycarbonyl or benzyloxycarbonyl; R^1 is alkyl or a protecting group such as *tert*-butoxycarbonyl, benzyloxycarbonyl or *p*-toluenesulfonyl; and R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are each independently selected from H or optionally substituted alkyl) can be prepared by treating compounds of formula **3** (wherein R^5 is alkyl, acyl or a protecting group such as *tert*-butoxycarbonyl or benzyloxycarbonyl and R^1 is alkyl or a protecting group such as *tert*-butoxycarbonyl, benzyloxycarbonyl or *p*-toluenesulfonyl) 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 **12** (wherein B is aryl, heteroaryl or cycloalkyl; R^2, R^3, R^4 are each independently selected from H, -O-alkyl, -S-alkyl, alkyl, halo, $-CF_3$, and -CN; L is $-CH_2-O-$, $-CH=CH-$, $-CH_2CH_2-$, or a bond; and Y is CH or N). Removal of the N2-protecting group R^5 followed by reductive amination or alkylation can provide compounds of formula **18**, wherein R^5 is an optionally substituted alkyl group.

Alternatively, following deprotection, N2 can be acylated to give compounds of formula **18** wherein R^5 is $-C(=O)-R^6$ or $-C(=O)-O-R^7$, and R^6 and R^7 are each optionally substituted alkyl or optionally substituted heterocycle. Additionally, in the case where R^1 is a protecting group, the protecting group can be removed to give compounds of formula **18** wherein R^1 is H.

Alternatively, following removal of the R^1 protecting group, N5 can be alkylated to give compounds of formula **18** wherein R^5 is an optionally substituted alkyl.

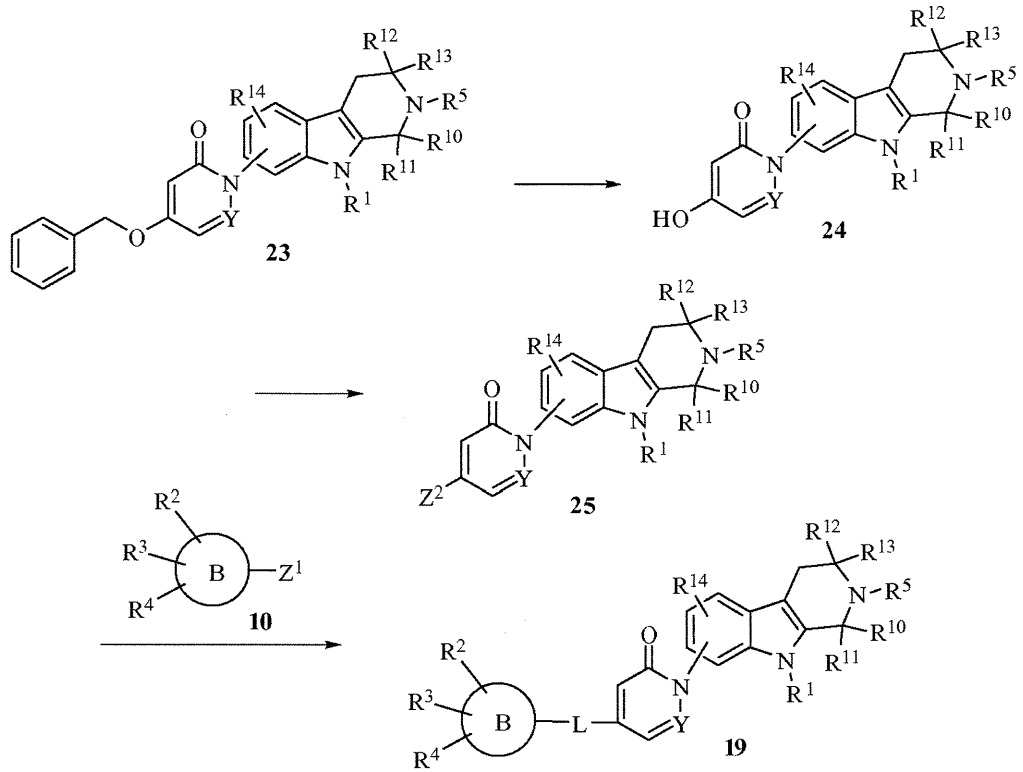
Scheme 8



Compounds of formula **20** (wherein Y is CH or N; R^{14} is H or halogen; R^5 is alkyl, acyl or a protecting group such as *tert*-butoxycarbonyl or benzyloxycarbonyl; R^1 is alkyl or

a protecting group such as *tert*-butoxycarbonyl, benzyloxycarbonyl or *p*-toluenesulfonyl; and R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are each independently selected from H or optionally substituted alkyl) can be treated with hydrogen and a catalyst such as palladium on carbon to provide compounds of formula **21**. The hydroxyl group on compounds of formula **21** can be converted to an appropriate activating group to give compounds of formula **22**. In the case where Z^2 is triflate, compounds of formula **21** 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 **22**. Treatment of compounds of formula **22** with compounds of formula **10** (wherein B is aryl or heteroaryl; R^2, R^3, R^4 are each independently selected from H, -O-alkyl, -S-alkyl, alkyl, halo, $-CF_3$, and -CN; Z^1 = -CH=CH-$B(OR^{17})_2$, $B(OH)_2$, $B(OR^{17})_2$, $SnR^{17}{}_3$ or the like and R^{17} = alkyl), a catalyst such as palladium(0), and a base such as potassium carbonate under heated conditions can provide compounds of formula **18**, wherein L is -CH=CH- or a direct bond. In the case where L is -CH=CH-, compounds of formula **18** can be treated with palladium on carbon under an atmosphere of hydrogen to give compounds of formula **18**, where L is $-CH_2CH_2-$.

Scheme 9



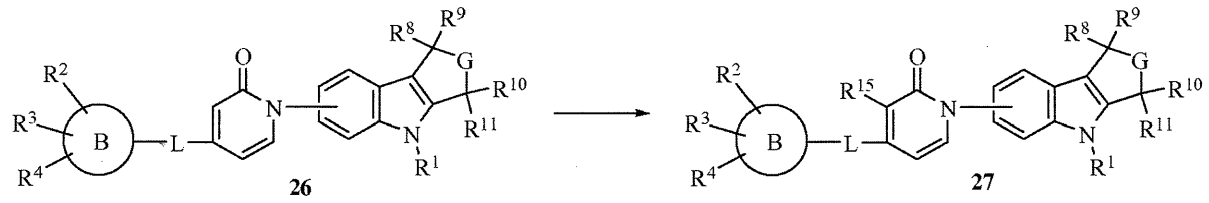
Compounds of formula **23** (wherein Y is CH or N; R^{14} is H or halogen; R^5 is alkyl, acyl or a protecting group such as *tert*-butoxycarbonyl or benzyloxycarbonyl; R^1 is alkyl or a protecting group such as *tert*-butoxycarbonyl, benzyloxycarbonyl or *p*-toluenesulfonyl; and R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are each independently selected from H or optionally substituted alkyl) can be treated with hydrogen and a catalyst such as palladium on carbon to provide compounds of formula **24**. The hydroxyl group on compounds of formula **24** can be converted to an appropriate activating group to give compounds of formula **25**. In the case where Z^2 is triflate, compounds of formula **24** 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 **25**.

Treatment of compounds of formula **25** with compounds of formula **10** (wherein B is aryl or heteroaryl; R^2, R^3, R^4 are each independently selected from H, -O-alkyl, -S-alkyl, alkyl, halo, $-CF_3$, and -CN; Z^1 = $-CH=CH-B(OR^{17})_2$, $B(OH)_2$, $B(OR^{17})_2$, $SnR^{17}{}_3$ or the like and R^{17} = alkyl), a catalyst such as palladium(0), and a base such as potassium carbonate

under heated conditions can provide compounds of formula **19**, wherein L is -CH=CH- or a direct bond. .

In the case where L is -CH=CH-, compounds of formula **18** can be treated with palladium on carbon under an atmosphere of hydrogen to give compounds of formula **18**, where L is $-CH_2CH_2-$.

Scheme 10



Compounds of formula **26** (wherein B is aryl or heteroaryl; R^2, R^3, R^4 are each independently selected from H, -O-alkyl, -S-alkyl, alkyl, halo, $-CF_3$, and –CN; L is $-CH_2-O-$, $-CH=CH-$, $-CH_2CH_2-$, or a bond; G is $-CR^{12}R^{13}-NH-$ or $-NH-CR^{12}R^{13}-$; R^1 is alkyl; and R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are each independently selected from H or optionally substituted alkyl) can be treated under halogenation conditions such as 2-bromopropane under heated conditions to provide compounds of formula **27** wherein R^{15} is a halogen such as bromine.

Examples

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
25	1.0	10.0	90.0

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

Method B:

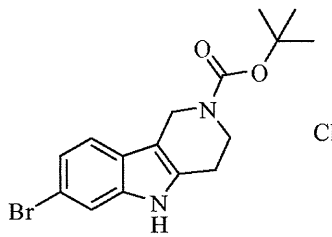
Time (min)	Flow (mL/min)	%A	%B
0.0	1.0	98.0	2.0
25	1.0	10.0	90.0
30	1.0	10.0	90.0

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

Example 1

Preparation of 4-(Benzyloxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

a) *tert*-Butyl 7-bromo-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate

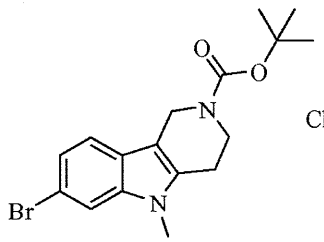


Chemical Formula: $C_{16}H_{19}BrN_2O_2$
Exact Mass: 350.06
Molecular Weight: 351.24

3-Bromophenylhydrazine (40.0 g, 0.179 mol) and *N*-Boc-4-oxo-piperidine (35.4 g, 0.179 mol) were dissolved in ethanol (368 mL), and conc. HCl (72 mL) was added. The reaction mixture was then heated to reflux for 18 h, concentrated and basified using 10% NH_4OH in methanol (10%, 100 mL). The solvent was removed, and the residue was suspended in CH_2Cl_2 (1.2 L). Boc_2O (39.2 g, 0.179 mol) followed by DMAP (195 mg, 1.6 mmol) and

triethylamine (46.4 mL, 0.358 mol) were then added, and the reaction progressed at room temperature for 18 h. The mixture was washed with 0.5 N HCl, and the organic phase was removed, dried over Na_2SO_4, filtered and concentrated to dryness. The resulting mixture of regioisomers was purified by flash column chromatography (silica gel, hexanes/EtOAc, 100:0 to 80:20 to 50:50 then 25:75) to give the more polar title compound (26.2 g, 42%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (br s, 1H), 7.42 (s, 1H), 7.28 (d, J = 8.1 Hz, 1H, partially masked by solvent), 7.18 (d, J = 8.1 Hz, 1H), 4.60 (s, 2H), 3.80 (t, J = 5.5 Hz, 2H), 2.79 (t, J = 5.6 Hz, 2H), 1.51 (s, 9H).

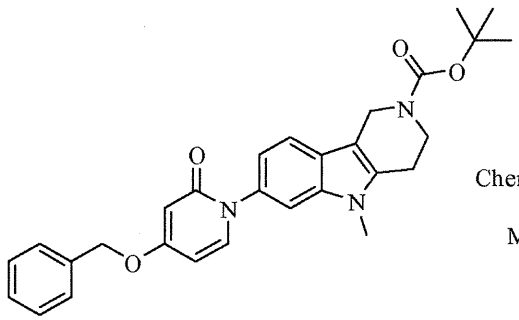
b) *tert*-Butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{17}H_{21}BrN_2O_2$
Exact Mass: 364.08
Molecular Weight: 365.26

Sodium hydride (60% weight dispersion in mineral oil, 4.19 g, 0.105 mol) was added portionwise to a solution of *tert*-butyl 7-bromo-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (23.6 g, 0.07 mol) in DMF (300 mL) at room temperature under N_2. After 1 h, methyl iodide (14.8 g, 6.47 mL, 0.105 mol) was added, and the reaction was allowed to proceed for an additional 2 h. The mixture was quenched with H_2O, upon which a solid precipitated out of solution. The suspension was therefore diluted to 2 L with H_2O and filtered. The solids were washed thoroughly with water, then dissolved in CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated to dryness. This provided the title compound (22.4g, 91%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 4.60 (s, 2H), 3.81 (br t, 2H), 3.58 (s, 3H), 2.77 (t, J = 5.4 Hz, 2H), 1.50 (s, 9H).

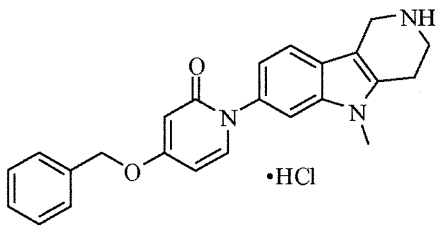
c) *tert*-Butyl 7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{29}H_{31}N_3O_4$
Exact Mass: 485.23
Molecular Weight: 485.57

tert-Butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (7.0 g, 19 mmol), 4-benzyloxypyridone (3.85 g, 19.2 mmol), K_2CO_3 (2.91 g, 21.1 mmol) and 8-hydroxyquinoline (418 mg, 2.88 mmol) were suspended in DMSO (50 mL) and the air removed under vacuum for 15 min. The system was then flushed with N_2. This process was repeated and then copper iodide (547 mg, 2.88 mmol) was added. The evacuation/N_2 flushing process was repeated twice more, and the reaction mixture was heated to 100–120 °C for 18 h. The mixture was cooled, partitioned between EtOAc and sat. NH_4Cl and the organic phase removed, dried over Na_2SO_4, filtered and concentrated to dryness. Purification by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 100:0 to 98:2 to 95:5 to 92:8 then 90:10) gave the title compound (4.71 g, 51%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 8.2 Hz, 1H), 7.43–7.35 (m, 5H), 7.32–7.29 (m, 2H), 7.01 (d, J = 7.9 Hz, 1H), 6.10–6.03 (m, 2H), 5.06 (s, 2H), 4.64 (s, 2H), 3.89 (br t, 2H), 3.63 (s, 3H), 2.82 (br t, 2H), 1.50 (s, 9H).

d) 4-(Benzyloxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



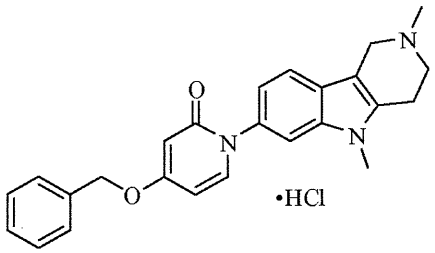
Chemical Formula: $C_{24}H_{24}ClN_3O_2$
Exact Mass: 421.16
Molecular Weight: 421.92

tert-Butyl 7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (12.0 g, 24.7 mmol) was dissolved in MeOH (100 mL), and 2

N HCl in Et_2O (300 mL) was added. The reaction was allowed to proceed for 18 h. The mixture was concentrated, and the residue was partitioned between CH_2Cl_2 and sat. Na_2CO_3 solution. The organic phase was removed, and the aqueous phase was back extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness providing the free base of the title compound (8.1 g, 85%) as a yellow solid. A portion of the free base was converted to the HCl salt for biological testing. **Free base:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.34 (m, 6H), 7.32–7.28 (m, 2H), 6.98 (d, J = 7.1 Hz, 1H), 6.07 (d, J = 2.6 Hz, 1H), 6.04 (dd, J = 7.5, 2.6 Hz, 1H), 5.05 (s, 2H), 4.15 (s, 2H), 3.61 (s, 3H), 3.34 (br s, 2H), 2.78 (br s, 2H). **HCl salt:** melting point (mp) 296–302 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.61–7.57 (2 × d, 2H), 7.47–7.46 (m, 3H), 7.43–7.40 (m, 2H), 7.37–7.34 (m, 1H), 7.05 (dd, J = 8.3, 1.7 Hz, 1H), 6.33 (dd, J = 7.5, 2.7 Hz, 1H), 6.16 (d, J = 2.6 Hz, 1H), 5.19 (s, 2H), 4.57 (s, 2H), 3.73 (s, 3H), 3.67 (t, J = 6.2 Hz, 2H), 3.20 (t, J = 6.1 Hz, 2H); ESI MS m/z 386 $[M + H]^+$; HPLC (Method A) 95.7% (AUC), t_R = 13.6 min.

Example 2

Preparation of 4-(Benzyloxy)-1-(2,5-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



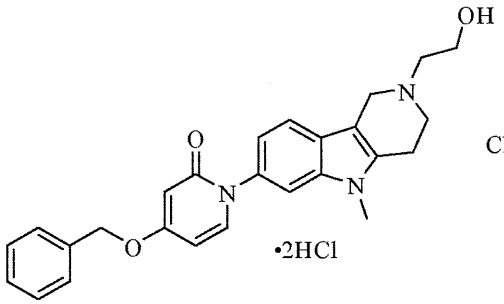
Chemical Formula: $C_{25}H_{26}ClN_3O_2$
Exact Mass: 435.17
Molecular Weight: 435.95

4-(Benzyloxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (8.1 g, 21.0 mmol) and 37% aqueous formaldehyde (2.56 mL, 31.5 mmol) were dissolved in MeOH (200 mL) and stirred at room temperature for 2 h. Sodium triacetoxyborohydride (8.9 g, 42.0 mmol) was then added, and the reaction was stirred at room temperature for an additional 1 h. The mixture was concentrated, and the residue was partitioned between CH_2Cl_2 and sat. Na_2CO_3 solution. The organic phase was removed and the aqueous phase was back extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered and concentrated to dryness. Purification by column

chromatography (120 g ISCO column eluting with methylene chloride and a methanol/ammonia mixture (10:1); gradient 100% methylene chloride to 85% methylene chloride over 60 min) provided the free base of the title compound. This was converted to the HCl salt using 2 N HCl in Et_2O providing the title compound (5.57 g, 61%) as a yellow solid: mp 268–274°C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.57 (dd, J = 7.6, 1.7 Hz, 2H), 7.47–7.46 (m, 3H) 7.43–7.34 (m, 3H), 7.06 (dd, J = 8.4, 1.9 Hz, 1H), 6.29 (dd, J = 7.6, 2.7 Hz, 1H), 6.13 (d, J = 2.6 Hz, 1H), 5.18 (s, 2H), 4.75 (d, J = 14.3 Hz, 1H), 4.38 (d, J = 14.2 Hz, 1H), 3.90 (m, 1H), 3.73 (s, 3H), 3.64–3.58 (m, 1H), 3.29–3.26 (m, 2H, partially masked by solvent), 3.13 (s, 3H); ESI MS m/z 400 $[M + H]^+$; HPLC (Method B) 97.4% (AUC), t_R = 14.7 min.

Example 3

Preparation of 4-(Benzyloxy)-1-(2-(2-hydroxyethyl)-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride



Chemical Formula: $C_{26}H_{29}Cl_2N_3O_3$
Exact Mass: 501.16
Molecular Weight: 502.43

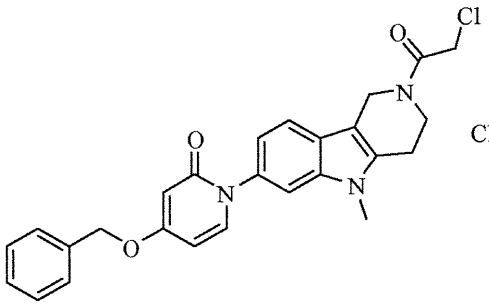
4-(Benzyloxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (75 mg, 0.16 mmol), 2-iodoethanol (17 μL, 36 mg, 0.21 mmol) and triethylamine (105 μL, 0.82 mmol) were dissolved in MeCN (2 mL) and heated to reflux for 3 h. The mixture was then concentrated and purified by flash column chromatography (4 g ISCO column eluting with methylene chloride and a methanol/ammonia mixture (10:1); gradient 100% methylene chloride to 85% methylene chloride over 30 min) providing the free base. This was converted to the HCl salt (2 N HCl/Et_2O) providing the title compound (22 mg, 27%) as a yellow solid: mp 162–168°C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.63 (dd, J = 7.6, 2.0 Hz, 2H), 7.51–7.50 (m, 3H) 7.46–7.43 (m, 2H), 7.41–7.38 (m, 1H), 7.09 (dd, J = 8.3, 1.7 Hz, 1H), 6.36 (dd, J = 7.6, 2.7 Hz, 1H), 6.18 (d, J = 2.7 Hz, 1H), 5.23 (s, 2H), 4.82 (d, 1H,

partially masked by solvent), 4.520 (d, J = 14.3 Hz, 1H), 4.06–4.02 (m, 3H), 3.77 (s, 3H), 3.70–3.68 (m, 1H), 3.55–3.51 (m, 2H), 3.33–3.31 (m, 2H, partially masked by solvent); ESI MS m/z 430 $[M + H]^+$; HPLC (Method B) 95.1% (AUC), t_R = 12.4 min.

Example 4

Preparation of 4-(Benzyloxy)-1-(5-methyl-2-(2-(pyrrolidin-1-yl)acetyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

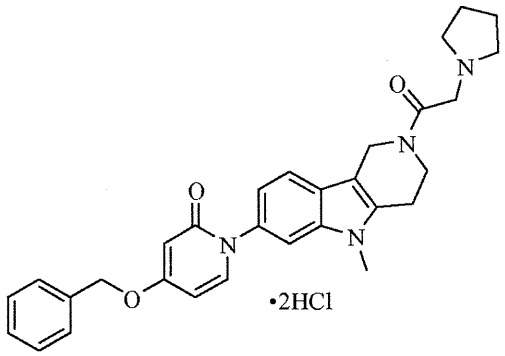
a) 4-(Benzyloxy)-1-(2-(2-chloroacetyl)-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one



Chemical Formula: $C_{26}H_{24}ClN_3O_3$
Exact Mass: 461.15
Molecular Weight: 461.94

4-(Benzyloxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (75 mg, 0.16 mmol) was dissolved in a mixture of CH_2Cl_2 (1 mL) and sat. $NaHCO_3$ solution (1 mL) and chloroacetyl chloride (28 mg, 0.25 mmol) was added. The reaction mixture was vigorously stirred for 1 h then the phases were separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness providing the title compound (74 mg, 97%) as a beige solid which was a mixture of rotamers: ESI MS m/z 462 $[M + H]^+$.

b) 4-(Benzyloxy)-1-(5-methyl-2-(2-(pyrrolidin-1-yl)acetyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride



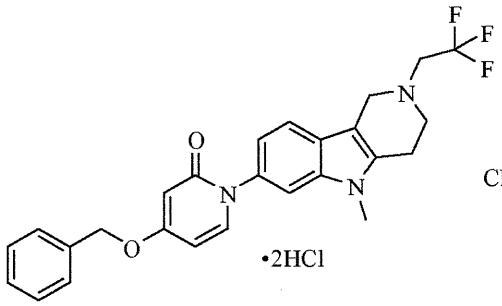
•2HCl

Chemical Formula: $C_{30}H_{34}Cl_2N_4O_3$
Exact Mass: 568.20
Molecular Weight: 569.52

4-(Benzyloxy)-1-(2-(2-chloroacetyl)-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (70 mg, 0.15 mmol) was dissolved in MeCN (0.5 mL) and pyrrolidine (54 mg, 0.76 mmol) was added. The reaction mixture was refluxed for 2 h, concentrated and the residue purified by preparative HPLC. The fractions were concentrated, and the residue was converted to the free base by partitioning between CH_2Cl_2 and sat. Na_2CO_3 solution. The organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness. Conversion to the HCl salt (2 N HCl/Et_2O) provided the title compound (74 mg, 97%) as a beige solid: ^{1}H NMR (500 MHz, CD_3OD) δ 7.62 (dd, J = 7.7, 1.9 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H) 7.46–7.44 (m, 2H), 7.41–7.35 (m, 4H), 7.06 (dd, J = 8.0, 1.7 Hz, 1H), 6.36 (d, J = 7.6 Hz, 1H), 6.18 (s, 1H), 5.25 (s, 2H), 4.90 (m, 1H, masked by solvent), 4.82 (s, 1H), 4.53 (d, J = 14.2 Hz, 2H), 4.09 (t, J = 6.5 Hz, 1H), 3.91 (t, J = 6.4 Hz, 1H), 3.89–3.86 (m, 2H), 3.77 (s, 3H), 3.20–3.18 (m, 2H), 3.05–3.03 (m, 1H), 2.99–2.97 (m, 1H), 2.12–2.10 (m, 2H), 2.08–2.05 (m, 2H); ESI MS *m/z* 497 [M + H]$^+$; HPLC (Method B) 95.0% (AUC), t_R = 13.1 min.

Example 5

Preparation of 4-(Benzyloxy)-1-(5-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

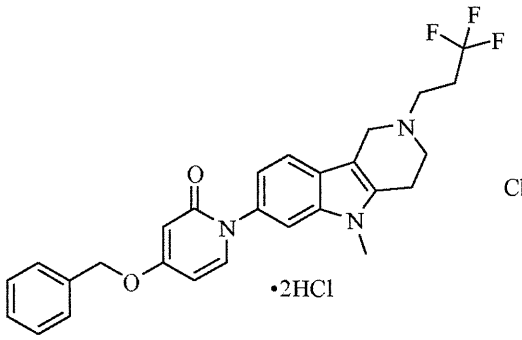


Chemical Formula: $C_{26}H_{26}Cl_2F_3N_3O_2$
Exact Mass: 539.14
Molecular Weight: 540.40

4-(Benzyloxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (75 mg, 0.16 mmol) and triethylamine (105 μL, 0.753 mmol) were dissolved in MeCN (2 mL) and 1,1,1-trifluoro-2-bromoethane (32 mg, 0.20 mmol) was added. The reaction mixture was heated to reflux for 4 h, but no reaction occurred. The mixture was concentrated, DMF (2 mL) and NaI (5 mg) were added, and the reaction mixture was heated to reflux. Again, no reaction occurred. 1,1,1-trifluoroethyl triflate (76 mg, 0.328 mmol) was then added, and the mixture was heated to reflux. After 1.5 h, the mixture was concentrated and purified by flash column chromatography (4 g ISCO column eluting with methylene chloride and a methanol/ammonia mixture (10:1); gradient 100% methylene chloride to 85% methylene chloride over 30 min). Further purification by preparative HPLC, followed by conversion to the HCl salt (2 N HCl/Et_2O) provided the title compound (6 mg, 7%) as a white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.48 (d, J = 7.5 Hz, 1H), 7.40–7.24 (m, 7H), 6.87 (dd, J = 8.3, 1.9 Hz, 1H), 6.19 (dd, J = 7.6, 2.7 Hz, 1H), 6.03 (d, J = 2.7 Hz, 1H), 5.08 (s, 2H), 3.96 (s, 2H), 3.58 (s, 3H), 3.37 (q, J = 9.7 Hz, 2H), 3.15–3.14 (m, 2H, partially masked by solvent), 2.87 (t, J = 5.5 Hz, 2H); ESI MS *m/z* 468 $[M + H]^+$; HPLC (Method B) 98.9% (AUC), t_R = 17.3 min.

Example 6

Preparation of 4-(Benzyloxy)-1-(5-methyl-2-(3,3,3-trifluoropropyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride



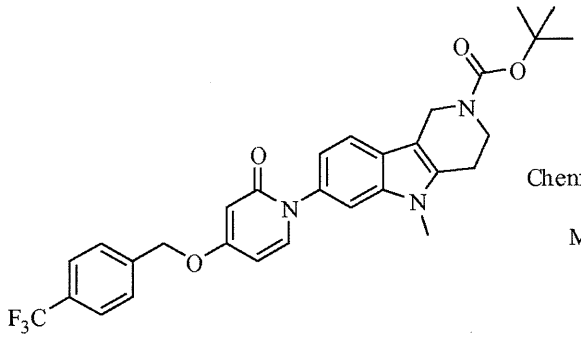
Chemical Formula: $C_{27}H_{28}Cl_2F_3N_3O_2$
Exact Mass: 553.15
Molecular Weight: 554.43

4-(Benzyloxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (63 mg, 0.14 mmol) and K_2CO_3 (97 mg, 0.70 mmol) were suspended in DMF (1 mL) and 1,1,1-trifluoro-3-bromopropane (50 mg, 0.28 mmol) was added. The reaction mixture was heated to 80 °C for 18 h, cooled and partitioned between ethyl acetate and water. The aqueous phase was removed and the organic phase washed with 5% LiCl (5×), dried over Na_2SO_4, filtered and concentrated to dryness. Purification by flash column chromatography (4 g ISCO column eluting with methylene chloride and a methanol/ammonia mixture (10:1); gradient 100% methylene chloride to 85% methylene chloride over 30 min) followed by conversion to the HCl salt (2 N HCl/Et_2O) provided the title compound (12 mg, 16%) as a yellow solid: ^{1}H NMR (500 MHz, CD_3OD) δ 7.66 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.52–7.51 (m, 3H), 7.48–7.45 (m, 2H), 7.43 (d, J = 7.2 Hz, 1H), 7.11 (dd, J = 8.3, 1.7 Hz, 1H), 6.36 (dd, J = 7.6, 2.7 Hz, 1H), 6.19 (d, J = 2.7 Hz, 1H), 5.24 (s, 2H), 4.96 (m, 6H, masked by solvent), 3.79–3.74 (m, 5H), 3.03–3.02 (m, 2H); ESI MS *m/z* 482 $[M + H]^+$; HPLC (Method B) 95.6% (AUC), t_R = 14.3 min.

Example 7

Preparation of 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(4-(trifluoromethyl)benzyloxy)pyridin-2(1*H*)-one dihydrochloride

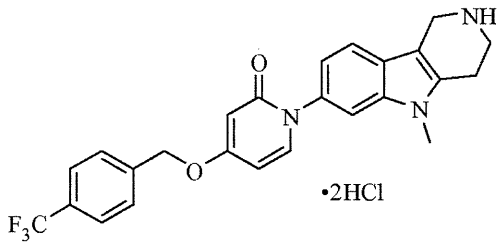
a) *tert*-Butyl 5-methyl-7-(2-oxo-4-(4-(trifluoromethyl)benzyloxy)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{30}H_{30}F_3N_3O_4$
Exact Mass: 553.22
Molecular Weight: 553.57

The compound was prepared from *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (250 mg, 0.701 mmol) and 4-(4-(trifluoromethyl)benzyloxy)pyridin-2(1*H*)-one (142 mg, 0.526 mmol) according to the procedure in Example 1 (step c). Purification by flash column chromatography (silica gel, hexanes/EtOAc, 100:0 to 80:20 to 50:50 to 25:75 then 0:100) provided the title compound (73 mg, 19%) as a solid, that contained an impurity: ESI MS *m/z* 554 $[M + H]^+$.

b) 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(4-(trifluoromethyl)benzyloxy)pyridin-2(1*H*)-one dihydrochloride



Chemical Formula: $C_{25}H_{24}Cl_2F_3N_3O_2$
Exact Mass: 525.12
Molecular Weight: 526.38

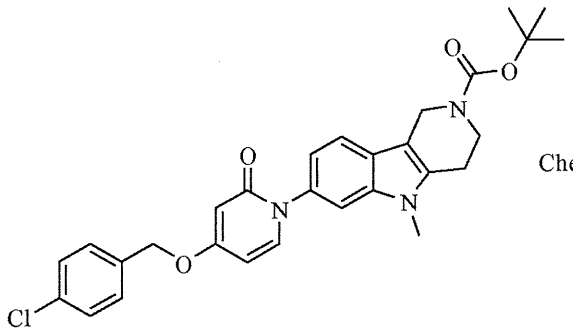
tert-Butyl 5-methyl-7-(2-oxo-4-(4-(trifluoromethyl)benzyloxy)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (73 mg, 0.13 mmol) was dissolved in MeOH (0.5 mL) and 2 N HCl in Et_2O (3 mL) was added. The reaction was allowed to proceed for 3 h. The mixture was concentrated and purified by preparative HPLC. Converion to the HCl salt (2 N HCl/Et_2O) provided the title compound (26 mg, 38%) as a yellow solid: mp 311–315 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.77 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.50 (s, 1H), 7.09 (dd, J = 8.3, 1.8 Hz, 1H), 6.38 (dd, J = 7.6, 2.7 Hz, 1H), 6.17 (d, J = 2.7 Hz, 1H), 5.33

(s, 2H), 4.51 (s, 2H), 3.77 (s, 3H), 3.71 (t, J = 6.2 Hz, 2H), 3.24 (t, J = 6.1 Hz, 2H); ESI MS m/z 454 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 14.2 min.

Example 8

Preparation of 4-(4-Chlorobenzyloxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

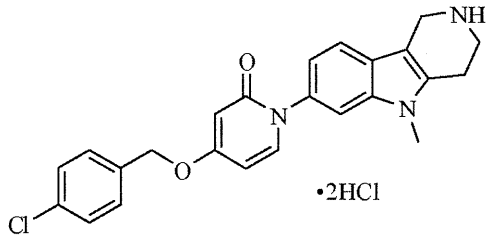
a) *tert*-Butyl 7-(4-(4-chlorobenzyloxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{29}H_{30}ClN_3O_4$
Exact Mass: 519.19
Molecular Weight: 520.02

The compound was prepared from *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (200 mg, 0.548 mmol) and 4-(4-chlorobenzyloxy)pyridin-2(1*H*)-one (129 mg, 0.548 mmol) according to the procedure in Example 1 (step c). Purification by flash column chromatography (silica gel, hexanes/EtOAc, 100:0 to 80:20 to 50:50 to 25:75 then 0:100) provided the title compound (143 mg, 50%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 8.0 Hz, 1H), 7.43–7.29 (m, 6H), 7.01 (d, J = 7.9 Hz, 1H), 6.05–6.02 (m, 2H), 5.02 (s, 2H), 4.64 (br s, 2H), 3.84 (br s, 2H), 3.63 (s, 3H), 2.82 (br s, 2H), 1.50 (s, 9H).

b) 4-(4-Chlorobenzyloxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride



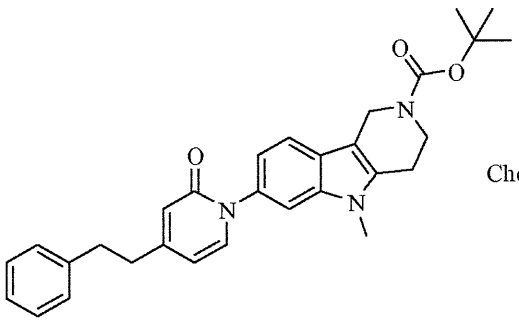
Chemical Formula: $C_{24}H_{24}Cl_3N_3O_2$
Exact Mass: 491.09
Molecular Weight: 492.83

tert-Butyl-7-(4-(4-chlorobenzyloxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (143 mg, 0.275 mmol) was dissolved in MeOH (1 mL) and 2 N HCl in Et_2O (5 mL) was added. The reaction was allowed to proceed for 3 h. The resulting precipitate was collected by filtration and washed with Et_2O to provide the title compound (95 mg, 71%) as a yellow solid: mp 305–310 °C dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (br s, 2H), 7.57 (m, 2H), 7.51 (s, 5H), 6.99 (d, J = 7.8 Hz, 1H), 6.12 (dd, J = 7.8, 2.7 Hz, 1H), 5.99 (d, J = 2.7 Hz, 1H), 5.16 (s, 2H), 4.33 (br s, 2H), 3.68 (s, 3H), 3.52–3.48 (m, 2H), 3.12–3.08 (m, 2H); ESI MS *m/z* 420 $[M + H]^+$; HPLC (Method B) 97% (AUC), t_R = 13.99 min.

Example 9

Preparation of 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-phenethylpyridin-2(1*H*)-one dihydrochloride

a) *tert*-Butyl 5-methyl-7-(2-oxo-4-phenethylpyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate

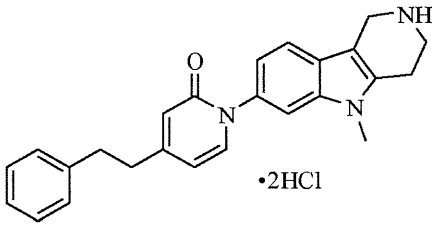


Chemical Formula: $C_{30}H_{33}N_3O_3$
Exact Mass: 483.25
Molecular Weight: 483.60

The compound was prepared from *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (200 mg, 0.548 mmol) and 4-phenethylpyridin-2(1*H*)-one (109 mg, 0.548 mmol) according to the procedure in Example 1 (step c). Purification by flash column chromatography (silica gel, hexanes/EtOAc, 100:0 to 80:20 to 50:50 to 25:75 then 0:100) provided the title compound (126 mg, 48%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J = 8.2 Hz, 1H), 7.34–7.30 (m, 4H), 7.24–7.20 (m, 3H, partially masked by solvent), 7.03 (d, J = 7.8 Hz, 1H), 6.52 (s, 1H), 6.10 (dd, J = 7.9,

1.7 Hz, 1H), 4.65 (br s, 2H), 3.84 (br s, 2H), 3.63 (s, 3H), 2.98–2.93 (m, 2H), 2.84–2.81 (m, 4H), 1.51 (s, 9H).

b) 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-phenethylpyridin-2(1*H*)-one dihydrochloride



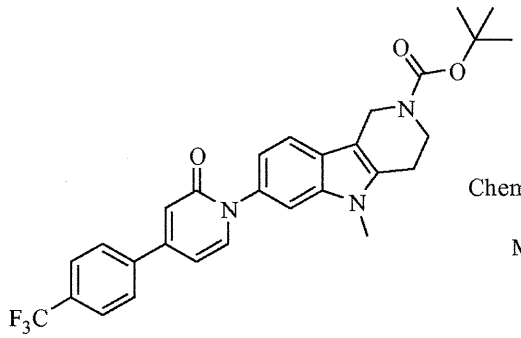
Chemical Formula: $C_{25}H_{27}Cl_2N_3O$
Exact Mass: 455.15
Molecular Weight: 456.41

tert-Butyl 5-methyl-7-(2-oxo-4-phenethylpyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (120 mg, 0.248 mmol) was dissolved in MeOH (1.5 mL) and 2 N HCl in Et_2O (5 mL) was added. The reaction was allowed to proceed for 3 h. The resulting precipitate was collected by filtration and washed with Et_2O to provide the title compound (90 mg, 80%) as a yellow solid: mp 282–286°C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.70 (d, J = 6.9 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.52 (s, 1H), 7.33–7.26 (m, 4H), 7.22 (t, J = 7.2 Hz, 1H), 7.09 (dd, J = 8.3, 1.6 Hz, 1H), 6.59–6.56 (m, 2H), 4.50 (s, 2H), 3.76 (s, 3H), 3.70 (t, J = 6.2 Hz, 2H), 3.24 (t, J = 6.0 Hz, 2H), 3.04–3.01 (m, 2H), 2.98–2.95 (m, 2H); ESI MS *m/z* 384 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 13.3 min.

Example 10

Preparation of 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one dihydrochloride

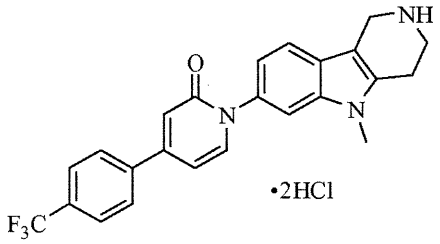
a) *tert*-Butyl 5-methyl-7-(2-oxo-4-(4-(trifluoromethyl)phenyl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{29}H_{28}F_3N_3O_3$
Exact Mass: 523.21
Molecular Weight: 523.55

The compound was prepared from *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (153 mg, 0.418 mmol) and 4-(4-(trifluoromethy)phenyl)pyridine-2(1*H*)-one (100 mg g, 0.418 mmol) according to the procedure in Example 1 (step c). Purification by flash column chromatography (silica gel, hexanes/EtOAc, 100:0 to 80:20 to 50:50 to 25:75 then 0:100) provided the title compound (98 mg, 45%) as a yellow/green solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 4H), 7.57–7.53 (m, 2H), 7.37 (s, 1H), 7.09 (d, J = 8.0 Hz, 1H), 6.92 (s, 1H), 6.50 (d, J = 6.7 Hz, 1H), 4.67 (s, 2H), 3.86 (br s, 2H), 3.60 (s, 3H), 2.84 (br s, 2H), 1.51 (s, 9H).

b) 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one dihydrochloride



Chemical Formula: $C_{24}H_{22}Cl_2F_3N_3O$
Exact Mass: 495.11
Molecular Weight: 496.35

tert-Butyl 5-methyl-7-(2-oxo-4-(4-(trifluoromethyl)phenyl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (95 mg, 0.18 mmol) was dissolved in MeOH (2 mL) and 2 N HCl in Et_2O (10 mL) was added. The reaction was allowed to proceed for 3 h. The resulting precipitate was collected by filtration and washed with Et_2O to provide the title compound (45 mg, 50%) as a pale yellow solid: mp 318–323 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.95 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H), 7.81 (d, J = 7.1 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.57 (s, 1H), 7.14 (dd, J = 8.3, 1.3 Hz, 1H), 6.96 (d, J = 1.6 Hz, 1H), 6.87 (dd, J = 7.1, 1.7 Hz, 1H), 4.50 (s, 2H), 3.76 (s, 3H), 3.68 (t, J = 6.1

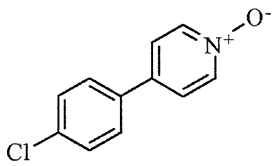
Hz, 2H), 3.22 (t, J = 6.1 Hz, 2H); ESI MS m/z 424 $[M + H]^+$; HPLC (Method B) 97.6% (AUC), t_R = 13.9 min.

Example 11

Preparation of 4-(4-Chlorophenyl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

a) 4-(4-Chlorophenyl)pyridine 1-oxide

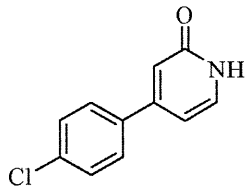
Beilstein Registry Number 5510914



Chemical Formula: $C_{11}H_8ClNO$
Exact Mass: 205.03
Molecular Weight: 205.64

4-Chloropyridine-*N*-oxide (1.5 g, 12 mmol), 4-chlorophenylboronic acid (2.7 g, 17 mmol) and K_2CO_3 (4.78 g, 34.6 mmol) were suspended in DMSO (15 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) ($PdCl_2$(dppf)) (225 mg, 0.276 mmol) was added. The reaction mixture was placed under vacuum for 20 min and then flushed with N_2. This process was repeated, and the reaction mixture was heated to 120 °C for 3 h, cooled and partitioned between ethyl acetate and brine. The aqueous phase was removed, and the organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. Purification by flash column chromatography (silica gel, hexanes/EtOAc, 100:0 to 80:20 to 50:50 then 25:75 followed by methylene chloride/MeOH 100:0 to 95:5 then 90:10) provided the title compound (1.05 g, 44%) as a grey solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, J = 7.1 Hz, 2H), 7.58–7.43 (m, 6H).

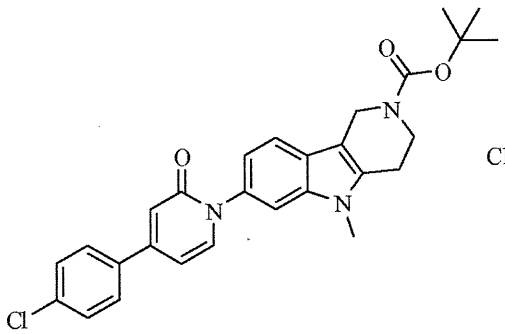
b) 4-(4-Chlorophenyl)pyridin-2(1*H*)-one



Chemical Formula: $C_{11}H_8ClNO$
Exact Mass: 205.03
Molecular Weight: 205.64

4-(4-Chlorophenyl)pyridine 1-oxide (1.04 g, 5.07 mmol) and acetic anhydride (25 mL) were heated to reflux for 24 h. The mixture was then concentrated, and 1 N NaOH (10 mL) in MeOH (10 mL) was added. The reaction mixture was heated to reflux for 1 h, then cooled, concentrated, and purified by flash column chromatography (silica gel, methylene chloride/MeOH 100:0 to 98:2 to 95:5 then 90:10) providing the title compound (500 mg, 48%) as an off-white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.64 (s, 1H), 7.73 (d, J = 8.6 Hz, 2H), 7.54 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 6.8 Hz, 1H), 6.60 (d, J = 1.4 Hz, 1H), 6.50 (dd, J = 6.9, 1.8 Hz, 1H).

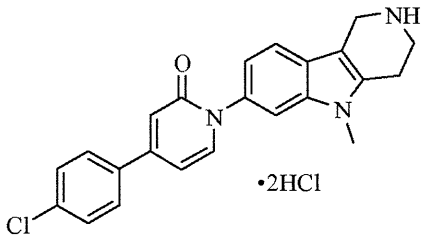
c) *tert*-Butyl 7-(4-(4-chlorophenyl)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{28}H_{28}ClN_3O_3$
Exact Mass: 489.18
Molecular Weight: 489.99

The compound was prepared from *tert*-Butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (250 mg, 0.685 mmol) and 4-(4-chlorophenyl)pyridine-2(1*H*)-one (100 mg, 0.418 mmol) according to the procedure in Example 1 (step c). Purification by flash column chromatography (silica gel, hexanes/EtOAc, 100:0 to 80:20 to 50:50 to 25:75 then 0:100) provided the title compound (59 mg, 18%) as a solid, that contained an impurity: ESI MS *m/z* 490 $[M + H]^+$.

d) 4-(4-Chlorophenyl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride



•2HCl

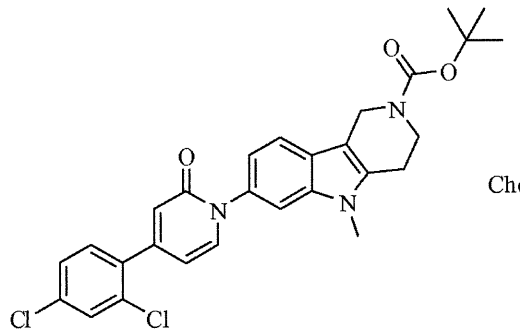
Chemical Formula: $C_{23}H_{22}Cl_3N_3O$
Exact Mass: 461.08
Molecular Weight: 462.80

tert-Butyl 7-(4-(4-chlorophenyl)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (59 mg, 0.12 mmol) was dissolved in MeOH (0.5 mL) and 2 N HCl in Et_2O (3 mL) was added. The reaction was allowed to proceed for 3 h. The mixture was concentrated and purified by preparative HPLC. Conversion to the HCl salt (2 N HCl in Et_2O) provided the title compound (22 mg, 40%) as a pale yellow solid: ^{1}H NMR (500 MHz, CD_3OD) δ 7.80–7.78 (m, 3H), 7.66 (d, J = 8.5 Hz, 1H), 7.58–7.57 (m, 3H), 7.16 (dd, J = 8.3, 1.7 Hz, 1H), 6.94 (d, J = 1.8 Hz, 1H), 6.87 (dd, J = 7.1, 1.9 Hz, 1H), 6.17 (d, J = 2.7 Hz, 1H), 4.53 (s, 2H), 3.79 (s, 3H), 3.72 (t, J = 5.9 Hz, 2H), 3.25 (t, J = 5.9 Hz, 2H); ESI MS *m/z* 390 $[M + H]^+$; HPLC (Method B) 98.2% (AUC), t_R = 16.3 min.

Example 12

Preparation of 4-(2,4-Dichlorophenyl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

a) *tert*-Butyl 7-(4-(2,4-dichlorophenyl)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate

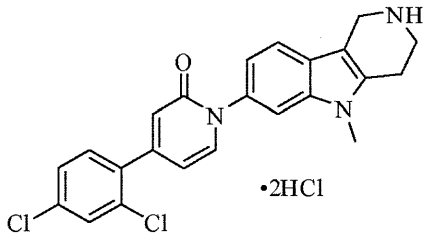


Chemical Formula: $C_{28}H_{27}Cl_2N_3O_3$
Exact Mass: 523.14
Molecular Weight: 524.44

The compound was prepared from *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (200 mg, 0.548 mmol) and 4-(2,4-dichlorophenyl)pyridine-2(1*H*)-one (132 mg, 0.548 mmol) according to the procedure in Example 1 (step c). Purification by flash column chromatography (silica gel,

hexanes/EtOAc, 100:0 to 80:20 to 50:50 then 25:75) provided the title compound (56 mg, 20%) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.52 (m, 2H), 7.47 (d, J = 7.0 Hz, 1H), 7.39–7.32 (m, 3H), 7.10 (br s, 1H), 6.69 (s, 1H), 6.35 (d, J = 5.7 Hz, 1H), 4.66 (s, 2H), 3.85 (br s, 2H), 3.65 (s, 3H), 2.84 (br s, 2H), 1.51 (s, 9H).

b) 4-(2,4-Dichlorophenyl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride



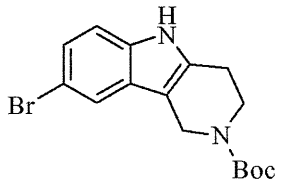
Chemical Formula: $C_{23}H_{21}Cl_4N_3O$
Exact Mass: 495.04
Molecular Weight: 497.24

tert-Butyl 7-(4-(2,4-dichlorophenyl)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (56 mg, 0.11 mmol) was dissolved in MeOH (1 mL) and 2 N HCl in Et_2O (5 mL) was added. The reaction was allowed to proceed for 3 h. The mixture was concentrated and purified by preparative HPLC. Conversion to the HCl salt (2 N HCl in Et_2O) provided the title compound (22 mg, 42%) as a yellow solid: mp 321–324 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.80 (d, J = 7.0 Hz, 1H), 7.70 (s, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.62 (s, 1H), 7.54 (s, 2H), 7.13 (d, J = 7.0 Hz, 1H), 6.73 (s, 1H), 6.61 (d, J = 7.2 Hz, 1H), 4.54 (s, 2H), 3.80 (s, 3H), 3.72 (t, J = 6.0 Hz, 2H), 3.26 (t, J = 5.9 Hz, 2H); ESI MS *m/z* 424 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 14.1 min.

Example 13

Preparation of 4-(Benzyloxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl)pyridin-2(1*H*)-one hydrochloride

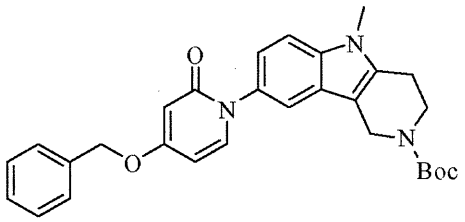
a) *tert*-Butyl 8-bromo-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{16}H_{19}BrN_2O_2$
Exact Mass: 350.0630
Molecular Weight: 351.2383

To a mixture of 4-bromophenylhydryzine hydrochloride (1.00 g, 4.47 mmol) and *tert*-butyl 4-oxopiperidine-1-carboxylate (0.89 g, 4.5 mmol) were added EtOH (10 mL) and conc. HCl (3 mL). The reaction mixture was heated to 90 °C and stirred at 90 °C until the reaction was complete. Then the mixture was concentrated and the residue was dissolved in CH_2Cl_2 (10 mL) and CH_3OH (5 mL). To the above solution were added Boc_2O (1.46 g, 6.69 mmol), TEA (0.94 mL, 6.7 mmol) and DMAP (55 mg, 0.45 mmol). The reaction mixture was stirred at room temperature until it was complete. The mixture was concentrated and the residue was dissolved in CH_2Cl_2, washed with H_2O and brine, dried with Na_2SO_4, filtered and concentrated. Purification by flash column chromatography (silica gel, hexanes/EtOAc, 1:1) gave the title compound (1.12 g, 72%) as a yellow foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.57 (s, 1H), 7.17–7.24 (m, 2H), 4.58 (s, 2H), 3.81 (m, 2H), 2.83 (m, 2H), 1.5 (s, 9H); ESI MS *m/z* 351 $[M + H]^+$.

b) *tert*-Butyl 8-4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2-(5*H*)-carboxylate



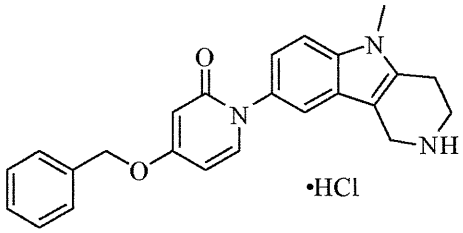
Chemical Formula: $C_{29}H_{31}N_3O_4$
Exact Mass: 485.2315
Molecular Weight: 485.5741

To a solution of *tert*-butyl 8-bromo-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (0.53g, 1.5 mmol) in DMF (6 mL) was added NaH (60% weight dispersion in mineral oil, 91 mg, 2.3 mmol) and CH_3I (0.14 mL, 2.3 mmol). The reaction mixture was stirred at room temperature until the reaction was complete. Then the reaction was quenched with H_2O 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 to give *tert*-butyl 8-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate, which was used directly without purification.

To a mixture of *tert*-butyl 8-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (0.48 g, 1.3 mmol), 4-(benzyloxy)pyridin-2(1*H*)-one (264 mg, 1.31 mmol), 8-hydroxyquinoline (29 mg, 0.20 mmol), K_2CO_3 (217 mg, 1.57 mmol) and CuI (38

mg, 0.20 mmol) was added DMSO (5 mL). The reaction mixture was degassed and back-filled with N_2. The reaction mixture was heated to 130 °C and stirred at 130 °C overnight. After it was cooled, the mixture was filtered through a layer of Celite. The filtrate was diluted with CH_2Cl_2, washed with H_2O and 5% LiCl, dried with Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (silica gel, 5% CH_3OH in CH_2Cl_2) gave the title compound (0.28 g, 44%) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.29 (m, 8H), 7.13 (d, J = 8.0 Hz, 1H), 6.09 (d, J = 2.0 Hz, 1H), 6.03 (dd, J = 7.5, 2.0 Hz, 1H), 5.05 (s, 2H), 4.61 (s, 2H), 3.84 (m, 2H), 3.66 (s, 3H), 2.82 (m, 2H), 1.49 (s, 9H); ESI MS m/z 486 $[M + H]^+$.

c) 4-(Benzyloxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl)pyridin-2(1*H*)-one hydrochloride

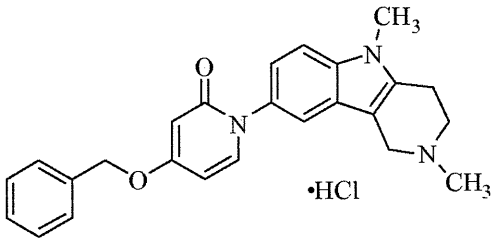


Chemical Formula: $C_{24}H_{24}ClN_3O_2$
Exact Mass: 421.16
Molecular Weight: 421.92

To a solution of *tert*-butyl 8-4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2-(5*H*)-carboxylate (180 mg, 0.37 mmol) in CH_3OH (2 mL) was added 1 N HCl in Et_2O (2 mL). The reaction mixture was stirred at room temperature until the reaction was complete. The resulting solid was dried under vacumn to give the title compound (142 mg, 91%) as a yellow solid: mp 280–285 °C (decompose); ^{1}H NMR (500 MHz, CD_3OD) δ 7.59 (d, J = 7.5 Hz, 1H), 7.54 (d, J = 9.0 Hz, 1H), 7.48–7.40 (m, 5H), 7.38–7.36 (m, 1H), 7.17 (dd, J = 8.5, 1.5 Hz, 1H), 6.33 (dd, J = 7.5, 2.5 Hz, 1H), 6.16 (d, J = 2.5 Hz, 1H), 5.20 (s, 2H), 4.45 (s, 2H), 3.77 (s, 3H), 3.67 (t, J = 6.0 Hz, 2H), 3.21 (t, J = 6.0 Hz, 2H); ESI MS m/z 386 $[M + H]^+$; HPLC (Method B) 98.8% (AUC), t_R = 12.9 min.

Example 14

Preparation of 4-(Benzyloxy)-1-(2,5-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl)pyridin-2(1*H*)-one hydrochloride

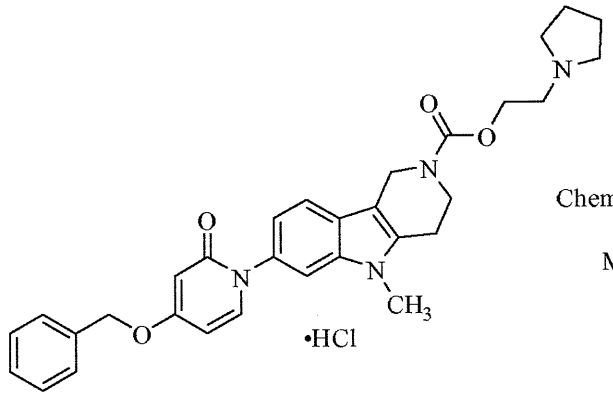


Chemical Formula: $C_{25}H_{26}ClN_3O_2$
Exact Mass: 435.17
Molecular Weight: 435.95

To a solution of 4-(benzyloxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl)pyridin-2(1*H*)-one (100 mg, 0.26 mmol) in CH_3OH (3 mL) was added formaldehyde (30 μL, 0.29 mmol) and $NaBH(OAc)_3$ (110 mg, 0.52 mmol). The reaction mixture was stirred at room temperature until the reaction was complete. Then the mixture was concentrated and the residue was dissolved in CH_2Cl_2. The organic layer was washed with H_2O and 5% LiCl, dried with Na_2SO_4, filtered and concentrated. Purification by flash column chromatography (silica gel, 10% CH_3OH in CH_2Cl_2) gave 4-(benzyloxy)-1-(2,5-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl)pyridin-2(1*H*)-one (102 mg, 98%) as a yellow solid. The free base was converted to the HCl salt to give the title compound (100 mg, 90%) as a yellow solid: mp 264–268 °C (decompose); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.26 (s, 1H), 7.56–7.36 (m, 8H), 7.10 (dd, J = 8.5, 1.5 Hz, 1H), 6.10 (dd, J = 7.5, 3.0 Hz, 1H), 5.97 (d, J = 3.0 Hz, 1H), 5.15 (s, 2H), 4.58 (m, 1H), 4.27 (m, 1H), 3.78 (m, 1H), 3.72 (s, 3H), 3.50 (m, 1H), 3.18 (m, 2H), 2.97 (s, 3H); ESI MS *m/z* 400 $[M + H]^+$; HPLC (Method B) > 99% (AUC), t_R = 12.9 min.

Example 15

Preparation of 2-(Pyrrolidin-1-yl)ethyl-7-4-(benzyloxy)-2-oxopyridin-1(2*H*)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate hydrochloride

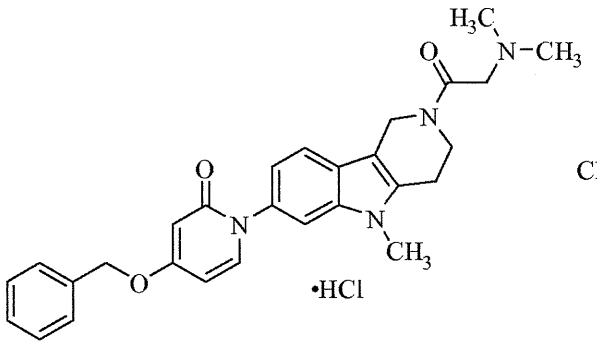


Chemical Formula: $C_{31}H_{35}ClN_4O_4$
Exact Mass: 562.23
Molecular Weight: 563.09

To a solution of 4-benzyloxy-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride (100 mg, 0.24 mmol) in DMSO (2 mL) was added 1-(2-chloroethyl)pyrrolidine hydrochloride (53 mg, 0.29 mmol) and Cs_2CO_3 (313 mg, 1.06 mmol). The reaction mixture was stirred at room temperature under Ar until the reaction was complete. 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. Purification by flash column chromatography (silica gel, 5% CH_3OH in CH_2Cl_2) gave 2-(pyrrolidin-1-yl)ethyl-7-4-(benzyloxy)-2-oxopyridin-1(2*H*)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (56 mg, 44%) as a yellow foam. The free base was converted to the HCl salt to give the title compound (44 mg, 73%) as a yellow solid: mp 95–97 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.78–7.75 (m, 1H), 7.57–7.54 (m, 1H), 7.49–7.37 (m, 6H), 7.04–7.01 (m, 1H), 6.55–6.52 (m, 1H), 6.33–6.31 (m, 1H), 5.26 (s, 2H), 4.80–4.73 (m, 2H), 4.49–4.48 (m, 2H), 3.94–3.93 (m, 2H), 3.82–3.72 (m, 2H), 3.69 (s, 3H), 3.58–3.57 (m, 2H), 3.20–3.14 (m, 2H), 2.98–2.94 (m, 2H), 2.15–1.99 (m, 4H); ESI MS *m/z* 527 $[M + H]^+$; HPLC (Method B) > 99 % (AUC), t_R = 13.8 min.

Example 16

Preparation of 4-(Benzyloxy)-1-(2-(2-(dimethylamino)acetyl)-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



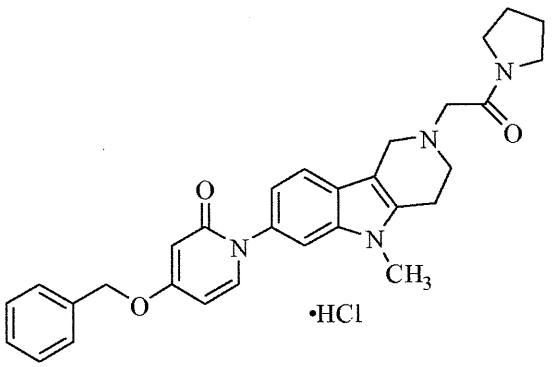
Chemical Formula: $C_{28}H_{31}ClN_4O_3$
Exact Mass: 506.21
Molecular Weight: 507.02

To a solution of 4-benzyloxy-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (100 mg, 0.26 mmol) in CH_2Cl_2 (2 mL) was added 2-chloroacetyl chloride (29 μL, 0.36 mmol) and Et_3N (0.1 mL, 0.7 mmol). The reaction mixture was stirred at room temperature until the reaction was complete. After the solvent was removed, the residue was dissolved in DMF. To the DMF solution was added

$(CH_3)_2NH$ (64 μL, 1.2 mmol) and K_2CO_3 (166 mg, 1.2 mmol). The reaction mixture was heated to 70 °C and stirred at 70 °C until the reaction was complete. After it was cooled, 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. Purification by flash column chromatography (silica gel, 10% CH_3OH in CH_2Cl_2) gave 4-(benzyloxy)-1-(2-(2-(dimethylamino)acetyl)-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (58 mg, 51%) as a yellow foam. The free base was converted to the HCl salt to give the title compound (31 mg, 50%) as a yellow solid and as a mixture of rotamers: mp 135–140 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.75–7.71 (m, 1H), 7.59–7.55 (m, 1H), 7.49–7.37 (m, 6H), 7.05–7.01 (m, 1H), 6.49–6.45 (m, 1H), 6.28–6.26 (m, 1H), 5.24 (s, 2H), 4.87 (br s, 1H), 4.69 (br s, 1H), 4.44–4.41 (m, 2H), 4.11–4.07 (m, 1H), 3.85–3.82 (m, 1H), 3.70 (2 × s, 3H), 3.06–2.92 (m, 2H), 2.97–2.94 (2 × s, 6H); ESI MS *m/z* 471 $[M + H]^+$; HPLC (Method B) 97.0 % (AUC), t_R = 13.2 min.

Example 17

Preparation of 4-(Benzyloxy)-1-(5-methyl-2-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridine-2(1*H*)-one hydrochloride



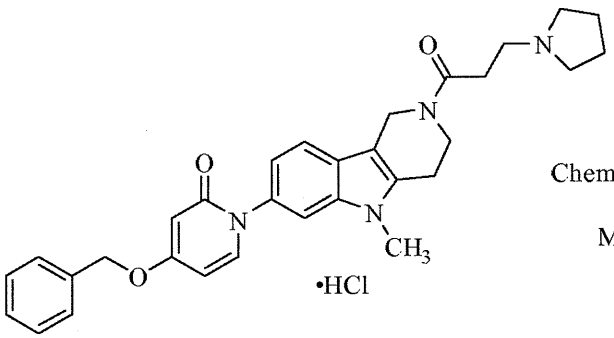
Chemical Formula: $C_{30}H_{33}ClN_4O_3$
Exact Mass: 532.22
Molecular Weight: 533.06

To a solution of 4-benzyloxy-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (100 mg, 0.26 mmol) in DMF (3 mL) was added 2-chloro-1-(pyrrolidin-1-yl)ethanone (77 mg, 0.52 mmol) and K_2CO_3 (72 mg, 0.52 mmol). The reaction mixture was heated to 70 °C and stirred at 70 °C until the reaction was complete. After it was cooled, 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. Purification by flash column chromatography (silica gel, 5% CH_3OH in CH_2Cl_2) gave 4-(benzyloxy)-1-(5-methyl-2-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridine-2(1*H*)-one (35 mg, 27%) as a yellow foam. The free base was converted to the HCl salt to the give title compound (30 mg, 80%) as a yellow solid: mp 162–166 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.60 (d, J = 7.5 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.49–7.35 (m, 6H), 7.06 (dd, J = 8.5, 1.5 Hz, 1H), 6.33 (dd, J = 7.5, 3.0 Hz, 1H), 6.16 (d, J = 3.0 Hz, 1H), 5.20 (s, 2H), 4.80 (d, J = 14.5 Hz, 1H), 4.54 (d, J = 14.5 Hz, 1H), 4.36 (s, 2H), 4.00–3.98 (m, 1H), 3.75 (s, 3H), 3.68–3.65 (m, 1H), 3.54 (t, J = 7.0 Hz, 2H), 3.49–3.45 (m, 2H), 3.35–3.33 (m, 2H), 2.05–1.92 (m, 4H); ESI MS *m/z* 497 $[M + H]^+$; HPLC (Method B) 97.9 % (AUC), t_R = 13.4 min.

Example 18

Preparation of 4-(Benzyloxy)-1-(5-methyl-2-(3-(pyrrolidin-1-yl)propanoyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridine-2(1*H*)-one hydrochloride



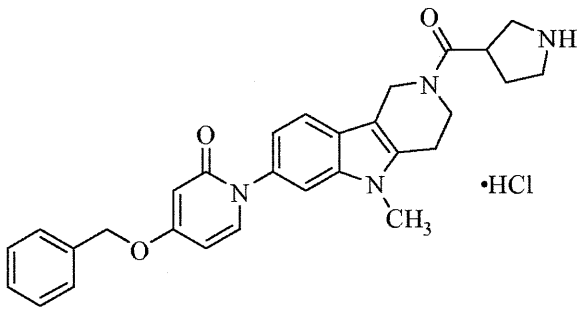
Chemical Formula: $C_{31}H_{35}ClN_4O_3$
Exact Mass: 546.24
Molecular Weight: 547.09

To a solution of 4-benzyloxy-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (100 mg, 0.26 mmol) in DMF (3 mL) was added *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*'*N*'-tetramethyluronium hexafluorophosphate (HATU) (148 mg, 0.389 mmol), 3-(pyrrolidin-1-yl)propanoic acid hydrochloride (56 mg, 0.31 mmol), and Et_3N (73 μL, 0.52 mmol). The reaction mixture was stirred at room temperature under Ar until the reaction was complete. 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. Purification by flash column chromatography (silica gel, 5% CH_3OH in CH_2Cl_2) gave 4-(benzyloxy)-1-(5-methyl-2-(3-(pyrrolidin-1-yl)propanoyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridine-2(1*H*)-one as a yellow foam. The

free base was converted to the HCl salt to give the title compound (75 mg, 86%) as a yellow solid: mp 110–115 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.79–7.76 (m, 1H), 7.61–7.55 (m, 1H), 7.49–7.36 (m, 6H), 7.05–7.02 (m, 1H), 6.55–6.52 (m, 1H), 6.33–6.32 (m, 1H), 5.26 (s, 2H), 4.06 (t, J = 5.5 Hz, 1H), 3.94 (t, J = 5.5 Hz, 1H), 3.70–3.69 (m, 5H), 3.54–3.50 (m, 2H), 3.18–2.89 (m, 8H), 2.18–2.04 (m, 4H); ESI MS *m/z* 511 $[M + H]^+$; HPLC (Method B) 97.7 % (AUC), t_R = 13.6 min.

Example 19

Preparation of 4-(Benzyloxy)-1-(5-methyl-2-(pyrrolidine-3-carbonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

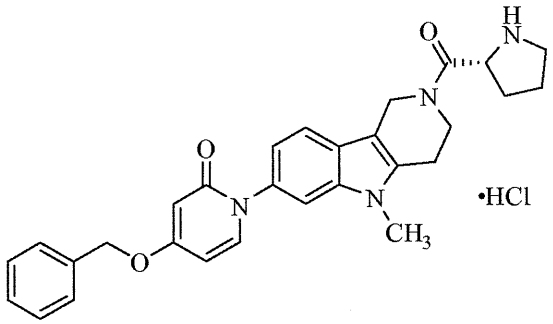


Chemical Formula: $C_{29}H_{31}ClN_4O_3$
Exact Mass: 518.21
Molecular Weight: 519.03

Following the procedure of Example 18, but substituting 1-(*tert*-butoxycarbonyl)pyrrolidine-3-carboxylic acid for 3-(pyrrolidin-1-yl)propanoic acid hydrochloride, a yellow solid was obtained in 78% yield (118 mg). The yellow solid was dissolved in CH_3OH (3 mL) and was treated with 1 N HCl in Et_2O (2 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (90 mg, 90%) as a green-yellow powder: ^{1}H NMR (500 MHz, CD_3OD) δ 7.75–7.72 (m, 1H), 7.63–7.55 (m, 1H), 7.49–7.36 (m, 6H), 7.05–7.02 (m, 1H), 6.51–6.46 (m, 1H), 6.29–6.27 (m, 1H), 5.25 (s, 2H), 4.79–4.76 (m, 2H), 4.14–3.97 (m, 2H), 3.87–3.82 (m, 1H), 3.71–3.69 (m, 4H), 3.60–3.50 (m, 1H), 3.45–3.36 (m, 3H), 3.04–3.03 (m, 1H), 2.94–2.92 (m, 1H), 2.52–2.36 (m, 1H), 2.18–2.00 (m, 1H); ESI MS *m/z* 483 $[M + H]^+$; HPLC (Method B) 98.1 % (AUC), t_R = 13.2 min.

Example 20

Preparation of (*R*)-4-(Benzyloxy)-1-(5-methyl-2-(pyrrolidine-2-carbonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

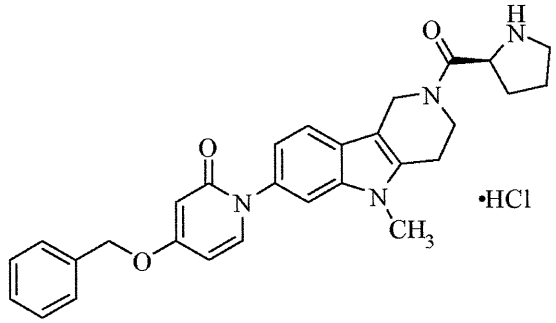


Chemical Formula: $C_{29}H_{31}ClN_4O_3$
Exact Mass: 518.21
Molecular Weight: 519.03

Following the procedure of Example 19, but substituting (*R*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid for 1-(*tert*-butoxycarbonyl)pyrrolidine-3-carboxylic acid, the title compound (67 mg, 50%) was obtained as a yellow solid and as a mixture of rotamers: ^{1}H NMR (500 MHz, CD_3OD) δ 7.82–7.79 (m, 1H), 7.66–7.56 (m, 1H), 7.49–7.36 (m, 6H), 7.07–7.03 (m, 1H), 6.59–6.56 (m, 1H), 6.36 (dd, J = 5.0, 2.5 Hz, 1H), 5.28 (s, 2H), 4.82–4.81 (m, 2H), 4.14–4.05 (m, 1H), 3.97–3.95 (m, 1H), 3.71–3.69 (2 × s, 3H), 3.58–3.34 (m, 3H), 3.07–2.94 (m, 2H), 2.70–2.57 (m, 1H), 2.17–1.85 (m, 3H); ESI MS *m/z* 483 $[M + H]^+$; HPLC (Method B) >99 % (AUC), t_R = 13.3 min.

Example 21

Preparation of (*S*)-4-(Benzyloxy)-1-(5-methyl-2-(pyrrolidine-2-carbonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



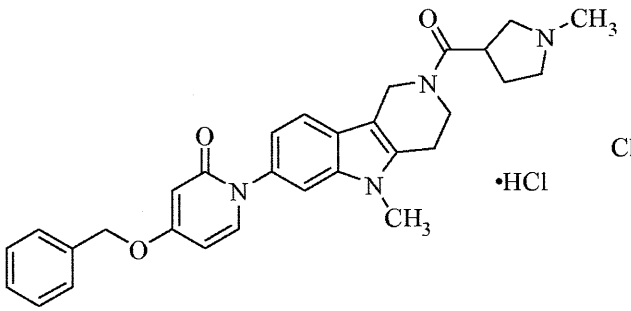
Chemical Formula: $C_{29}H_{31}ClN_4O_3$
Exact Mass: 518.21
Molecular Weight: 519.03

Following the procedure of Example 20, but substituting (*S*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid for (*R*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid, the title compound (47 mg, 72%) was obtained as a yellow solid and as

a mixture of rotamers: ^{1}H NMR (500 MHz, CD_3OD) δ 7.82–7.79 (m, 1H), 7.66–7.56 (m, 1H), 7.49–7.36 (m, 6H), 7.07–7.03 (m, 1H), 6.59–6.56 (m, 1H), 6.36 (dd, J = 5.0, 2.5 Hz, 1H), 5.28 (s, 2H), 4.82–4.81 (m, 2H), 4.14–4.05 (m, 1H), 3.97–3.95 (m, 1H), 3.71–3.69 (2 × s, 3H), 3.58–3.34 (m, 3H), 3.07–2.94 (m, 2H), 2.70–2.57 (m, 1H), 2.17–1.85 (m, 3H); ESI MS *m/z* 483 $[M + H]^+$; HPLC (Method B) >99 % (AUC), t_R = 13.3 min.

Example 22

Preparation of 4-(Benzyloxy)-1-(5-methyl-2-(1-methylpyrrolidine-3-carbonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



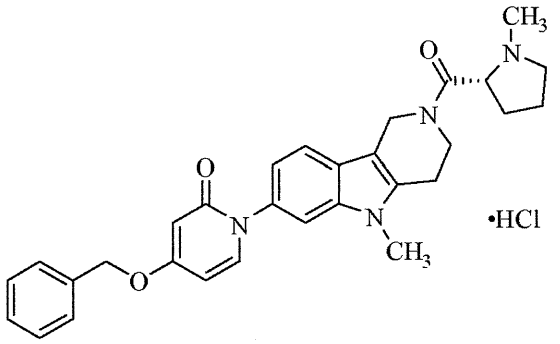
Chemical Formula: $C_{30}H_{33}ClN_4O_3$
Exact Mass: 532.22
Molecular Weight: 533.06

To a solution of 4-(benzyloxy)-1-(5-methyl-2-(pyrrolidine-3-carbonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride (105 mg, 0.197 mmol) in CH_3OH (3 mL) was added Et_3N (40 μL, 0.29 mmol), formaldehyde (23 μL, 0.29 mmol), and $NaBH(OAc)_3$ (86 mg, 0.41 mmol). The reaction mixture was stirred at room temperature until the reaction was complete. Then the mixture was concentrated and the residue was dissolved in CH_2Cl_2. The organic layer was washed with H_2O and 5% LiCl, dried with Na_2SO_4, filtered and concentrated. Purification by flash column chromatography (silica gel, 10% CH_3OH in CH_2Cl_2) gave 4-(benzyloxy)-1-(5-methyl-2-(1-methylpyrrolidine-3-carbonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (60 mg, 60%) as a yellow solid. The free base was converted to the HCl salt to give the title compound (43 mg, 80%) as a yellow solid and as a mixture of rotamers: mp 132–136 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.61–7.33 (m, 8H), 7.02–6.98 (m, 1H), 6.29–6.27 (m, 1H), 6.12–6.11 (m, 1H), 5.17 (s, 2H), 4.79–4.76 (m, 2H), 4.09–3.97 (m, 2H), 3.81–3.79 (m, 1H), 3.69–3.67 (m, 4H), 3.49–3.42 (m, 1H), 3.22–3.16 (m, 2H), 3.00 (m,

1H), 2.92–2.91 (m, 1H), 2.81–2.78 (2 × s, 3H), 2.52–2.36 (m, 1H), 2.18–2.00 (m, 1H); ESI MS *m/z* 497 $[M + H]^+$; HPLC (Method B) 98.7 % (AUC), t_R = 13.6 min.

Example 23

Preparation of (*R*)-4-(Benzyloxy)-1-(5-methyl-2-(1-methylpyrrolidine-2-carbonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

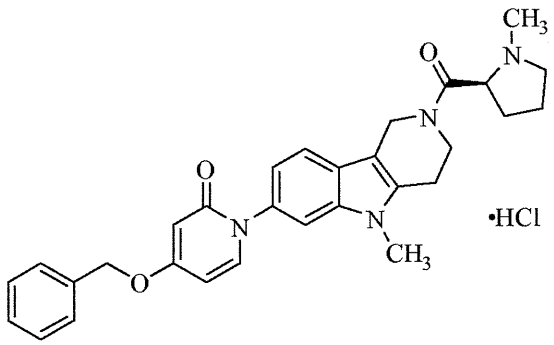


Chemical Formula: $C_{30}H_{33}ClN_4O_3$
Exact Mass: 532.22
Molecular Weight: 533.06

Following the procedure of Example 22, but substituting (*R*)-4-(benzyloxy)-1-(5-methyl-2-(pyrrolidine-2-carbonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride for 4-(benzyloxy)-1-(5-methyl-2-(pyrrolidine-3-carbonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride, the title compound (80 mg, 67%) was obtained as a yellow solid and as a mixture of rotamers: mp 158–162 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.61–7.33 (m, 8H), 7.03–6.99 (m, 1H), 6.30 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.13 (d, *J* = 2.5 Hz, 1H), 5.18 (s, 2H), 4.80–4.70 (m, 2H), 4.12–4.09 (m, 1H), 3.92–3.90 (m, 1H), 3.78–3.72 (m, 1H), 3.69–3.68 (2s, 3H), 3.49–3.42 (m, 1H), 3.28–3.20 (m, 1H), 3.07–3.00 (m, 2H), 2.96–2.94 (2s, 3H), 2.79–2.65 (m, 1H), 2.21–2.09 (m, 1H), 2.09–1.86 (m, 2H); ESI MS *m/z* 497 $[M + H]^+$; HPLC (Method B) > 99 % (AUC), t_R = 13.4 min.

Example 24

Preparation of (*S*)-4-(Benzyloxy)-1-(5-methyl-2-(1-methylpyrrolidine-2-carbonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



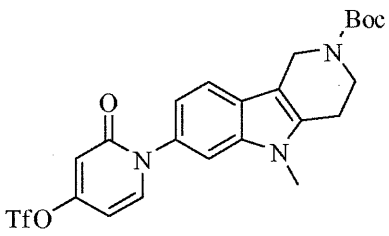
Chemical Formula: $C_{30}H_{33}ClN_4O_3$
Exact Mass: 532.22
Molecular Weight: 533.06

Following the procedure of Example 22, but substituting (*S*)-4-(benzyloxy)-1-(5-methyl-2-(pyrrolidine-2-carbonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride for 4-(benzyloxy)-1-(5-methyl-2-(pyrrolidine-3-carbonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride, the title compound (40 mg, 61%) was obtained as a yellow solid and as a mixture of rotamers: mp 154–160 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.61–7.33 (m, 8H), 7.03–6.99 (m, 1H), 6.30 (dd, J = 7.5, 2.5 Hz, 1H), 6.13 (d, J = 2.5 Hz, 1H), 5.18 (s, 2H), 4.80–4.70 (m, 2H), 4.12–4.09 (m, 1H), 3.92–3.90 (m, 1H), 3.78–3.72 (m, 1H), 3.69–3.68 (2s, 3H), 3.49–3.42 (m, 1H), 3.28–3.20 (m, 1H), 3.07–3.00 (m, 2H), 2.96–2.94 (2 × s, 3H), 2.79–2.65 (m, 1H), 2.21–2.09 (m, 1H), 2.09–1.86 (m, 2H); ESI MS *m/z* 497 $[M + H]^+$; HPLC (Method B) 98.9 % (AUC), t_R = 13.3 min.

Example 25

Preparation of 1-(2,5-Dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(4-fluorophenyl)pyridine-2(1*H*)-one hydrochloride

a) *tert*-Butyl 5-methyl-7-(2-oxo-4-(trifluoromethylsulfonyloxy)pyridine-1(2*H*)-yl)3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate

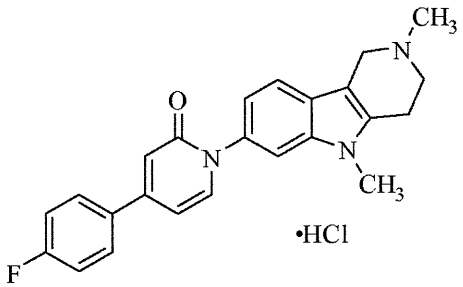


Chemical Formula: $C_{23}H_{24}F_3N_3O_6S$
Exact Mass: 527.13
Molecular Weight: 527.51

To a solution of *tert*-butyl 7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (0.98g, 2.0 mmol) in CH_3OH (30 mL) was added 5% Pd/C (0.3g) and ammonium formate (0.32g, 5 mmol) under Ar atmosphere. The reaction mixture was heated to 90°C and stirred at 90°C until the reaction was complete. After it was cooled, the reaction mixture was filtered through a layer of Celite. The solvent was concentrated to give *tert*-butyl 7-(4-hydroxy-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate, which was used directly without purification.

To a solution of *tert*-butyl 7-(4-hydroxy-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (800 mg, 2.02 mmol) in THF (10 mL) was added $LiN(SiMe_3)_2$ (2.6 mL, 2.6 mmol) followed by $PhN(Tf)_2$ (0.94g, 2.6 mmol) under Ar atmosphere. The reaction mixture was stirred at room temperature until the reaction was complete. Then the mixture was concentrated and the residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 1:1) to give the title compound (0.42 g, 40%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.53 (m, 2H), 7.30 (d, J = 1.5 Hz, 1H), 7.02–6.99 (m, 1H), 6.60 (d, J = 2.7 Hz, 1H), 6.27 (dd, J = 7.8, 2.7 Hz, 1H), 4.65 (s, 2H), 3.85 (m, 2H), 3.65 (s, 3H), 2.84 (m, 2H), 1.51 (s, 9H); ESI MS *m/z* 528 $[M + H]^+$.

b) 1-(2,5-Dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(4-fluorophenyl)pyridine-2(1*H*)-one hydrochloride



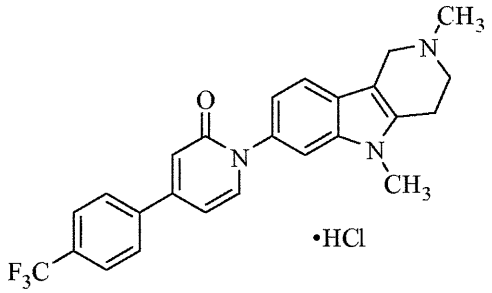
Chemical Formula: $C_{24}H_{23}ClFN_3O$
Exact Mass: 423.15
Molecular Weight: 423.91

To a solution of *tert*-butyl 5-methyl-7-(2-oxo-4-(trifluloromethylsulfonyloxy) pyridine-1-(2*H*)-yl)3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (100 mg, 0.19 mmol) in DMSO (2 mL) was added 4-fluorophenylboronic acid (66 mg, 0.48 mmol), K_2CO_3 (66 mg, 0.48 mmol), and $PdCl_2$(dppf) (14 mg, 0.019 mmol). 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. Purification by flash column chromatography (silica gel, 5% CH_3OH in CH_2Cl_2) gave a yellow solid (120 mg, >100%). The solid was dissolved in CH_3OH (2 mL) and treated with 1 N HCl in Et_2O (1.9 mL). The reaction mixture was stirred at room temperature until the reaction was complete. After the solvent was removed, the resulting solid was dissolved in CH_3OH (3 mL). Et_3N (40 μL), formaldehyde (22 μL, 0.29 mmol), and $NaBH(OAc)_3$ were added sequentially. The reaction mixture was stirred at room temperature until the reaction was was complete. The solvent was removed and the residue was dissolved in CH_2Cl_2. The organic layer was washed with H_2O and 5% LiCl, dried with Na_2SO_4, filtered and concentrated. Purification by flash column chromatography (silica gel, 5% CH_3OH in CH_2Cl_2) gave 1-(2,5-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(4-fluorophenyl)pyridine-2(1*H*)-one (37 mg 50% yield over three steps) as a yellow solid. The free base was converted to the HCl salt to give the title compound (36.5 mg, 91%) as a yellow solid: mp 276–280 °C (decompose); ^{1}H NMR (500 MHz, CD_3OD) δ 7.82–7.79 (m, 2H), 7.75 (d, J = 7.0 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.56 (d, J = 1.5 Hz, 1H), 7.29–7.25 (m, 2H), 7.14 (dd, J = 8.5, 1.5 Hz, 1H), 6.88 (d, J = 2.0 Hz, 1H), 6.82 (dd, J = 7.0, 2.0 Hz, 1H), 4.77 (d, J = 14.0 Hz, 1H), 4.41 (d, J = 14.0 Hz, 1H), 3.93–3.90 (m, 1H), 3.76 (s, 3H), 3.66–3.60 (m, 1H), 3.27 (m, 2H), 3.15 (s, 3H); ESI MS *m/z* 388 $[M + H]^+$; HPLC (Method B) 98.1 % (AUC), t_R = 12.8 min.

Example 26

Preparation of 1-(2,5-Dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(4-(trifluoromethylphenyl)pyridin-2(1*H*)-one hydrochloride

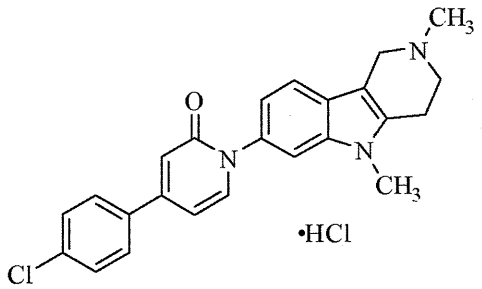


Chemical Formula: $C_{25}H_{23}ClF_3N_3O$
Exact Mass: 473.15
Molecular Weight: 473.92

Following the procedure of Example 25 (step b), but substituting 4-trifluoromethylphenylboronic acid for 4-fluorophenylboronic acid, the title compound (47 mg, 53%) was obtained as a yellow solid: mp 270–274 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.95 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 1.5 Hz, 1H), 7.15 (dd, J = 8.5, 2.0 Hz, 1H), 6.96 (d, J = 1.5 Hz, 1H), 6.87 (dd, J = 7.5, 2.0 Hz, 1H), 4.78 (d, J = 14.0 Hz, 1H), 4.41 (d, J = 14.0 Hz, 1H), 3.93–3.90 (m, 1H), 3.77 (s, 3H), 3.66–3.60 (m, 1H), 3.27 (m, 2H), 3.15 (s, 3H); ESI MS m/z 438 $[M + H]^+$; HPLC (Method B) >99 % (AUC), t_R = 13.8 min.

Example 27

Preparation of 4-(4-Chlorophenyl)-1-(2,5-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)- pyridin-2(1*H*)-one hydrochloride



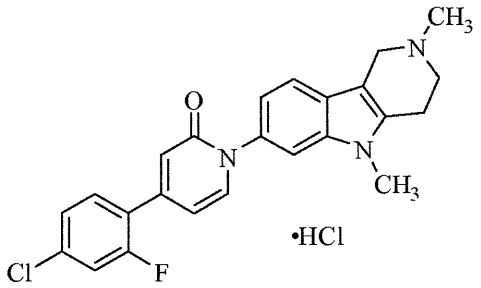
Chemical Formula: $C_{24}H_{23}Cl_2N_3O$
Exact Mass: 439.12
Molecular Weight: 440.36

Following the procedure of Example 25 (step b), but substituting 4-chlorophenylboronic acid for 4-fluorophenylboronic acid, the title compound (55 mg, 65%) was obtained as a yellow solid: mp 276-280 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.77–7.75 (m, 3H), 7.62 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.56–7.54 (m, 2H), 7.15 (dd, J = 8.5, 2.0 Hz, 1H), 6.91 (d, J = 2.0 Hz, 1H), 6.84 (dd, J = 7.0, 2.0 Hz, 1H), 4.78 (d, J = 14.0 Hz, 1H), 4.41 (d, J = 14.0 Hz, 1H), 3.93–3.90 (m, 1H), 3.77 (s, 3H), 3.66–3.60

(m, 1H), 3.27 (m, 2H), 3.15 (s, 3H); ESI MS *m/z* 404 $[M + H]^+$; HPLC (Method B) 98 % (AUC), t_R = 13.4 min.

Example 28

Preparation of 4-(4-Chloro-2-fluorophenyl)-1-(2,5-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)- pyridin-2(1*H*)-one hydrochloride

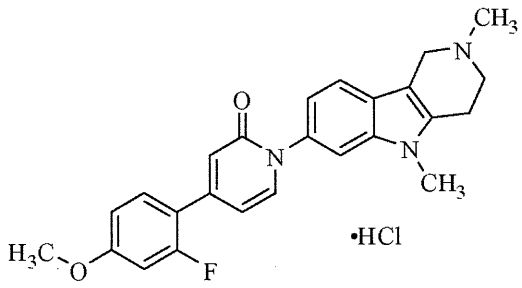


Chemical Formula: $C_{24}H_{22}Cl_2FN_3O$
Exact Mass: 457.11
Molecular Weight: 458.36

Following the procedure of Example 25 (step b), but substituting 4-chloro-2-fluorophenylboronic acid for 4-fluorophenylboronic acid, the title compound (20 mg, 32%) was obtained as a yellow solid: mp 270–274 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.76 (d, *J* = 7.0 Hz, 1H), 7.66–7.57 (m, 2H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.42–7.39 (m, 2H), 7.15 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.84 (s, 1H), 6.73–6.71 (m, 1H), 4.77 (d, *J* = 14.0 Hz, 1H), 4.41 (d, *J* = 14.0 Hz, 1H), 3.93–3.90 (m, 1H), 3.76(s, 3H), 3.64–3.61 (m, 1H), 3.27 (m, 2H), 3.15 (s, 3H); ESI MS *m/z* 422 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 12.9 min.

Example 29

Preparation of 1-(2,5-Dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(2-fluoro-4-methoxyphenyl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{25}H_{25}ClFN_3O_2$
Exact Mass: 453.16
Molecular Weight: 453.94

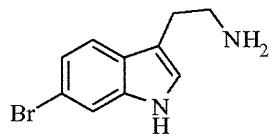
Following the procedure of Example 25 (step b), but substituting 2-fluoro-4-methoxyphenylboronic acid for 4-fluorophenylboronic acid, the title compound (46 mg, 53%) was obtained as a yellow solid: mp 280–282 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.72 (d, J = 7.0 Hz, 1H), 7.63–7.56 (m, 3H), 7.15 (dd, J = 8.5, 1.5 Hz, 1H), 6.92 (dd, J = 8.5, 2.5 Hz, 1H), 6.87 (dd, J = 13.0, 2.0 Hz, 1H), 6.83 (s, 1H), 6.76 (d, J = 7.0 Hz, 1H), 4.77 (d, J = 14.0 Hz, 1H), 4.41 (d, J = 14.0 Hz, 1H), 3.94–3.90 (m, 1H), 3.88 (s, 3H), 3.76 (s, 3H), 3.66–3.60 (m, 1H), 3.27 (m, 2H), 3.15 (s, 3H); ESI MS *m/z* 418 $[M + H]^+$; HPLC (Method B) >99 % (AUC), t_R = 12.9 min.

Example 30

Preparation of 4-(Benzyloxy)-1-(2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

a) 2-(6-Bromo-1*H*-indol-3-yl)ethanamine

Beilstein Registry Number 6056308

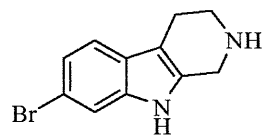


Chemical Formula: $C_{10}H_{11}BrN_2$
Exact Mass: 238.01
Molecular Weight: 239.11

3-Bromophenylhydrazine hydrochloride (20.0 g, 85.8 mmol) was reacted according to the procedure of Mascal et al. (Rinehart, Kenneth L.; Kobayashi, Jun'ichi; Harbour, Gary C.; Gilmore, Jeremy; Mascal, Mark; et al. *J. Am. Chem. Soc.* **1987**, *109*, 3378–3387) to provide the title compound as a 1:1 mixture of the 6-bromo and 7-bromo-regioisomers (13.2 g, 65%), obtained as an orange solid: ESI MS *m/z* 239 $[M + H]^+$.

b) 7-Bromo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole

Beilstein Registry Number 5935540

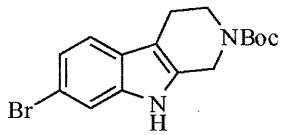


Chemical Formula: $C_{11}H_{11}BrN_2$
Exact Mass: 250.01
Molecular Weight: 251.12

2-(6-Bromo-1*H*-indol-3-yl)ethanamine (13.2 g, 55.2 mmol) was reacted according to the procedure of Mascal et al. (Rinehart, Kenneth L.; Kobayashi, Jun'ichi; Harbour,

Gary C.; Gilmore, Jeremy; Mascal, Mark; et al. *J. Am. Chem. Soc.* **1987**, *109*, 3378–3387) to provide the title compound as a 1:1 mixture of the 7-bromo and 8-bromo-regioisomers (8.8 g, 63%), obtained as an orange solid: ESI MS *m/z* 251 $[M + H]^+$.

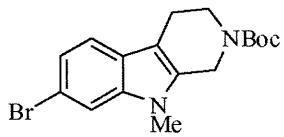
c) *tert*-Butyl 7-bromo-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{16}H_{19}BrN_2O_2$
Exact Mass: 350.06
Molecular Weight: 351.24

7-Bromo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (8.81 g, 35.1 mmol, present as a mixture with the 8-bromo regioisomer) was suspended in CH_2Cl_2 (100 mL) and THF (10 mL). Boc anhydride (7.83 g, 38.6 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) were added. After 24 h, the mixture was concentrated. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, 97:3 to 70:30) separated the 7- and 8-regioisomers and gave the title compound (3.37 g, 27%) as a white powder: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.45 (d, J = 1.6 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.19 (dd, J = 8.3, 1.3 Hz, 1H), 4.61 (br s, 2H), 3.75 (br s, 2H), 2.76 (br s, 2H), 1.50 (s, 9H).

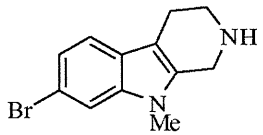
d) *tert*-Butyl 7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{17}H_{21}BrN_2O_2$
Exact Mass: 364.08
Molecular Weight: 365.26

tert-Butyl 7-bromo-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (1.96 g, 5.58 mmol) was dissolved in DMF (20 mL), and sodium hydride (60% weight dispersion in mineral oil, 330 mg, 8.37 mmol) was added. After 30 minutes, methyl iodide (0.52 mL, 8.4 mmol) was added, and the reaction stirred for a further 2 h. The mixture was diluted with methylene chloride and washed with 5% lithium chloride solution (5×), dried and concentrated. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, 97:3 to 75:25) gave the title compound (1.75 g, 86%) as a white powder: ^{1}H NMR (500 MHz, CD_3OD) δ 7.41 (d, J = 1.5 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.18 (dd, J = 8.4, 1.6 Hz, 1H), 4.60 (br s, 2H), 3.73 (br s, 2H), 3.59 (s, 3H), 2.76 (br s, 2H), 1.50 (s, 9H).

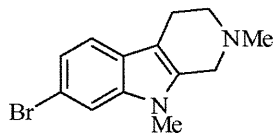
e) 7-Bromo-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole



Chemical Formula: $C_{12}H_{13}BrN_2$
Exact Mass: 264.03
Molecular Weight: 265.15

tert-Butyl-7-bromo-9-methyl-3,4-dihydro-*1H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (1.75 g, 4.79 mmol) was dissolved in CH_2Cl_2 (10 mL) and trifluoroacetic acid (TFA) (10 mL) was added. After stirring for 1 h, the mixture was diluted with methylene chloride (50 mL), washed with saturated Na_2CO_3 solution, dried over sodium sulfate and concentrated to provide the title compound (1.24 g, 97%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J = 1.4 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.17 (dd, J = 8.3, 1.4 Hz, 1H), 4.01 (s, 2H), 3.55 (s, 3H), 3.15 (t, J = 6.0 Hz, 2H), 2.72 (t, J = 5.7 Hz, 2H).

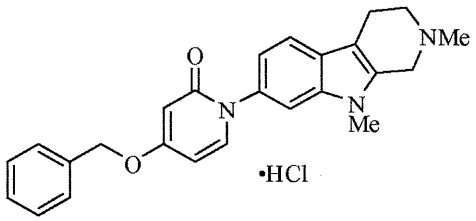
f) 7-Bromo-2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole



Chemical Formula: $C_{13}H_{15}BrN_2$
Exact Mass: 278.04
Molecular Weight: 279.18

7-Bromo-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (1.24 g, 4.68 mmol) was dissolved in a mixture of MeOH (20 mL) and CH_2Cl_2 (5 mL) and formaldehyde (0.56 mL, 37% aqueous solution) was added. After stirring for 1 h, $NaBH(OAc)_3$ (1.98 g, 9.34 mmol) was added and the mixture stirred for a further 10 minutes. The mixture was diluted with methylene chloride (50 mL), washed with saturated Na_2CO_3 solution, concentrated and 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 90% methylene chloride over 30 min at 40 mL/min) to provide the title compound (1.15 g, 88%) as a white powder: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 1.6 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.16 (dd, J = 8.3, 1.7 Hz, 1H), 3.61 (s, 2H), 3.55 (s, 3H), 2.86–2.76 (m, 4H), 2.56 (s, 3H).

g) 4-(Benzyloxy)-1-(2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



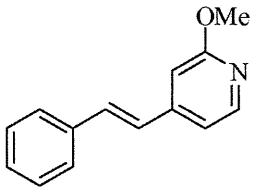
Chemical Formula: $C_{25}H_{26}ClN_3O_2$
Exact Mass: 435.17
Molecular Weight: 435.95

A stirred solution of 7-bromo-2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (250 mg, 0.895 mmol) in DMSO (4 mL) under nitrogen was treated sequentially with 4-(benzyloxy)pyridin-2(1*H*)-one (180 mg, 0.895 mmol), 8-hydroxyquinoline (20 mg, 0.14 mmol), CuI (196 mg, 1.04 mmol) and K_2CO_3 (142 mg, 1.04 mmol). The mixture was placed under vacuum for 30 minutes and then flushed with nitrogen. After stirring overnight at 130 °C, the mixture was allowed to cool to room temperature, diluted with CH_2Cl_2, washed with brine, dried over Na_2SO_4 and concentrated. Purification by flash column chromatography (12 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 25 mL/min) provided the free-base. This was dissolved in methylene chloride (2 mL) and treated with 2 N HCl in Et_2O (1 equivalent) and the mixture was concentrated to provide the title compound (131 mg, 33%) as a yellow solid: mp 270–274 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.67–7.63 (m, 2H), 7.50–7.40 (m, 3H), 7.43–7.35 (m, 3H), 7.08 (dd, J = 8.3, 1.6 Hz, 1H), 6.40 (dd, J = 7.5, 2.6 Hz, 1H), 6.21 (d, J = 2.6 Hz, 1H), 5.22 (s, 2H), 4.81–4.80 (m, 1H), 4.58 (d, J = 15.3 Hz, 1H), 3.88–3.84 (m, 1H), 3.72 (s, 3H), 3.55–3.49 (m, 1H), 3.21–3.16 (m, 5H); ESI MS *m/z* 400 $[M + H]^+$; HPLC (Method B) >98.9% (AUC), t_R = 13.0 min.

Example 31

Preparation of 1-(2,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-phenethylpyridin-2(1*H*)-one hydrochloride

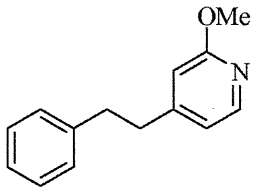
a) (*E*)-2-Methoxy-4-styrylpyridine



Chemical Formula: $C_{14}H_{13}NO$
Exact Mass: 211.10
Molecular Weight: 211.26

4-Bromo-2-methoxypyridine (1.85 g, 9.84 mmol), (*E*)-phenylvinylboronic acid (4.3 g, 30 mmol), K_2CO_3 (4.0 g, 30 mmol) and $PdCl_2$(dppf) (400 mg, 0.5 mmol) were stirred in DMSO (15 mL) under vacuum for 30 min. The flask was flushed with nitrogen and the mixture was heated to 90 °C for 30 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 (silica gel, hexanes/ethyl acetate, 97:3 to 75:25) to provide the title compound (1.93 g, 93%) as an orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 5.2 Hz, 1H), 7.51 (m, 2H), 7.40–7.22 (m, 4H), 7.02–6.94 (m, 2H), 6.78 (s, 1H), 3.95 (s, 3H).

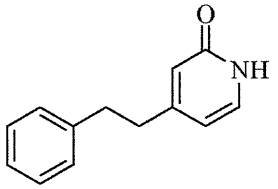
b) 2-Methoxy-4-phenethylpyridine



Chemical Formula: $C_{14}H_{15}NO$
Exact Mass: 213.12
Molecular Weight: 213.28

(*E*)-2-Methoxy-4-styrylpyridine (22.15 g, 104.8 mmol) was dissolved in MeOH (400 mL) and degassed with a nitrogen stream for 10 minutes. Palladium on charcoal (10%, wet, 5 g) was added and the reaction mixture was stirred under an atmosphere of hydrogen for 24 h. The reaction mixture was degassed again, and the catalyst was removed by filtration. Concentration of the filtrate provided the title compound (22 g, 98%) as a green oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 5.3 Hz, 1H), 7.29–7.24 (m, 2H), 7.21–7.15 (m, 3H), 6.69–6.67 (m, 1H), 6.54 (s, 1H), 3.91 (s, 3H), 2.91–2.89 (m, 2H), 2.87–2.84 (m, 2H).

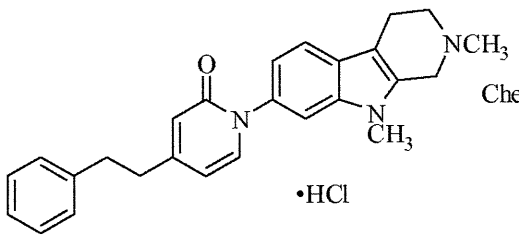
c) 4-Phenethylpyridin-2(1*H*)-one



Chemical Formula: $C_{13}H_{13}NO$
Exact Mass: 199.10
Molecular Weight: 199.25

2-Methoxy-4-phenethylpyridine (22.0 g, 102 mmol) was stirred in concentrated hydrochloric acid (200 mL) at 120 °C for 18 h and then concentrated. The residue was dissolved in MeOH (100 mL) and made basic with aqueous 6 N NaOH and re-concentrated until most of the solvent had been removed. The solids were filtered off, washed with water and dried under vacuum to provide the title compound (21.3 g, 95%) as a beige solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.31 (br s, 1H), 7.28–7.21 (m, 5H), 7.17 (t, J = 7.1 Hz, 1H), 6.10–6.08 (m, 2H), 2.85–2.82 (m, 2H), 2.70–2.67 (m, 2H).

d) 1-(2,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-phenethylpyridin-2(1*H*)-one hydrochloride



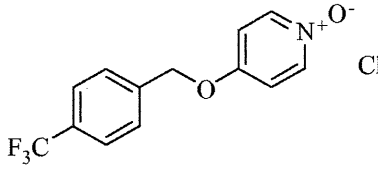
Chemical Formula: $C_{26}H_{28}ClN_3O$
Exact Mass: 433.19
Molecular Weight: 433.97

4-Phenethylpyridin-2(1*H*)-one (82 mg, 0.41 mmol) and 7-bromo-2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (115 mg, 0.412 mmol) were reacted following the procedure for Example 30 (step g) to provide the title compound (54 mg, 30%) as a yellow solid: mp 299–304 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.67–7.64 (m, 2H), 7.51 (d, J = 1.8 Hz, 1H), 7.30–7.24 (m, 4H), 7.20–7.17 (m, 1H), 7.08 (dd, J = 8.4, 1.9 Hz, 1H), 6.56 (dd, J = 6.9, 1.9 Hz, 1H), 6.53 (s, 1H), 4.85 (m, 1H), 4.49 (d, J = 15.3 Hz, 1H), 3.89–3.84 (m, 1H), 3.72 (s, 3H), 3.55–3.50 (m, 1H), 3.21–3.19 (m, 2H), 3.16 (s, 3H), 3.02–2.99 (m, 2H), 2.96–2.93 (m, 2H); ESI MS *m/z* 398 $[M + H]^+$; HPLC (Method B) 98.1% (AUC), t_R = 13.5 min.

Example 32

Preparation of 1-(2,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(4-(trifluoromethyl)benzyloxy)pyridin-2(1*H*)-one hydrochloride

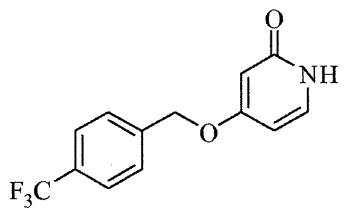
a) 4-(4-(Trifluoromethyl)benzyloxy)pyridine 1-oxide



Chemical Formula: $C_{13}H_{10}F_3NO_2$
Exact Mass: 269.07
Molecular Weight: 269.22

4-Trifluoromethylbenzylalcohol (4.2 g, 23 mmol) was dissolved in DMF (20 mL) and NaH (60% weight dispersion in mineral oil, 0.92 g, 23 mmol) was added. After stirring for 30 minutes, 4-chloropyridine-*N*-oxide (1.5 g, 11.5 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 (0.6 g, 19%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J = 7.8 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 7.52 (d, J = 8.1 Hz, 2H), 6.86 (d, J = 7.8 Hz, 2H), 5.15 (s, 2H).

b) 4-(4-(Trifluoromethyl)benzyloxy)pyridin-2(1*H*)-one

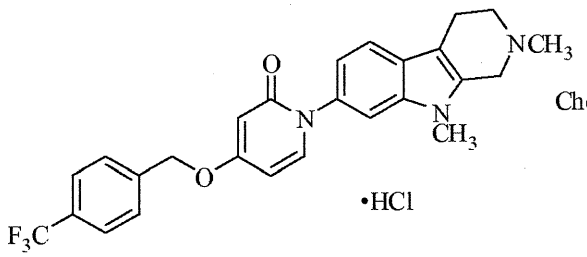


Chemical Formula: $C_{13}H_{10}F_3NO_2$
Exact Mass: 269.07
Molecular Weight: 269.22

4-(4-(Trifluoromethyl)benzyloxy)pyridine 1-oxide (600 mg, 2.22 mmol) was heated to 140 °C in acetic anhydride (20 mL) for 2 h. The mixture was concentrated and then heated at 80 °C for 1 h in a mixture of MeOH (10 mL) and aqueous 1 N NaOH (10mL). The resultant black solution was concentrated to a volume of 10 mL and extracted with $CHCl_3$/EtOH (3:1). The organic layer was removed and concentrated to

provide the title compound (550 mg, 91%) as a tan solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.70–7.60 (m, 4H), 7.41 (d, J = 7.0 Hz, 1H), 6.17 (dd, J = 7.0, 2.5 Hz, 1H), 5.96 (d, J = 2.4 Hz, 1H), 5.18 (s, 2H).

c) 1-(2,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(4-(trifluoromethyl)benzyloxy)pyridin-2(1*H*)-one hydrochloride



•HCl

Chemical Formula: $C_{26}H_{25}ClF_3N_3O_2$
Exact Mass: 503.16
Molecular Weight: 503.94

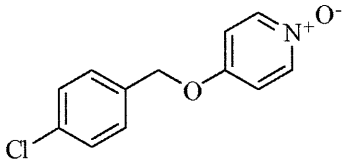
4-(4-(Trifluoromethyl)benzyloxy)pyridin-2(1*H*)-one (100 mg, 0.37 mmol) and 7-bromo-2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (103 mg, 0.47 mmol) were reacted following the procedure for Example 30 (step g) to provide the title compound (67 mg, 36%) as a light-brown solid: mp 280–285 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.78–7.73 (m, 3H), 7.69–7.64 (m, 3H), 7.52 (d, J = 1.8 Hz, 1H), 7.18–7.08 (m, 1H), 6.55–6.52 (m, 1H), 6.28 (d, J = 2.6 Hz, 1H), 5.35 (s, 2H), 4.82–4.80 (m, 1H), 4.50 (d, J = 15.4 Hz, 1H), 3.89–3.85 (m, 1H), 3.73 (s, 3H), 3.55–3.50 (m, 1H), 3.22–3.16 (m, 5H); ESI MS *m/z* 468 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 14.4 min.

Example 33

Preparation of 4-(4-Chlorobenzyloxy)-1-(2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

a) 4-(4-Chlorobenzyloxy)pyridine 1-oxide

Beilstein Registry Number 7707045

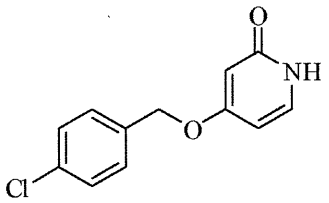


Chemical Formula: $C_{12}H_{10}ClNO_2$
Exact Mass: 235.04
Molecular Weight: 235.67

4-Chlorobenzylalcohol (5.0 g, 35 mmol) was dissolved in DMF (25 mL) and NaH (60% weight dispersion in mineral oil, 0.92 g, 23 mmol) was added. After stirring for 30 minutes, 4-chloropyridine-*N*-oxide (2.27 g, 17.5 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 (12 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 25 mL/min) provided the title compound (1.9 g, 47%) as an orange solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 7.7 Hz, 2H), 7.40 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 7.7 Hz, 2H), 5.06 (s, 2H).

b) 4-(4-Chlorobenzyloxy)pyridin-2(1*H*)-one

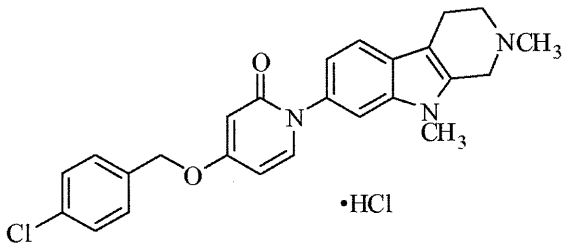
Beilstein Registry Number 7707762



Chemical Formula: $C_{12}H_{10}ClNO_2$
Exact Mass: 235.04
Molecular Weight: 235.67

4-(4-Chlorobenzyloxy)pyridine 1-oxide (1.95 g, 8.24 mmol) was reacted according to the procedure of Example 32 (step b), and the crude product 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 90% methylene chloride over 30 min at 40 mL/min) to provide the title compound (1.0 g, 51%) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.70 (br s, 1H), 7.37 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 7.3 Hz, 1H), 6.02 (dd, J = 7.3, 2.5 Hz, 1H), 5.93 (d, J = 2.5 Hz, 1H), 4.98 (s, 2H).

c) 4-(4-Chlorobenzyloxy)-1-(2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



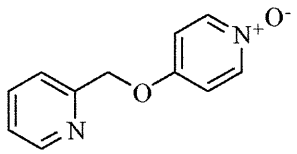
Chemical Formula: $C_{25}H_{25}Cl_2N_3O_2$
Exact Mass: 469.13
Molecular Weight: 470.39

4-(4-Chlorobenzyloxy)pyridin-2(1*H*)-one (82 mg, 0.34 mmol) and 7-bromo-2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (97 mg, 0.34 mmol) were reacted following the procedure for Example 30 (step g) to provide the title compound (28 mg, 17%) as a yellow solid: mp 290–296 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.83 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.50–7.46 (m, 3H), 7.44–7.42 (m, 2H), 7.08 (dd, J = 8.3, 1.8 Hz, 1H), 6.41 (dd, J = 7.6, 2.6 Hz, 1H), 6.21 (d, J = 2.6 Hz, 1H), 5.21 (s, 2H), 4.86–4.84 (m, 1H), 4.49 (d, J = 15.4 Hz, 1H), 3.88–3.84 (m, 1H), 3.72 (s, 3H), 3.55–3.50 (m, 1H), 3.21–3.16 (m, 5H); ESI MS *m/z* 434 $[M + H]^+$; HPLC (Method B) 98.6% (AUC), t_R = 14.0 min.

Example 34

Preparation of 1-(2,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(pyridin-2-ylmethoxy)pyridin-2(1*H*)-one dihydrochloride

a) 4-(Pyridin-2-ylmethoxy)pyridine 1-oxide

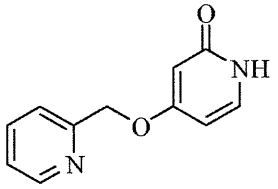


Chemical Formula: $C_{11}H_{10}N_2O_2$
Exact Mass: 202.07
Molecular Weight: 202.21

2-Pyridylbenzylalcohol (1.67 g, 15.3 mmol) was dissolved in 1,4-dioxane (25 mL) and NaH (60% weight dispersion in mineral oil, 0.92 g, 23 mmol) was added. After stirring for 30 minutes, 4-chloropyridine-*N*-oxide (2.27 g, 17.5 mmol) was added and the reaction mixture was heated for 1 h at 120 °C. Upon cooling, the mixture 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 90% methylene chloride over 30 min at 40 mL/min) to provide the title compound (600 mg, 38%) as a brown solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62–8.61 (m, 1H), 8.13–8.10 (m, 2H), 7.74

(overlapping ddd, J = 7.8, 1.4 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 4.8 Hz, 1H), 6.92–6.89 (m, 2H), 5.23 (s, 2H).

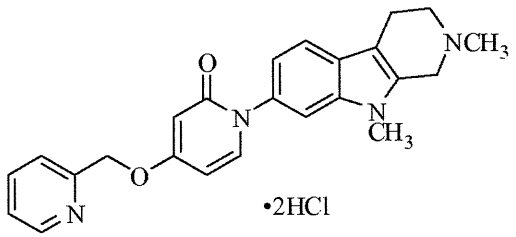
b) 4-(Pyridin-2-ylmethoxy)pyridin-2(1*H*)-one



Chemical Formula: $C_{11}H_{10}N_2O_2$
Exact Mass: 202.07
Molecular Weight: 202.21

4-(Pyridin-2-ylmethoxy)pyridine 1-oxide (9.0 g, 45 mmol) was heated to 140 °C in acetic anhydride (100 mL) for 2 h. The solution was concentrated and then heated at 80 °C for 1 h in a mixture of MeOH (50 mL) and H_2O (50 mL). The resultant black solution was concentrated and the residue was dissolved in hot *i*-PrOH (40 ml). Et_2O (250 mL) was added and the mixture was placed in the freezer for 16 h. The solid was filtered off to provide the title compound (1.9 g, 21%) as a brown solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.13 (br s, 1H), 8.58 (d, J = 4.7 Hz, 1H), 7.85 (overlapping ddd, J = 7.9, 1.6 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.38–7.34 (m, 1H), 7.26 (d, J = 7.3 Hz, 1H), 5.96 (dd, J = 7.3, 2.5 Hz, 1H), 5.76 (d, J = 3.4 Hz, 1H), 5.12 (s, 2H).

c) 1-(2,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(pyridin-2-ylmethoxy)pyridin-2(1*H*)-one dihydrochloride



Chemical Formula: $C_{24}H_{26}Cl_2N_4O_2$
Exact Mass: 472.14
Molecular Weight: 473.39

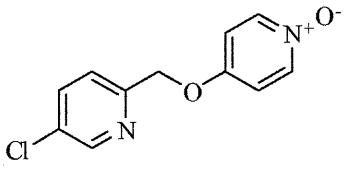
4-(Pyridin-2-ylmethoxy)pyridin-2(1*H*)-one (109 mg, 0.539 mmol) and 7-bromo-2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (97 mg, 0.34 mmol) were reacted following the procedure for Example 30 (step g) to provide the title compound (28 mg, 11%) as a yellow solid: mp 160–175 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.90 (dd, J = 5.8, 1.8 Hz, 1H), 8.65 (overlapping ddd, J = 7.9, 1.6 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.07 (overlapping dd, J = 6.4 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.65 (d, J = 6.4 Hz, 1H), 7.49

(d, J = 1.7 Hz, 1H), 7.07 (dd, J = 6.8, 1.8 Hz, 1H), 6.63 (dd, J = 7.6, 2.7 Hz, 1H), 6.21 (d, J = 2.7 Hz, 1H), 5.59 (s, 2H), 4.80 (m, 1H), 4.50 (d, J = 15.3 Hz, 1H), 3.88–3.85 (m, 1H), 3.73 (s, 3H), 3.55–3.50 (m, 1H), 3.21–3.16 (m, 5H); ESI MS m/z 401 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 9.3 min.

Example 35

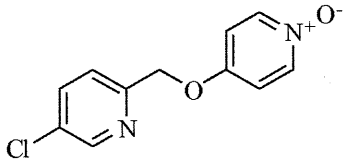
Preparation of 4-((5-Chloropyridin-2-yl)methoxy)-1-(2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

a) 4-((5-Chloropyridin-2-yl)methoxy)pyridine 1-oxide



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

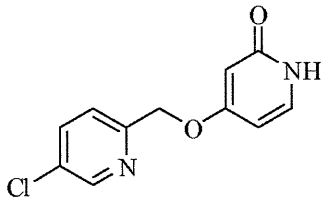
5-Chloro-2-pyridylbenzylalcohol (4.9 g, 34 mmol) and 4-chloropyridine-*N*-oxide (2.94 g, 22.7 mmol) were reacted according to Example 34 (step a) to provide the title compound (2.2 g, 40%) as a tan solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, J = 2.2 Hz, 1H), 8.13 (d, J = 7.7 Hz, 2H), 7.74 (dd, J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



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

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 34 (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), 7.76–7.72 (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).

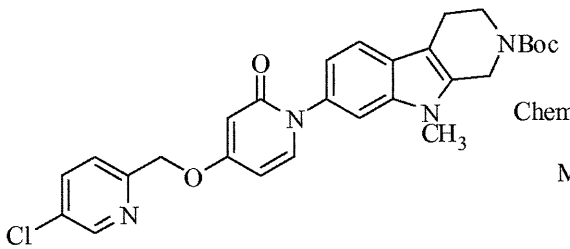
b) 4-((5-Chloropyridin-2-yl)methoxy)pyridin-2(*1H*)-one



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

4-((5-Chloropyridin-2-yl)methoxy)pyridine 1-oxide (2.2 g, 9.2 mmol) was reacted according to Example 34 (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).

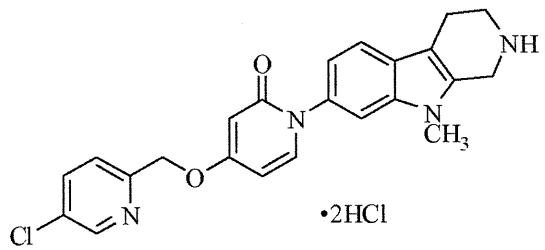
c) *tert*-Butyl 7-(4-((5-chloropyridin-2-yl)methoxy)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{28}H_{29}ClN_4O_4$
Exact Mass: 520.19
Molecular Weight: 521.01

4-((5-Chloropyridin-2-yl)methoxy)pyridin-2(1*H*)-one (259 mg, 1.09 mmol) and *tert*-butyl 7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (400 mg, 1.1 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (145 mg, 25%) as a yellow solid: ESI MS *m/z* 521 $[M + H]^+$.

d) 4-((5-Chloropyridin-2-yl)methoxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride



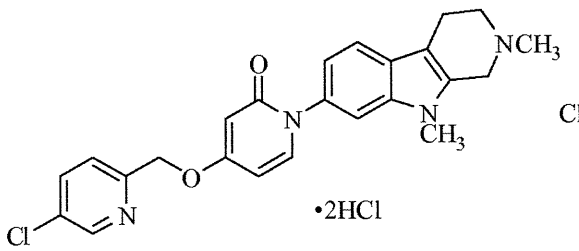
Chemical Formula: $C_{23}H_{23}Cl_3N_4O_2$
Exact Mass: 492.09
Molecular Weight: 493.81

tert-Butyl 7-(4-((5-chloropyridin-2-yl)methoxy)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (145 mg, 0.278 mmol) was

deprotected and converted to the dihydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (114 mg, 94%) as a yellow solid: mp 275–280 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.61 (s, 1H), 7.77 (dd, J = 8.3, 3.8 Hz, 1H), 7.64–7.62 (m, 3H), 7.47 (d, J = 1.6 Hz, 1H), 7.03 (dd, J = 8.4, 1.8 Hz, 1H), 6.37 (dd, J = 7.6, 3.8 Hz, 1H), 6.15 (d, J = 2.7 Hz, 1H), 5.28 (s, 2H), 4.54 (s, 2H), 3.71 (s, 3H), 3.60 (t, J = 6.1 Hz, 2H), 3.12 (t, J = 6.0 Hz, 2H); ESI MS m/z 421 $[M + H]^+$; HPLC (Method B) 98.5% (AUC), t_R = 12.1 min

Example 36

Preparation of 4-((5-Chloropyridin-2-yl)methoxy)-1-(2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

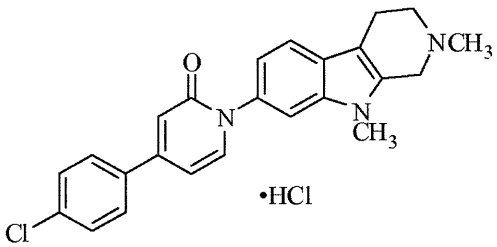


Chemical Formula: $C_{24}H_{25}Cl_3N_4O_2$
Exact Mass: 506.10
Molecular Weight: 507.84

4-((5-Chloropyridin-2-yl)methoxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one (80 mg, 0.19 mmol) was dissolved a mixture of MeOH (3 mL) and CH_2Cl_2 (1 mL) and formaldehyde (9.0 mg, 0.29 mmol, 37% aqueous solution) was added. After stirring for 45 minutes, $NaBH(OAc)_3$ (80 mg, 0.38 mmol) was added and the reaction mixture was stirred for a further 10 minutes. The mixture was diluted with CH_2Cl_2, washed with saturated Na_2CO_3 solution and concentrated to provide the free base. Conversion to the dihydrochloride salt using the procedure of Example 30 (step g) provided the title compound (83 mg, 86%) as an orange solid: mp 202–210 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.68 (br s, 1H), 8.05 (dd, J = 8.0, 2.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 1.6 Hz, 1H), 7.09 (dd, J = 8.3, 1.8 Hz, 1H), 6.53 (dd, J = 7.6, 1.7 Hz, 1H), 6.28 (d, J = 1.6 Hz, 1H), 5.36 (s, 2H), 4.85–4.80 (m, 1H), 4.49 (d, J = 15.3 Hz, 1H), 3.89–3.84 (m, 1H), 3.72 (s, 3H), 3.53–3.47 (m, 1H), 3.22–3.19 (m, 2H), 3.16 (s, 3H); ESI MS m/z 435 $[M + H]^+$; HPLC (Method B) 97.8% (AUC), t_R = 12.2 min.

Example 37

Preparation of 4-(4-Chlorophenyl)-1-(2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



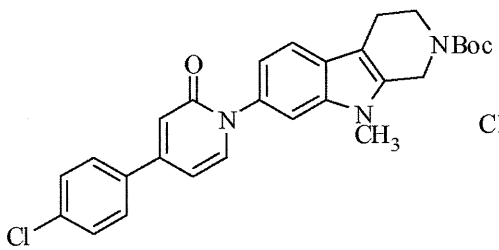
Chemical Formula: $C_{24}H_{23}Cl_2N_3O$
Exact Mass: 439.12
Molecular Weight: 440.36

4-(4-Chlorophenyl)pyridin-2(1*H*)-one (80 mg, 0.33 mmol) and 7-bromo-2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (49 mg, 0.33 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (28 mg, 19%) as a yellow-green solid: mp 316–323 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.0 (br s, 1H), 7.83 (dd, J = 6.8, 1.9 Hz, 2H), 7.76 (d, J = 7.1 Hz, 1H), 7.62–7.57 (m, 4H), 7.07 (dd, J = 8.3, 1.8 Hz, 1H), 6.81 (d, J = 2.0 Hz, 1H), 6.69 (dd, J = 7.2, 2.1 Hz, 1H), 4.79 (d, J = 15.2 Hz, 1H), 4.44 (dd, J = 15.2, 6.0 Hz, 1H), 3.74–3.68 (m, 4H), 3.48–3.38 (m, 1H), 3.10–2.99 (m, 5H); ESI MS *m/z* 404 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 13.5 min.

Example 38

Preparation of 4-(4-Chlorophenyl)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

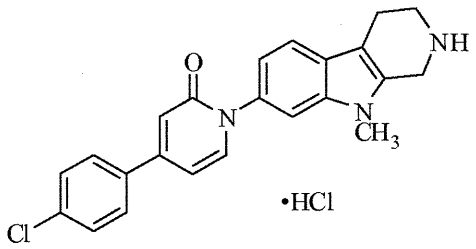
a) *tert*-Butyl 7-(4-(4-chlorophenyl)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{28}H_{28}ClN_3O_3$
Exact Mass: 489.18
Molecular Weight: 489.99

4-(4-Chlorophenyl)pyridin-2(1*H*)-one (74 mg, 0.32 mmol) and *tert*-butyl 7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (74 mg, 0.36 mmol) were coupled following the procedure of Example 30 (step g) to provide the title compound (85 mg, 54%) as a yellow solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.58–7.55 (m, 3H), 7.51–7.44 (m, 3H), 7.35 (s, 1H), 7.07 (dd, J = 8.2, 1.6 Hz, 1H), 6.87 (d, J = 1.8 Hz, 1H), 6.47 (dd, J = 7.1, 1.8 Hz, 1H), 4.65 (br m, 2H), 3.75 (br m, 2H), 3.64 (s, 3H), 2.81 (br m, 2H), 1.52 (s, 9H).

b) 4-(4-Chlorophenyl)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



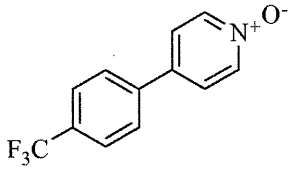
Chemical Formula: $C_{23}H_{21}Cl_2N_3O$
Exact Mass: 425.11
Molecular Weight: 426.34

tert-Butyl 7-(4-(4-chlorophenyl)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (85 mg, 0.17 mmol) was deprotected and converted to the hydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (38 mg, 52%) as a yellow solid: mp 310–315 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.78–7.75 (m, 3H), 7.67 (d, J = 8.3 Hz, 1H), 7.55–7.53 (m, 3H), 7.13 (dd, J = 8.3, 1.8 Hz, 1H), 6.91 (d, J = 1.9 Hz, 1H), 6.84 (dd, J = 7.1, 2.0 Hz, 1H), 4.56 (s, 2H), 3.74 (s, 3H), 3.61 (t, J = 6.0 Hz, 2H), 3.14 (t, J = 6.0 Hz, 2H); ESI MS *m/z* 390 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 13.6 min.

Example 39

Preparation of 1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one hydrochloride hydrochloride

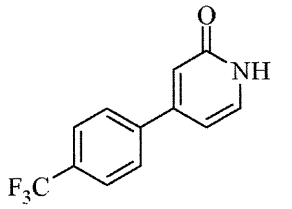
a) 4-(4-(Trifluoromethyl)phenyl)pyridine 1-oxide



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

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 $[M + H]^+$.

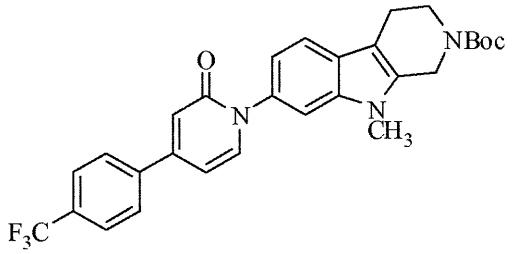
b) 4-(4-(Trifluoromethyl)phenyl)pyridin-2(1*H*)-one



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

4-(4-(Trifluoromethyl)phenyl)pyridine-1-oxide (1.9 g, 7.9 mmol) was reacted according to the procedure of Example 32 (step b) 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).

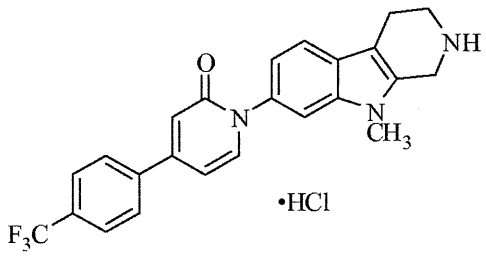
c) *tert*-Butyl 9-methyl-7-(2-oxo-4-(4-(trifluoromethyl)phenyl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{29}H_{28}F_3N_3O_3$
Exact Mass: 523.21
Molecular Weight: 523.55

4-(4-(Trifluoromethyl)phenyl)pyridin-2(1*H*)-one (86 mg, 0.36 mmol) and *tert*-butyl 7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (120 mg, 0.32 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (97 mg, 58%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 4H), 7.58–7.52 (m, 2H), 7.36 (s, 1H), 7.08 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.92 (d, *J* = 1.9 Hz, 1H), 6.50 (dd, *J* = 7.2, 2.0 Hz, 1H), 4.65 (br m, 2H), 3.76 (br m, 2H), 3.65 (s, 3H), 2.81 (br m, 2H), 1.52 (s, 9H).

d) 1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one hydrochloride

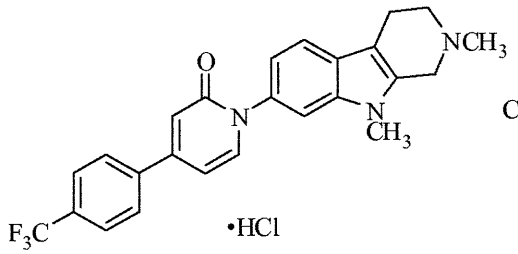


Chemical Formula: $C_{24}H_{21}ClF_3N_3O$
Exact Mass: 459.13
Molecular Weight: 459.89

tert-Butyl 9-methyl-7-(2-oxo-4-(4-(trifluoromethyl)phenyl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (97 mg, 0.19 mmol) was deprotected and converted to the hydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (53 mg, 62%) as a yellow solid: mp 316–321 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.97 (d, *J* = 8.1 Hz, 2H), 7.87–7.80 (m, 3H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 1.5 Hz, 1H), 7.14 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.96 (d, *J* = 1.8 Hz, 1H), 6.87 (dd, *J* = 7.2, 1.8 Hz, 1H), 4.56 (s, 2H), 3.74 (s, 3H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.14 (t, *J* = 6.0 Hz, 2H); ESI MS *m/z* 424 $[M + H]^+$; HPLC (Method B) 96.3% (AUC), t_R = 14.0 min.

Example 40

Preparation of 1-(2,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one hydrochloride



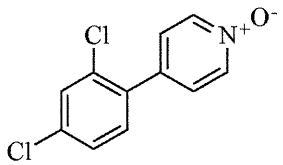
Chemical Formula: $C_{25}H_{23}ClF_3N_3O$
Exact Mass: 473.15
Molecular Weight: 473.92

4-(4-(Trifluoromethyl)phenyl)pyridin-2(1*H*)-one (100 mg, 0.42 mmol) and 7-bromo-2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (117 mg, 0.419 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (70 mg, 35%) as a yellow-brown solid: mp 294–299 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.96 (d, J = 8.2 Hz, 2H), 7.85–7.83 (m, 3H), 7.68 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 1.6 Hz, 1H), 7.16 (dd, J = 8.3, 1.7 Hz, 1H), 6.98 (d, J = 1.8 Hz, 1H), 6.90 (dd, J = 7.1, 1.9 Hz, 1H), 4.87–4.86 (m, 1H), 4.51 (d, J = 15.3 Hz, 1H), 3.90–3.86 (m, 1H), 3.74 (s, 3H), 3.57–3.51 (m, 1H), 3.23–3.20 (m, 2H), 3.17 (s, 3H); ESI MS *m/z* 438 $[M + H]^+$; HPLC (Method B) 95.6% (AUC), t_R = 14.1 min.

Example 41

Preparation of 4-(2,4-Dichlorophenyl)-1-(2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

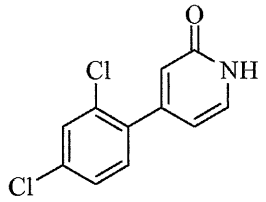
a) 4-(2,4-Dichlorophenyl)pyridine 1-oxide



Chemical Formula: $C_{11}H_7Cl_2NO$
Exact Mass: 238.99
Molecular Weight: 240.09

4-Chloropyridine-*N*-oxide (1.5 g, 12 mmol), 2,4-dichlorophenylboronic acid (5.4 g, 29 mmol) were reacted according to the procedure of Example 39 (step a) to provide the title compound (1.40 g, 50%) as a grey solid: ^{1}H NMR (500 MHz, CD_3OD) δ 8.26 (d, J = 6.9 Hz, 2H), 7.53 (d, J = 2.0 Hz, 1H), 7.37–7.35 (m, 3H), 7.29 (d, J = 8.3 Hz, 1H).

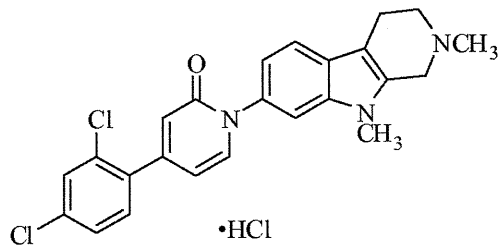
b) 4-(2,4-Dichlorophenyl)pyridin-2(1*H*)-one



Chemical Formula: $C_{11}H_7Cl_2NO$
Exact Mass: 238.99
Molecular Weight: 240.09

4-(2,4-Dichlorophenyl)pyridine 1-oxide (1.4 g, 5.8 mmol) was reacted according to the procedure of Example 32 (step b) to provide the title compound (0.95 g, 67%) as a brown solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.75 (br m, 1H), 7.75 (s, 1H), 7.51–7.46 (m, 3H), 6.31–6.22 (m, 2H).

c) 4-(2,4-Dichlorophenyl)-1-(2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



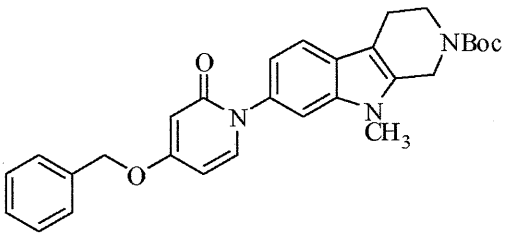
Chemical Formula: $C_{24}H_{22}Cl_3N_3O$
Exact Mass: 473.08
Molecular Weight: 474.81

4-(2,4-Dichlorophenyl)pyridin-2(1*H*)-one (103 mg, 0.429 mmol) and 7-bromo-2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (120 mg, 0.43 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (44 mg, 21%) as a yellow solid: mp 308–313 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.77 (d, J = 7.0 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.65 (overlapping dd, J = 1.1 Hz, 1H), 7.58 (d, J = 1.7 Hz, 1H), 7.49 (s, 2H), 7.16 (dd, J = 8.3, 1.8 Hz, 1H), 6.70 (d, J = 1.5 Hz, 1H), 6.62 (dd, J = 7.0, 1.9 Hz, 1H), 4.86 (m, 1H), 4.50 (d, J = 15.3 Hz, 1H), 3.89–3.85 (m, 1H), 3.74 (s, 3H), 3.56–3.55 (m, 1H), 3.23–3.20 (m, 2H), 3.16 (s, 3H); ESI MS *m/z* 438 $[M + H]^+$; HPLC (Method B) 98.5% (AUC), t_R = 14.3 min.

Example 42

Preparation of 4-(Benzyloxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

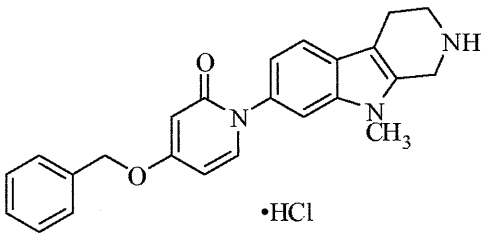
a) tert-Butyl 7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{29}H_{31}N_3O_4$
Exact Mass: 485.23
Molecular Weight: 485.57

4-(Benzyloxy)pyridin-2(1*H*)-one (580 mg, 0.28 mmol) and *tert*-butyl 7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (850 mg, 0.23 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (700 mg, 62%) as a green solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 8.2 Hz, 1H), 7.44–7.39 (m, 4H), 7.38–7.35 (m, 1H), 7.31–7.28 (m, 2H), 7.01 (dd, J = 8.3, 1.8 Hz, 1H), 6.09 (d, J = 2.6 Hz, 1H), 6.04 (dd, J = 7.6, 2.6 Hz, 1H), 5.05 (s, 2H), 4.64 (br m, 2H), 3.74 (br m, 2H), 3.62 (s, 3H), 2.79 (br m, 2H), 1.47 (s, 9H).

b) 4-(Benzyloxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

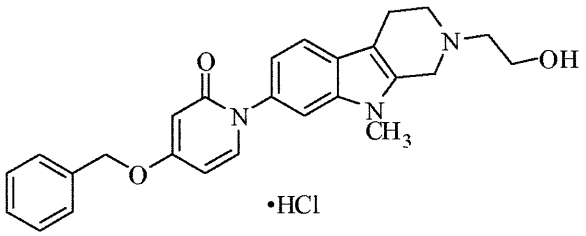


Chemical Formula: $C_{24}H_{24}ClN_3O_2$
Exact Mass: 421.16
Molecular Weight: 421.92

tert-Butyl 7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (700 mg, 1.44 mmol) was deprotected and converted to the hydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (530 mg, 83%) as a yellow solid: mp 251–257 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.71 (br s, 2H), 7.56 (d, J = 7.6 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.50–7.47 (m, 3H), 7.44–7.41 (m, 2H), 7.38–7.37 (m, 1H), 6.99 (dd, J = 8.3, 1.8 Hz, 1H), 6.11 (dd, J = 7.6, 2.8 Hz, 1H), 5.97 (d, J = 2.6 Hz, 1H), 5.15 (s, 2H), 4.45 (s, 2H), 3.81 (s, 3H), 3.42–3.41 (m, 2H), 2.98–2.97 (m, 2H); ESI MS m/z 386 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 12.9 min.

Example 43

Preparation of 4-(Benzyloxy)-1-(2-(2-hydroxyethyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



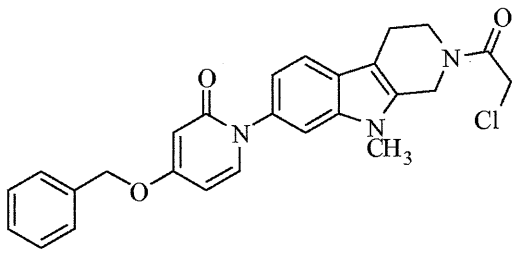
Chemical Formula: $C_{26}H_{28}ClN_3O_3$
Exact Mass: 465.18
Molecular Weight: 465.97

4-(Benzyloxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one (70 mg, 0.18 mmol), 2-iodoethanol (156 mg, 0.907 mmol) and K_2CO_3 (250 mg, 1.8 mmol) were combined in DMF (3 mL) and heated to 80 °C for 1 h. Upon cooling, the product was purified by preparative HPLC and then flash column chromatography (12 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 25 mL/min) to provide the free-base. This was converted to the hydrochloride salt as of Example 30 (step g) to provide the title compound (14.8 mg, 18%) as a yellow solid: ^{1}H NMR (500 MHz, CD_3OD) δ 7.63 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.47–7.46 (m, 3H), 7.42–7.39 (m, 2H), 7.36 (d, J = 7.1 Hz, 1H), 7.06 (dd, J = 8.3, 1.8 Hz, 1H), 6.33 (dd, J = 7.6, 2.6 Hz, 1H), 6.15 (d, J = 2.6 Hz, 1H), 5.19 (s, 2H), 4.81–4.79 (m, 1H), 4.59 (d, J = 15.3 Hz, 1H), 4.01 (t, J = 5.1 Hz, 2H), 3.97–3.94 (m, 1H), 3.73 (s, 3H), 3.58–3.50 (m, 3H), 3.21–3.16 (m, 2H); ESI MS *m/z* 430 $[M + H]^+$; HPLC (Method B) 97.2% (AUC), t_R = 12.8 min.

Example 44

Preparation of 4-(Benzyloxy)-1-(9-methyl-2-(2-(pyrrolidin-1-yl)acetyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

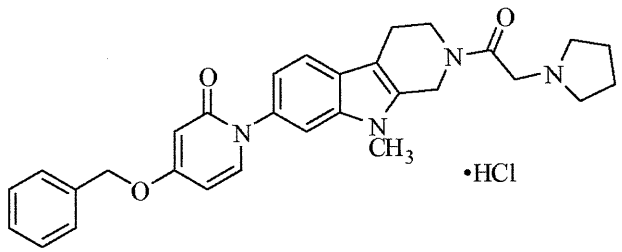
a) 4-(Benzyloxy)-1-(2-(2-chloroacetyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one



Chemical Formula: $C_{26}H_{24}ClN_3O_3$
Exact Mass: 461.15
Molecular Weight: 461.94

4-(Benzyloxy)-1-(2-(2-hydroxyethyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride (100 mg, 0.23 mmol) was stirred in a mixture of CH_2Cl_2 (2 mL) and saturated $NaHCO_3$ solution (2 mL) and chloroacetyl chloride (32 mg, 0.28 mmol) was added. After 1.5 h, the organic layer was removed and concentrated to provide the title compound (120 mg, 100%) as a yellow oil: ESI MS *m/z* 462 $[M + H]^+$.

b) 4-(Benzyloxy)-1-(9-methyl-2-(2-(pyrrolidin-1-yl)acetyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{30}H_{33}ClN_4O_3$
Exact Mass: 532.22
Molecular Weight: 533.06

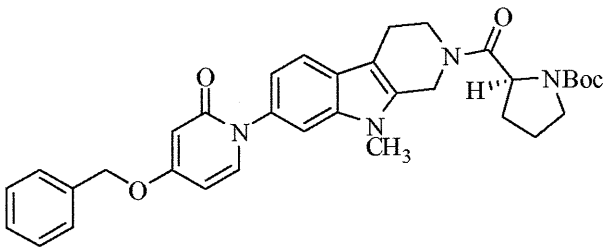
4-(Benzyloxy)-1-(2-(2-chloroacetyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one (120 mg. 0.23 mmol), pyrrolidine (85 mg, 1.2 mmol) and K_2CO_3 (331 mg, 2.39 mmol) were combined in DMF (3 mL) and heated to 80 °C for 1 h. Upon cooling, the mixture was diluted with methylene chloride and washed with 5% lithium chloride solution (5×), dried over Na_2SO_4 and concentrated. The residue was converted to the hydrochloride salt as of Example 30 (step g) to provide the title compound (110 mg, 60%) as a yellow solid: mp 190–200 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.86 (d, *J* = 7.5 Hz, 1H), 7.62 (dd, *J* = 8.2, 2.7 Hz, 1H), 7.51–7.50 (m, 3H), 7.46–7.43 (m, 2H), 7.41–7.40 (m, 1H), 7.08–7.06 (m, 1H), 6.63 (dd, *J* = 7.8, 2.6 Hz, 1H), 6.40 (d, *J* = 1.4 Hz, 1H), 5.31 (s, 2H), 4.93 (s, 1.3H), 4.77 (s, 0.7H), 4.56–4.55 (m, 2H), 4.04–4.02 (m, 0.6H), 3.81–3.78 (m, 3.4H), 3.76 (s, 3H), 3.24–3.19 (m, 2H), 2.79–2.97 (m, 1.3H), 2.92–2.85 (m,

0.7H), 2.22–2.19 (m, 2H), 2.11–2.19 (m, 2H); ESI MS *m/z* 497 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 13.7 min.

Example 45

Preparation of (*S*)-4-(Benzyloxy)-1-(9-methyl-2-(pyrrolidine-2-carbonyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

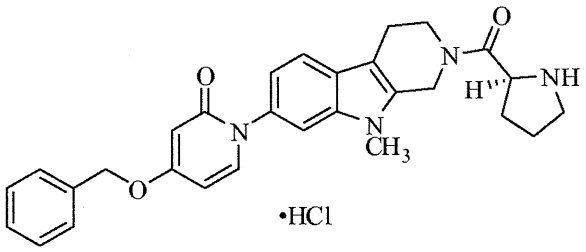
a) (*S*)-*tert*-Butyl 2-(7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-2-carbonyl)pyrrolidine-1-carboxylate



Chemical Formula: $C_{34}H_{38}N_4O_5$
Exact Mass: 582.28
Molecular Weight: 582.69

4-(Benzyloxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride (50 mg, 0.12 mmol) was stirred in DMF (1 mL) and saturated Boc-L-proline (30 mg, 0.14 mmol), HATU (68 mg, 0.18 mmol) and Et_3N (36 mg, 0.36 mmol) were added. After 16 h, the mixture was diluted with methylene chloride and washed with 5% lithium chloride solution (5×), dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (12 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 25 mL/min) to provide the title compound (55 mg, 78%) as a colorless oil: ESI MS *m/z* 583 $[M + H]^+$.

b) (*S*)-4-(Benzyloxy)-1-(9-methyl-2-(pyrrolidine-2-carbonyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{29}H_{31}ClN_4O_3$
Exact Mass: 518.21
Molecular Weight: 519.03

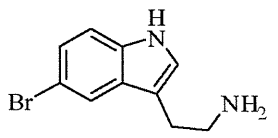
(*S*)-*tert*-Butyl 2-(7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-2-carbonyl)pyrrolidine-1-carboxylate (55 mg, 0.094 mmol) was stirred in a mixture of MeOH (2 mL) and 2 N HCl in Et_2O (8 mL) for 5 h. The reaction mixture was concentrated to provide the title compound (42 mg, 85%) as a yellow-green solid: mp 220–226 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.79 (dd, J = 7.5, 1.4 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.49–7.46 (m, 3H), 7.44–7.46 (m, 2H), 7.39–7.36 (m, 1H), 7.04 (dd, J = 8.3, 1.6 Hz, 1H), 6.57–6.55 (m, 1H), 6.34 (d, J = 2.5 Hz, 1H), 5.27 (s, 2H), 4.96–4.87 (m, 2H), 3.90–8.86 (m, 2H), 3.77 (s, 3H), 3.48–3.34 (m, 3H), 3.00–2.86 (m, 2H), 2.67–2.61 (m, 1H), 2.17–2.02 (m, 3H); ESI MS *m/z* 483 $[M + H]^+$; HPLC (Method B) 95.5% (AUC), t_R = 13.5 min.

Example 46

Preparation of 4-(Benzyloxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-6-yl)pyridin-2(1*H*)-one hydrochloride

a) 2-(5-Bromo-1*H*-indol-3-yl)ethanamine

Beilstein Registry Number 143491

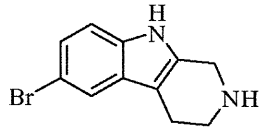


Chemical Formula: $C_{10}H_{11}BrN_2$
Exact Mass: 238.01
Molecular Weight: 239.11

4-Bromophenylhydrazine hydrochloride (20.0 g, 85.8 mmol) was reacted according to the procedure of Mascal et al. (Rinehart, Kenneth L.; Kobayashi, Jun'ichi; Harbour, Gary C.; Gilmore, Jeremy; Mascal, Mark; et al. *J. Am. Chem. Soc.* **1987**, *109*, 3378–3387) to provide the title compound (5.2 g, 25%) as an orange solid: ESI MS *m/z* 239 $[M + H]^+$.

b) 6-Bromo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole

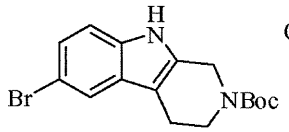
Beilstein Registry Number 911238



Chemical Formula: $C_{11}H_{11}BrN_2$
Exact Mass: 250.01
Molecular Weight: 251.12

2-(5-Bromo-1*H*-indol-3-yl)ethanamine (5.2 g, 22 mmol) was reacted according to the procedure of Mascal et al. (Rinehart, Kenneth L.; Kobayashi, Jun'ichi; Harbour, Gary C.; Gilmore, Jeremy; Mascal, Mark; et al. *J. Am. Chem. Soc.* **1987**, *109*, 3378–3387) to provide the title compound (2.6 g, 48%) as an orange solid: ESI MS *m/z* 251 $[M + H]^+$.

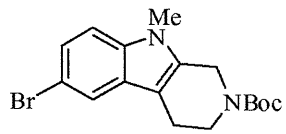
c) *tert*-Butyl 6-bromo-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{16}H_{19}BrN_2O_2$
Exact Mass: 350.06
Molecular Weight: 351.24

6-Bromo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (2.6 g, 10 mmol) was suspended in CH_2Cl_2 (50 mL) and THF (7.5 mL) and Boc_2O (2.3 g, 11 mmol) was added. After 2.5 h, the mixture was concentrated. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, 97:3 to 70:30) gave the title compound (1.15 g, 30%) as an orange powder: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.23 (d, J = 8.5 Hz, 1H), 7.18 (d, J = 8.5 Hz, 1H), 4.68–4.59 (br m, 2H), 3.80–3.70 (br m, 2H), 2.78–2.71 (br m, 2H), 1.50 (s, 9H).

d) *tert*-Butyl 6-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate

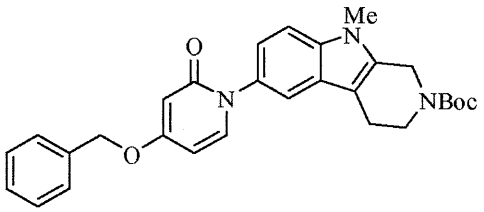


Chemical Formula: $C_{17}H_{21}BrN_2O_2$
Exact Mass: 364.08
Molecular Weight: 365.26

tert-Butyl 6-bromo-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (1.15 g, 3.26 mmol) was dissolved in DMF (20 mL) and sodium hydride (60% weight dispersion in mineral oil, 196 mg, 4.89 mmol) was added. After 1 h, methyl iodide (0.30 mL, 4.9 mmol) was added and the reaction mixture was stirred for a further 30 min. The mixture was diluted with methylene chloride and washed with 5% lithium chloride solution (5×), dried

over Na_2SO_4 and concentrated. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, 97:3 to 75:25) gave the title compound (740 mg, 36%) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.24 (d overlapped by solvent, J = 8.5, 1H), 7.14 (d, J = 8.5, 1H), 4.67–4.53 (br m, 2H), 3.79–3.67 (br m, 2H), 3.60 (s, 3H), 2.78–2.66 (br m, 2H), 1.51 (s, 9H).

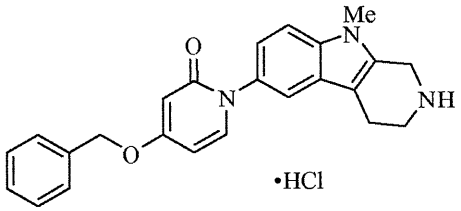
e) *tert*-Butyl 6-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{29}H_{31}N_3O_4$
Exact Mass: 485.23
Molecular Weight: 485.57

A solution of *tert*-Butyl-6-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (750 mg, 2.03 mmol) in DMSO (10 mL) was stirred under nitrogen and treated sequentially with 4-(benzyloxy)pyridin-2(1*H*)-one (448 mg, 2.23 mmol), 8-hydroxyquinoline (44 mg, 0.305 mmol), CuI (58 mg, 0.305 mmol) and K_2CO_3 (308 mg, 2.23 mmol). After stirring overnight at 130 °C, the mixture was allowed to cool to room temperature and a mixture of MeOH and NH_4OH (10:1, 10 mL) was added. After stirring for 15 min, the mixture was diluted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. Purification by flash column chromatography (40 g ISCO column eluting with a 1:1 ethylacetate/hexanes and a methanol/ammonia mixture (10:1); gradient 100% 1:1 ethylacetate/hexanes to 90% 1:1 ethylacetate/hexanes/ 10% methanol/ammonia mixture (10:1) over 30 min at 25 mL/min) provided the title compound (340 mg, 33%) as a yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.36 (m, 8H), 7.13 (d, J = 7.8, Hz, 1H), 6.09 (d, J = 2.6 Hz, 1H), 6.03 (dd, J =7.5, 2.7 Hz, 1H), 5.05 (s, 2H), 4.65 (br s, 2H), 3.73 (br s, 2H), 3.66 (s, 3H), 2.77 (br s, 2H), 1.51 (s, 9H).

f) 4-(Benzyloxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-6-yl)pyridin-2(1*H*)-one hydrochloride

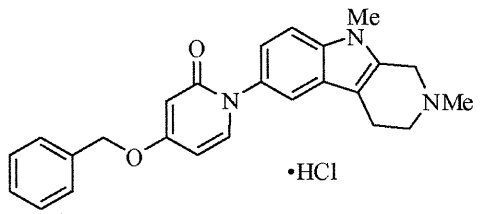


Chemical Formula: $C_{24}H_{24}ClN_3O_2$
Exact Mass: 421.16
Molecular Weight: 421.92

tert-Butyl 6-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (0.340 g, 0.70 mmol) was dissolved in MeOH (5 mL) and 2 N HCl in ether (15 mL) was added. After stirring for 1 h, the liquid was decanted off and the resultant solid was filtered and washed with ether (3×). This provided the title compound (267 mg, 98%) as a light yellow solid: mp 290–300 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.66 (d, J = 7.5 Hz, 1H), 7.57–7.52 (m, 2H), 7.46 (d, J = 7.7 Hz, 2H), 7.41 (overlapping dd, J = 7.3 Hz, 2H), 7.36 (d, J = 7.5 Hz, 1H), 7.19 (dd, J = 8.6, 2.0 Hz, 1H), 6.42 (dd, J = 7.5, 2.7 Hz, 1H), 6.22 (d, J = 2.6 Hz, 1H), 5.22 (s, 2H), 4.55 (s, 2H), 3.75 (s, 3H), 3.58 (t, J = 6.0 Hz, 2H), 3.10 (t, J = 6.0 Hz, 2H); ESI MS *m/z* 386 $[M + H]^+$; HPLC (Method B) 98.8% (AUC), t_R = 12.8 min.

Example 47

Preparation of 4-(Benzyloxy)-1-(2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{25}H_{26}ClN_3O_2$
Exact Mass: 435.17
Molecular Weight: 435.95

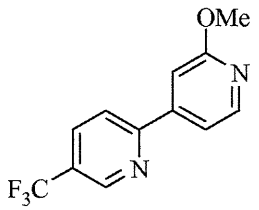
4-(Benzyloxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pydido[3,4-*b*]indol-6-yl)pyridine-2(1*H*)-one hydrochloride (126 mg, 0.325 mmol) was dissolved in MeOH (2 mL) and CH_2Cl_2 (0.5 mL) and formaldehyde (0.036 mL, 37% aqueous solution) was added. After stirring for 1 h, $NaBH(OAc)_3$ (138 mg, 0.651 mmol) was added and the mixture was stirred for a further 40 min. The mixture was diluted with methylene chloride (50 mL), washed with saturated Na_2CO_3 solution, concentrated and purified by flash column chromatography (12 g ISCO column eluting with methylene chloride and a methanol/ammonia mixture (10:1); gradient 100% methylene chloride to 85% methylene

chloride over 30 min at 40 mL/min), and further purified by preparative HPLC to provide the title compound (55.5 mg, 43%) as a white powder: mp 260–270 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.56–7.53 (m, 2H), 7.51 (d, J = 1.8, 1H), 7.46 (d, J = 7.3 Hz, 2H), 7.41 (overlapping dd, J = 7.4 Hz, 2H), 7.36 (d, J = 7.2 Hz, 1H), 7.19 (dd, J = 8.6, 2.0 Hz, 1H), 6.27 (dd, J = 7.6, 2.7 Hz, 1H), 6.11 (d, J = 2.6 Hz, 1H), 5.18 (s, 2H), 4.64 (br s, 2H), 3.75 (s, 3H), 3.67 (br s, 2H), 3.18–3.13 (m, 5H); ESI MS m/z 400 $[M + H]^+$; HPLC (Method B) >99 % (AUC), t_R = 12.9 min.

Example 48

Preparation of 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one dihydrochloride

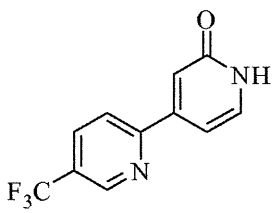
a) 2'-Methoxy-5-(trifluoromethyl)-2,4'-bipyridine



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

2-Bromo-5-trifluoromethylpyridine (410 mg, 2.13 mmol) and 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (500 mg, 1.81 mmol) were reacted according to Example 31 (step a) to provide the 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).

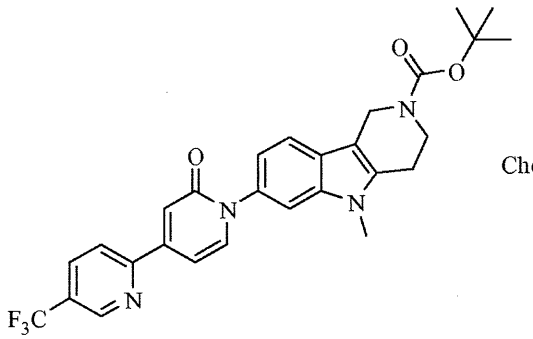
b) 4-(5-(Trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one



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

2'-Methoxy-5-(trifluoromethyl)-2,4'-bipyridine (337 mg, 1.32 mmol) was reacted reacted according to Example 31 (step c) 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).

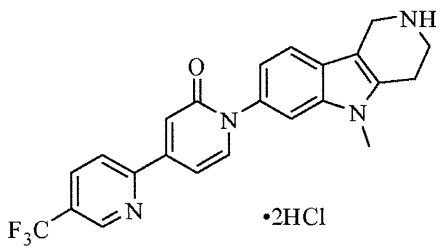
c) *tert*-Butyl 5-methyl-7-(2-oxo-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-b]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{28}H_{27}F_3N_4O_3$
Exact Mass: 524.20
Molecular Weight: 524.53

4-(5-(Trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one (100 mg, 0.41 mmol) and *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (152 mg, 0.416 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (83 mg, 38%) as a green solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.06 (dd, J = 8.3, 2.1 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 7.2 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.37 (d, J = 1.6 Hz, 1H), 7.25 (d, J = 1.6 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 7.03 (dd, J = 7.1, 1.8 Hz, 1H), 4.66 (s, 2H), 3.85 (br m, 2H), 3.66 (s, 3H), 2.84 (br m, 2H), 1.51 (s, 9H).

d) 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one dihydrochloride



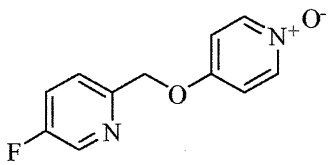
Chemical Formula: $C_{23}H_{21}Cl_2F_3N_4O$
Exact Mass: 496.10
Molecular Weight: 497.34

tert-Butyl 5-methyl-7-(2-oxo-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (83 mg, 0.16 mmol) was deprotected and converted to the dihydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (51 mg, 78%) as a yellow solid: mp 320-330 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 9.06 (s, 1H), 8.28 (dd, J = 8.4, 2.1 Hz, 1H), 8.23 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 7.1 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 1.6 Hz, 1H), 7.43 (d, J = 1.6 Hz, 1H), 7.29 (dd, J = Hz, 1H), 7.17 (dd, J = 8.3, 1.8 Hz, 1H), 4.50 (s, 2H), 3.76 (s, 3H), 3.69 (t, J = 6.0 Hz, 2H), 3.22 (t, J = Hz, 2H); ESI MS *m/z* 425 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 12.5 min.

Example 49

Preparation of 4-((5-Fluoropyridin-2-yl)methoxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

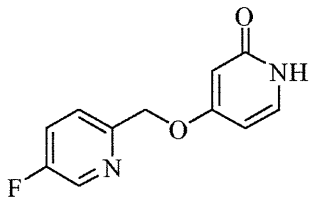
a) 4-((5-Fluoropyridin-2-yl)methoxy)pyridine 1-oxide



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

5-Fluoro-2-pyridylbenzylalcohol (3.00 g, 23.6 mmol) and 4-chloropyridine-*N*-oxide (2.03 g, 15.7 mmol) were reacted according to Example 34 (step a) to provide 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).

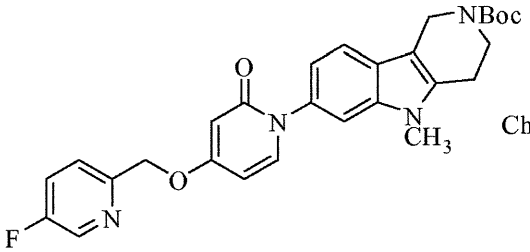
b) 4-((5-Fluoroyridin-2-yl)methoxy)pyridin-2(*1H*)-one



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

4-((5-Fluoropyridin-2-yl)methoxy)pyridine 1-oxide (1.76 g, 7.99 mmol) was reacted according to Example 34 (step b) 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).

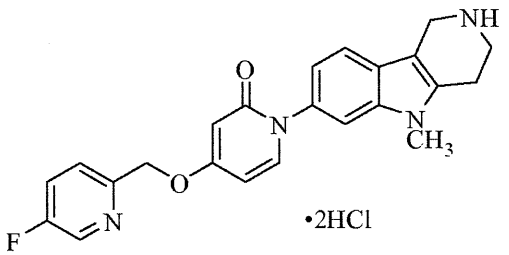
c) *tert*-Butyl 7-(4-((5-fluoropyridin-2-yl)methoxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{28}H_{29}FN_4O_4$
Exact Mass: 504.22
Molecular Weight: 504.55

4-((5-Fluoropyridin-2-yl)methoxy)pyridin-2(1*H*)-one (275 mg, 1.25 mmol) and *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (456 mg, 1.25 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (420 mg, 66%) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, J = 2.1 Hz, 1H), 7.50 (m, 3H), 7.36 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 1.6 Hz, 1H), 7.01 (d, J = 8.9 Hz, 1H), 6.11–6.08 (m, 2H), 5.18 (s, 2H), 4.65 (s, 2H), 3.87 (t, J = 5.3 Hz, 2H), 3.65 (s, 3H), 2.84 (t, J = 4.2 Hz, 2H), 1.60 (s, 9H).

d) 4-((5-Fluoropyridin-2-yl)methoxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(*1H*)-one dihydrochloride



Chemical Formula: $C_{23}H_{23}Cl_2FN_4O_2$
Exact Mass: 476.12
Molecular Weight: 477.36

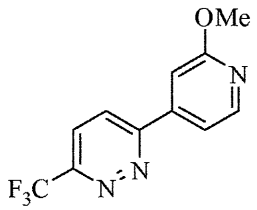
tert-Butyl 7-(4-((5-fluoropyridin-2-yl)methoxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (415 mg, 0.823 mmol) was deprotected and converted to the dihydrochloride according to procedure of Example 30

(steps e and g) to provide the title compound (328 mg, 84%) as a white solid: mp 174–180 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.70 (s, 1H), 8.00 (dt, J = 8.4, 2.8 Hz, 1H), 7.91–7.88 (m, 2H), 7.63 (d, J = 8.4 Hz, 1H), 7.55 (s, 1H), 7.11 (dd, J = 8.3, 1.7 Hz, 1H), 6.69 (dd, J = 7.5, 2.7 Hz, 1H), 6.45 (d, J = 2.6 Hz, 1H), 5.46 (s, 2H), 4.49 (s, 2H), 3.75 (s, 3H), 3.68 (t, J = 6.1 Hz, 2H), 3.22 (t, J = 6.1 Hz, 2H); ESI MS m/z 405 $[M + H]^+$; HPLC (Method B) 95.5% (AUC), t_R = 10.9 min.

Example 50

Preparation of 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(6-(trifluoromethyl)pyridazin-3-yl)pyridin-2(1*H*)-one hydrochloride

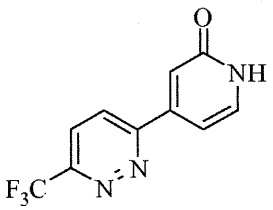
a) 3-(2-Methoxypyridin-4-yl)-6-(trifluoromethyl)pyridazine



Chemical Formula: $C_{11}H_8F_3N_3O$
Exact Mass: 255.06
Molecular Weight: 255.20

3-Chloro-6-(trifluoromethyl)pyridazine (137 mg, 0.751 mmol) and 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (176 mg, 0.749 mmol) were reacted according to Example 31 (step a) to provide the title compound (115 mg, 60%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 5.8 Hz, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.62 (dd, J = 5.4, 1.5 Hz, 1H), 7.45 (s, 1H), 4.03 (s, 3H).

b) 4-(6-(Trifluoromethyl)pyridazin-3-yl)pyridin-2(1*H*)-one

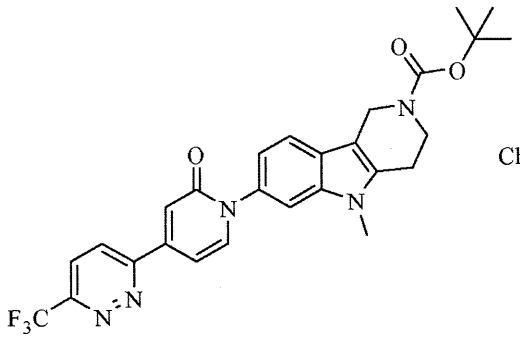


Chemical Formula: $C_{10}H_6F_3N_3O$
Exact Mass: 241.05
Molecular Weight: 241.17

3-(2-Methoxypyridin-4-yl)-6-(trifluoromethyl)pyridazine (115 mg, 0.451 mmol) was reacted according to Example 31 (step c) to provide the title compound (120 mg, quant) as a white solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.61 (d, J = 8.9

Hz, 1H), 8.42 (d, J = 8.9 Hz, 1H), 7.62 (d, J = 6.8 Hz, 1H), 7.19 (s, 1H), 7.01 (dd, J = 6.8, 1.6 Hz, 1H).

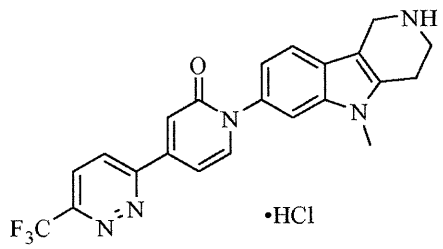
c) *tert*-Butyl 5-methyl-7-(2-oxo-4-(6-(trifluoromethyl)pyridazin-3-yl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{27}H_{26}F_3N_5O_3$
Exact Mass: 525.20
Molecular Weight: 525.52

4-(6-(Trifluoromethyl)pyridazin-3-yl)pyridin-2(1*H*)-one (60 mg, 0.25 mmol) and *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (90 mg, 0.25 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (60 mg, 46%) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 7.0 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.38 (d, J = 1.3 Hz, 1H), 7.26–7.24 (m, 2H), 7.10 (d, J = 7.8 Hz, 1H), 4.66 (s, 2H), 3.66 (t, J = 3.3 Hz, 2H), 3.86 (s, 3H), 2.84 (t, J = 3.3 Hz, 2H), 1.51 (s, 9H).

d) 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(6-(trifluoromethyl)pyridazin-3-yl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{22}H_{19}ClF_3N_5O$
Exact Mass: 461.12
Molecular Weight: 461.87

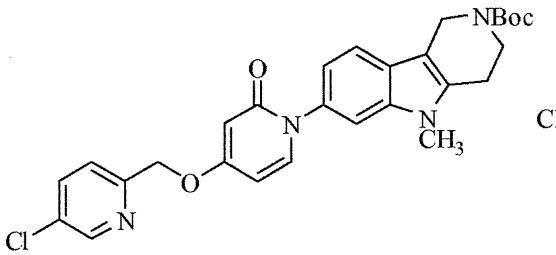
tert-Butyl 5-methyl-7-(2-oxo-4-(6-(trifluoromethyl)pyridazin-3-yl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (60 mg, 0.11 mmol) was deprotected and converted to the hydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (44 mg, 88%) as a yellow solid: mp 315–

320 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.54 (d, J = 8.8 Hz, 1H), 8.28 (d, J = 8.9 Hz, 1H), 7.91 (d, J = 7.0 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 1.5 Hz, 1H), 7.44 (d, J = 1.5 Hz, 1H), 7.35 (dd, J = 7.2, 1.9 Hz, 1H), 7.16 (dd, J = 8.3, 1.8 Hz, 1H), 4.50 (s, 2H), 3.77 (s, 3H), 3.69 (t, J = 6.1 Hz, 2H), 3.22 (t, J = 6.0 Hz, 2H); ESI MS *m/z* 426 $[M + H]^+$; HPLC (Method B) 95.9% (AUC), t_R = 11.7 min.

Example 51

Preparation of 4-((5-Chloropyridin-2-yl)methoxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

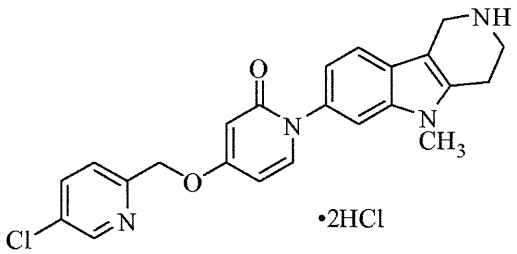
a) *tert*-Butyl 7-(4-((5-chloropyridin-2-yl)methoxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{28}H_{29}ClN_4O_4$
Exact Mass: 520.19
Molecular Weight: 521.01

4-((5-Chloropyridin-2-yl)methoxy)pyridin-2(1*H*)-one (127 mg, 0.537 mmol) and *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (200 mg, 1.1 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (113 mg, 40%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J = 2.4 Hz, 1H), 7.73 (dd, J = 8.4, 2.4 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.29 (d, J = 1.5 Hz, 1H), 7.01 (d, J = 7.9 Hz, 1H), 6.09 (dd, J = 7.5, 2.7 Hz, 1H), 6.05 (d, J = 2.5 Hz, 1H), 5.17 (s, 2H), 4.64 (s, 2H), 3.84 (t, J = 5.4 Hz, 2H), 3.63 (s, 3H), 2.82 (t, J = 5.4 Hz, 2H), 1.50 (s, 9H).

b) 4-((5-Chloropyridin-2-yl)methoxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

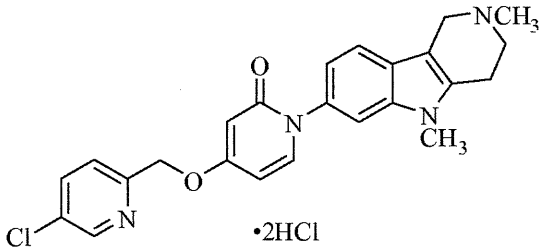


Chemical Formula: $C_{23}H_{23}Cl_3N_4O_2$
Exact Mass: 492.09
Molecular Weight: 493.81

tert-Butyl 7-(4-((5-chloropyridin-2-yl)methoxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-b]indole-2(5*H*)-carboxylate (108 mg, 0.207 mmol) was deprotected and converted to the dihydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (99 mg, 97%) as a white solid: mp 290–320 °C dec; ^{1}H NMR (300 MHz, CD_3OD) δ 8.61 (d, J = 2.1 Hz, 1H), 7.95 (dd, J = 8.4, 2.4 Hz, 1H), 7.62 (d, J = 7.6 Hz, 2H), 7.58 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 1.6 Hz, 1H), 7.05 (dd, J = 8.3, 1.8 Hz, 1H), 6.36 (dd, J = 7.6, 2.2 Hz, 1H), 6.13 (d, J = 2.6 Hz, 1H), 5.28 (s, 2H), 4.48 (s, 2H), 3.73 (s, 3H), 3.67 (t, J = 6.2 Hz, 2H), 3.02 (t, J = 6.2 Hz, 2H); ESI MS *m/z* 421 $[M + H]^+$; HPLC (Method B) 98.2% (AUC), t_R = 12.0 min.

Example 52

Preparation of 4-((5-Chloropyridin-2-yl)methoxy)-1-(2,5-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride



Chemical Formula: $C_{24}H_{25}Cl_3N_4O_2$
Exact Mass: 506.10
Molecular Weight: 507.84

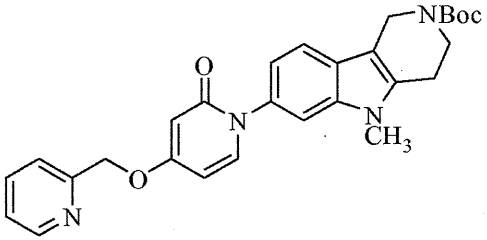
4-((5-Chloropyridin-2-yl)methoxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (50 mg, 0.12 mmol) was reacted according to the procedure of Example 47 to provide the free-base. Conversion to the dihydrochloride salt using the procedure of Example 30 (step g) provided the title compound (39 mg, 64%) as a white solid: mp 278–282 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 8.60 (d, J = 2.0 Hz, 1H), 7.96–7.92 (m, 1H), 7.61 (d, J = 7.7 Hz, 2H), 7.57 (d, J = 8.3 Hz, 1H), 7.47 (d, J = 1.4 Hz, 1H), 7.06 (dd, J = 8.4, 1.7 Hz, 1H), 6.34 (dd, J = 7.6, 2.6 Hz, 1H), 6.12 (d, J = 2.6 Hz, 1H), 5.27 (s, 2H), 4.75 (d, J = 14.2 Hz, 1H), 4.38 (d, J = 14.1 Hz, 1H), 3.95–3.85 (m, 1H),

3.73 (s, 3H), 3.63 (m, 1H), 3.31 (m overlapping with solvent, 2H), 3.13 (s, 3H); ESI MS *m/z* 435 $[M + H]^+$; HPLC (Method B) 98.9% (AUC), t_R = 12.1 min.

Example 53

Preparation of 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(pyridin-2-ylmethoxy)pyridin-2(1*H*)-one dihydrochloride

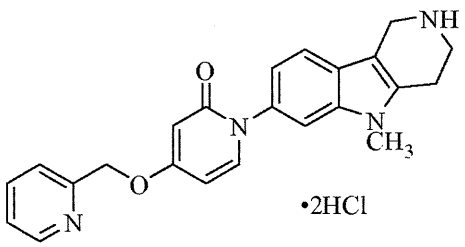
a) *tert*-Butyl 5-methyl-7-(2-oxo-4-(pyridin-2-ylmethoxy)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{28}H_{30}N_4O_4$
Exact Mass: 486.23
Molecular Weight: 486.56

4-(Pyridin-2-ylmethoxy)pyridin-2(1*H*)-one (110 mg, 0.54 mmol) and *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (200 mg, 0.54 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (113 mg, 43%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (ddd, *J* = 4.9, 1.6, 0.9 Hz, 1H), 7.75 (overlapping ddd, *J* = 7.6, 1.8 Hz, 1H), 7.49 (t, *J* = 7.3 Hz, 2H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 1.4 Hz, 1H), 7.26 (m overlapping with solvent, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.12–6.07 (m, 2H), 5.19 (s, 2H), 4.64 (s, 2H), 3.84 (t, *J* = 5.4 Hz, 2H), 3.62 (s, 3H), 2.82 (t, *J* = 5.4 Hz, 2H), 1.52 (s, 9H).

b)1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(pyridin-2-ylmethoxy)pyridin-2(1*H*)-one dihydrochloride

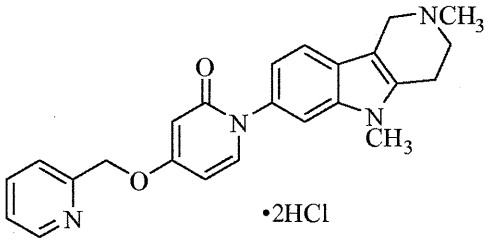


Chemical Formula: $C_{23}H_{24}Cl_2N_4O_2$
Exact Mass: 458.13
Molecular Weight: 459.37

tert-Butyl 5-methyl-7-(2-oxo-4-(pyridin-2-ylmethoxy)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (113 mg, 0.23 mmol) was deprotected and converted to the dihydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (81 mg, 77%) as a white solid: mp 206–211 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (d, J = 5.2 Hz, 1H), 8.59 (dd, J = 7.9, 1.5 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.01 (overlapping dd, J = 6.6 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 1.6 Hz, 1H), 7.06 (dd, J = 8.4, 1.8 Hz, 1H), 6.44 (dd, J = 7.6, 2.7 Hz, 1H), 6.21 (d, J = 2.7 Hz, 1H), 5.57 (s, 2H), 4.48 (s, 2H), 3.74 (s, 3H), 3.68 (t, J = 6.2 Hz, 2H), 3.21 (t, J = 6.2 Hz, 2H); ESI MS *m/z* 387 $[M + H]^+$; HPLC (Method B) 98% (AUC), t_R = 9.3 min.

Example 54

Preparation of 1-(2,5-Dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(pyridin-2-ylmethoxy)pyridin-2(1*H*)-one dihydrochloride



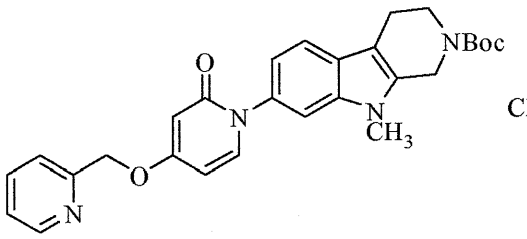
Chemical Formula: $C_{24}H_{26}Cl_2N_4O_2$
Exact Mass: 472.14
Molecular Weight: 473.39

1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(pyridin-2-ylmethoxy)pyridin-2(1*H*)-one (45 mg, 0.116 mmol) was reacted according to the procedure of Example 47 to provide the free-base. Conversion to the dihydrochloride salt using the procedure of Example 30 (step g) provided the title compound (54 mg, 98%) as a white solid: mp 260–265 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.87 (d, J = 5.7 Hz, 1H), 8.58 (overlapping dd, J = 8.2 Hz, 1H), 8.14 (d, J = 7.9 Hz, 1H), 8.00 (overlapping dd, J = 6.6 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.49 (s, 1H), 7.07 (dd, J = 8.3, 1.7 Hz, 1H), 6.44 (dd, J = 7.5, 2.6 Hz, 1H), 6.20 (d, J = 2.0 Hz, 1H), 5.56 (s, 2H), 4.76 (d, J = 14.2 Hz, 1H), 4.40 (d, J = 14.2 Hz, 1H), 3.91 (m, 1H), 3.74 (s, 3H), 3.61 (m, 1H), 3.29–3.17 (m overlapping with solvent, 2H), 3.13 (s, 3H); ESI MS *m/z* 401 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 9.2 min.

Example 55

Preparation of 1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(pyridin-2-ylmethoxy)pyridin-2(1*H*)-one dihydrochloride

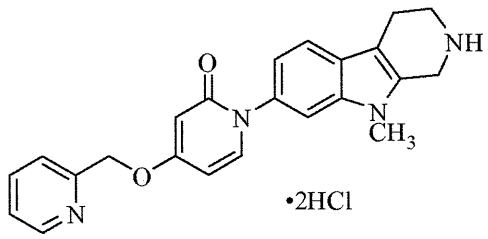
a) *tert*-Butyl 9-methyl-7-(2-oxo-4-(pyridin-2-ylmethoxy)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{28}H_{30}N_4O_4$
Exact Mass: 486.23
Molecular Weight: 486.56

4-(Pyridin-2-ylmethoxy)pyridin-2(1*H*)-one (138 mg, 0.682 mmol) and *tert*-butyl 7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (250 mg, 0.68 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (170 mg, 51%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, J = 4.1 Hz, 1H), 7.76 (overlapping ddd, J = 7.7, 1.7 Hz, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 7.4 Hz, 1H), 7.29–7.26 (m overlapping with solvent, 2H), 7.01 (dd, J = 8.2, 1.8 Hz, 1H), 6.12–6.07 (m, 2H), 5.19 (s, 2H), 4.63 (s, 2H), 3.74 (br s, 2H), 3.62 (s, 3H), 2.79 (s, 2H), 1.51 (s, 9H).

b)1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(pyridin-2-ylmethoxy)pyridin-2(1*H*)-one dihydrochloride



Chemical Formula: $C_{23}H_{24}Cl_2N_4O_2$
Exact Mass: 458.13
Molecular Weight: 459.37

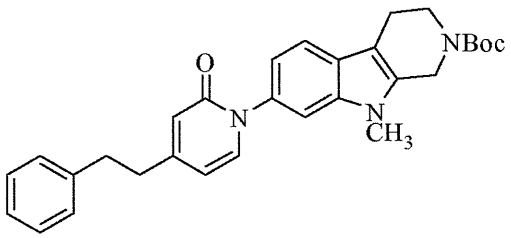
tert-Butyl 9-methyl-7-(2-oxo-4-(pyridin-2-ylmethoxy)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (167 mg, 0.34 mmol) was deprotected and converted to the dihydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (124 mg, 79%) as a yellow solid: mp 226–231 °C;

^{1}H NMR (500 MHz, CD_3OD) δ 8.89 (d, J = 5.4 Hz, 1H), 8.61 (overlapping ddd, J = 8.0, 1.6 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H), 8.02 (overlapping dd, J = 6.6 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 1.6 Hz, 1H), 7.06 (dd, J = 8.4, 1.8 Hz, 1H), 6.44 (dd, J = 7.6, 2.7 Hz, 1H), 6.21 (d, J = 2.6 Hz, 1H), 5.57 (s, 2H), 4.56 (s, 2H), 3.73 (s, 3H), 3.60 (t, J = 6.0, 2H), 3.13 (t, J = 6.0, 2H); ESI MS *m/z* 387 $[M + H]^+$; HPLC (Method B) 98.6% (AUC), t_R = 9.2 min.

Example 56

Preparation of 1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-phenethylpyridin-2(1*H*)-one dihydrochloride

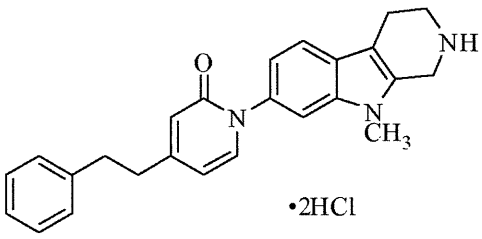
a) *tert*-Butyl 9-methyl-7-(2-oxo-4-phenethylpyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{30}H_{33}N_3O_3$
Exact Mass: 483.25
Molecular Weight: 483.60

4-Phenethylpyridin-2(1*H*)-one (817 mg, 4.10 mmol) and *tert*-butyl 7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (1.5 g, 4.1 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (1.2 g, 60%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 8.1 Hz, 1H), 7.34–7.29 (m, 4H), 7.26–7.20 (m, 3H), 7.03 (dd, J = 8.2, 1.5 Hz, 1H), 6.50 (s, 1H), 6.09 (dd, J = 6.9, 1.6 Hz, 1H), 4.63 (br s, 2H), 3.74 (br s, 2H), 3.63 (s, 3H), 2.98–2.91 (m, 2H), 2.84–2.79 (m, 4H), 1.51 (s, 9H).

b) 1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-phenethylpyridin-2(1*H*)-one dihydrochloride



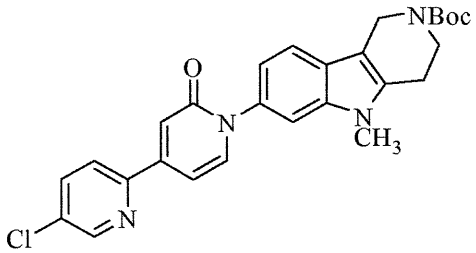
Chemical Formula: $C_{25}H_{27}Cl_2N_3O$
Exact Mass: 455.15
Molecular Weight: 456.41

tert-Butyl 9-methyl-7-(2-oxo-4-phenethylpyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (1.2 g, 2.4 mmol) was deprotected and converted to the dihydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (550 mg, 51%) as a yellow solid: mp 280–295 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.67 (s, 2H), 7.59–7.52 (m, 3H), 7.35–7.27 (m, 4H), 7.24–7.17 (m, 1H), 7.01 (dd, J = 7.4, 2.0 Hz, 1H), 6.38–6.27 (m, 2H), 4.45 (s, 2H), 3.67 (s, 3H), 3.42 (t, J = 6.4 Hz, 2H), 2.97–2.89 (m, 4H), 2.81–2.76 (m, 2H); ESI MS *m/z* 384 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 13.3 min.

Example 57

Preparation of 4-(5-Chloropyridin-2-yl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

a) *tert*-Butyl 7-(4-(5-chloropyridin-2-yl)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate

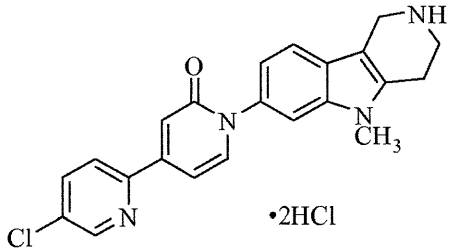


Chemical Formula: $C_{27}H_{27}ClN_4O_3$
Exact Mass: 490.18
Molecular Weight: 490.98

4-(5-Chloropyridin-2-yl)pyridin-2(1*H*)-one (111 mg, 0.537 mmol) and *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (200 mg, 0.54 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (80 mg, 30%) as a green solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, J = 2.2 Hz, 1H), 7.79 (dd, J = 8.5, 2.4 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.53 (d, J = 7.2 Hz, 2H),

7.36 (d, J = 1.5 Hz, 1H), 7.17 (d, J = 1.5 Hz, 1H), 7.07 (d, J = 7.4 Hz, 1H), 6.98 (dd, J = 7.1, 1.8 Hz, 1H), 4.65 (br s, 2H), 3.85 (br s, 2H), 3.65 (s, 3H), 2.83 (br s, 2H), 1.50 (s, 9H).

b) 4-(5-Chloropyridin-2-yl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

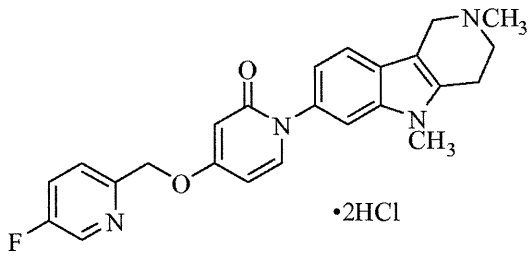


Chemical Formula: $C_{22}H_{21}Cl_3N_4O$
Exact Mass: 462.08
Molecular Weight: 463.79

tert-Butyl 7-(4-(5-chloropyridin-2-yl)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (80 mg, 0.16 mmol) was deprotected and converted to the dihydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (40 mg, 54%) as a white solid: ^{1}H NMR (500 MHz, CD_3OD) δ 8.74 (d, J = 2.4 Hz, 1H), 8.06 (d, J = 8.5 Hz, 1H), 8.02 (dd, J = 8.7, 2.4 Hz, 1H), 7.86 (d, J = 7.2 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 1.9 Hz, 1H), 7.37 (d, J = 1.5 Hz, 1H), 7.27 (dd, J = 8.5, 1.8 Hz, 1H), 7.15 (dd, J = 8.4, 1.8 Hz, 1H), 4.50 (s, 2H), 3.75 (s, 3H), 3.68 (t, J = 6.5 Hz, 2H), 3.22 (t, J = 6.5 Hz, 2H); ESI MS *m/z* 391 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 12.2 min.

Example 59

Preparation of 1-(2,5-Dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-((5-fluoropyridin-2-yl)methoxy)pyridin-2(1*H*)-one dihydrochloride



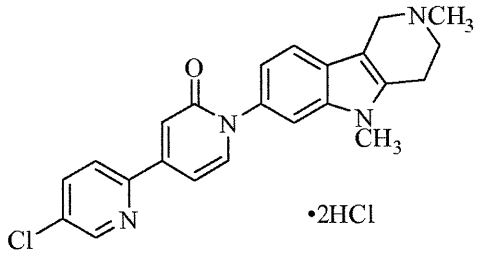
Chemical Formula: $C_{24}H_{25}Cl_2FN_4O_2$
Exact Mass: 490.13
Molecular Weight: 491.39

4-((5-Fluoropyridin-2-yl)methoxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(*1H*)-one (75 mg, 0.19 mmol) was reacted according to the procedure of Example 47 to provide the free-base. Conversion to the dihydrochloride salt

using the procedure of Example 30 (step g) provided the title compound (71 mg, 78%) as a white solid: mp 215–230 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.65 (d, J = 2.6 Hz, 1H), 7.91 (overlapping ddd, J = 9.6, 2.1 Hz, 1H), 7.83–7.20 (m, 2H), 7.61 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 1.8 Hz, 1H), 7.09 (dd, J = 8.4, 1.8 Hz, 1H), 6.59 (dd, J = 7.5, 2.6 Hz, 1H), 6.36 (d, J = 2.6 Hz, 1H), 5.41 (s, 2H), 4.76 (d, J = 14.2 Hz, 1H), 4.39 (d, J = 14.2 Hz, 1H), 3.94–3.82 (m, 2H), 3.74 (s, 3H), 3.65–3.58 (m, 2H), 3.13 (s, 3H); ESI MS *m/z* 419 $[M + H]^+$; HPLC (Method B) 95.8% (AUC), t_R = 11.0 min.

Example 60

Preparation of 4-(5-Chloropyridin-2-yl)-1-(2,5-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

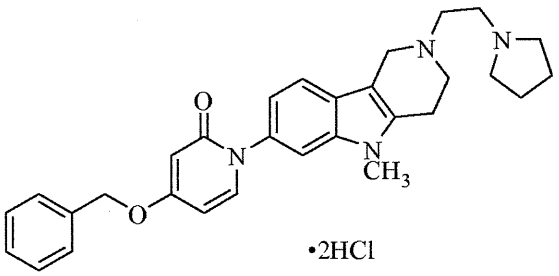


Chemical Formula: $C_{23}H_{23}Cl_3N_4O$
Exact Mass: 476.09
Molecular Weight: 477.81

4-(5-Chloropyridin-2-yl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (57 mg, 0.14 mmol) was reacted according to the procedure of Example 47 to provide the free-base. Conversion to the dihydrochloride salt using the procedure of Example 30 (step g) provided the title compound (54.5 mg, 81%) as a yellow solid: ^{1}H NMR (500 MHz, CD_3OD) δ 8.72 (d, J = 1.7 Hz, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.99 (dd, J = 8.2, 2.2 Hz, 1H), 7.79 (d, J = 7.1 Hz, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 1.3 Hz, 1H), 7.34 (d, J = 1.5 Hz, 1H), 7.19 (dd, J = 7.2, 1.8 Hz, 1H), 7.14 (dd, J = 8.3, 1.8 Hz, 1H), 4.80–4.72 (br m, 1H), 4.46–4.34 (m, 1H), 3.96–3.86 (m, 1H), 3.75 (s, 3H), 3.65–3.55 (br m, 1H), 3.28 (s, 2H), 3.14 (s, 3H); ESI MS *m/z* 405 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 12.0 min.

Example 61

Preparation of 4-(Benzyloxy)-1-(5-methyl-2-(2-(pyrrolidin-1-yl)ethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride



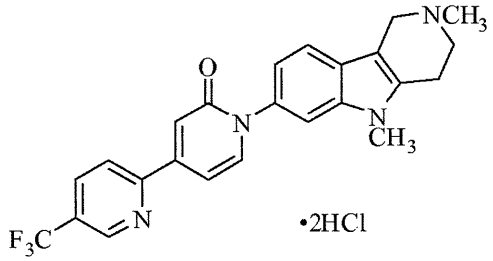
•2HCl

Chemical Formula: $C_{30}H_{36}Cl_2N_4O_2$
Exact Mass: 554.22
Molecular Weight: 555.54

4-(Benzyloxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (180 mg, 0.46 mmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (95 mg, 0.56 mmol), (*i*-Pr)$_2$EtN (0.25 mL, 1.4 mmol) were combined in ethanol (2 mL) and heated at 60 °C for 2 h. Purification by preparative HPLC and conversion to the dihydrochloride salt using the procedure of Example 30 (step g) provided the title compound as a white solid: mp 285–289 °C; ^{1}H NMR (300 MHz, D_2O) δ 7.50 (d, J = 8.3 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.42–7.31 (m, 6H), 6.96 (dd, J = 8.3, 1.6 Hz, 1H), 6.27 (dd, J = 7.7, 2.6 Hz, 1H), 6.10 (d, J = 2.6 Hz, 1H), 5.90 (s, 2H), 4.59 (br s, 2H), 3.81–3.59 (m, 8H), 3.55 (s, 3H), 3.20 (t, J = 5.7 Hz, 2H), 3.18–3.05 (br m, 2H), 2.15–1.90 (m, 4H); ESI MS *m/z* 483 $[M + H]^+$; HPLC (Method B) 98.8% (AUC), t_R = 11.3 min.

Example 62

Preparation of 1-(2,5-Dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one dihydrochloride



•2HCl

Chemical Formula: $C_{24}H_{23}Cl_2F_3N_4O$
Exact Mass: 510.12
Molecular Weight: 511.37

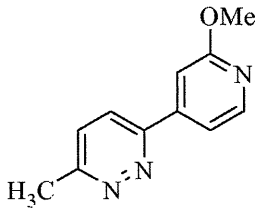
1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one (68 mg, 0.16 mmol) was reacted according to the procedure of Example 47 to provide the free-base. Conversion to the dihydrochloride salt using the procedure of Example 30 (step g) provided the title compound (39.6 mg, 48%) as a brown solid: mp 274–280 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 9.04 (s, 1H), 8.28 (dd, J = 8.7, 1.9 Hz, 1H), 8.21 (d, J = 2.1 Hz, 1H), 7.83 (d, J

= 7.1 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 1.3 Hz, 1H), 7.39 (d, J = 1.6 Hz, 1H), 7.24 (dd, J = 7.1, 1.9 Hz, 1H), 7.15 (dd, J = 8.3, 1.7 Hz, 1H), 4.80–4.71 (br m, 1H), 4.44–4.35 (br m, 1H), 3.96–3.86 (br m, 1H), 3.75 (s, 3H), 3.67–3.57 (br m, 1H), 3.28 (s, 2H), 3.14 (s, 3H); ESI MS *m/z* 439 $[M + H]^+$; HPLC (Method B) 96.4% (AUC), t_R = 12.6 min.

Example 63

Preparation of 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(6-methylpyridazin-3-yl)pyridin-2(1*H*)-one dihydrochloride

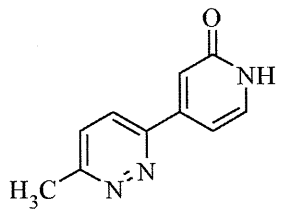
a) 3-(2-Methoxypyridin-4-yl)-6-methylpyridazine



Chemical Formula: $C_{11}H_{11}N_3O$
Exact Mass: 201.09
Molecular Weight: 201.22

3-Chloro-6-methylpyridazine (343 mg, 2.67 mmol) and 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (470 mg, 2.0 mmol) were reacted according to Example 31 (step a) to provide the title compound (183 mg, 45%) as a cream solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, J = 5.3 Hz, 1H), 7.62 (d, J = 8.7 Hz, 1H), 7.59 (dd, J = 5.3, 1.5 Hz, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.38 (s, 1H), 4.00 (s, 3H), 2.79 (s, 3H).

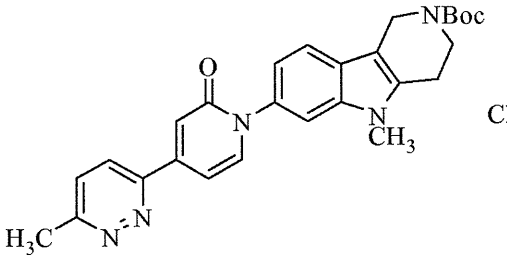
b) 4-(6-Methylpyridazin-3-yl)pyridin-2(1*H*)-one



Chemical Formula: $C_{10}H_9N_3O$
Exact Mass: 187.07
Molecular Weight: 187.20

3-(2-Methoxypyridin-4-yl)-6-methylpyridazine (183 mg, 0.909 mmol) was reacted according to Example 31 (step c) to provide the title compound (133 mg, 75%) as a white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 8.12 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 6.6 Hz, 1H), 7.17–7.14 (m, 2H), 2.75 (s, 3H).

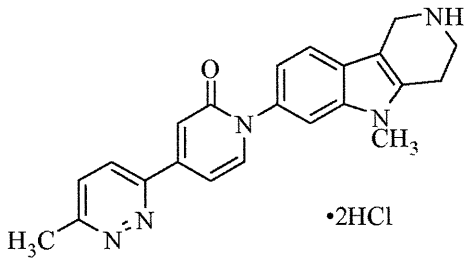
c) *tert*-Butyl 5-methyl-7-(4-(6-methylpyridazin-3-yl)-2-oxopyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{27}H_{29}N_5O_3$
Exact Mass: 471.23
Molecular Weight: 471.55

3-(2-Methoxypyridin-4-yl)-6-methylpyridazine (133 mg, 0.710 mmol) and *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (259 mg, 0.71 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (200 mg, 59%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 1.6 Hz, 1H), 7.29 (overlapping ddd, J = 7.3, 1.8 Hz, 1H), 7.17 (d, J = 1.8 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 4.67 (br s, 2H), 3.91–3.83 (br m, 2H), 3.67 (s, 3H), 2.89–2.83 (br m, 2H), 2.53 (s, 3H), 1.52 (s, 9H).

d) 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(6-methylpyridazin-3-yl)pyridin-2(1*H*)-one dihydrochloride



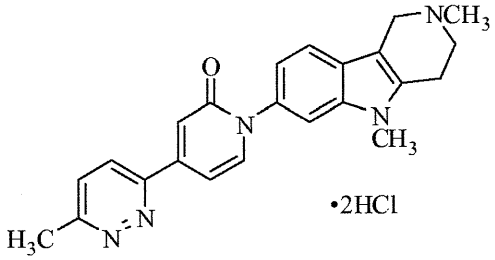
Chemical Formula: $C_{22}H_{23}Cl_2N_5O$
Exact Mass: 443.13
Molecular Weight: 444.36

tert-Butyl 5-methyl-7-(4-(6-methylpyridazin-3-yl)-2-oxopyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (200 mg, 0.42 mmol) was deprotected and converted to the dihydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (57 mg, 33%) as an orange solid: mp 310–315 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.47 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 7.4 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 1.6 Hz, 1H), 7.35 (d, J = 1.6 Hz,

1H), 7.25 (dd, J = 7.1, 1.9 Hz, 1H), 7.15 (dd, J = 8.3, 1.9 Hz, 1H), 4.49 (s, 2H), 3.75 (s, 3H), 3.68 (t, J = 6.2 Hz, 2H), 3.24 (t, J = 6.2 Hz, 2H), 2.85 (s, 3H); ESI MS m/z 372 [M + H]$^+$; HPLC (Method B) 98% (AUC), t_R = 9.3 min.

Example 64

Preparation of 1-(2,5-Dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(6-methylpyridazin-3-yl)pyridin-2(1*H*)-one dihydrochloride



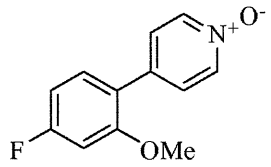
Chemical Formula: $C_{23}H_{25}Cl_2N_5O$
Exact Mass: 457.14
Molecular Weight: 458.38

1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(6-methylpyridazin-3-yl)pyridin-2(1*H*)-one (77 mg, 0.21 mmol) was reacted according to the procdure of Example 47 to provide the free-base. Conversion to the dihydrochloride salt using the procedure of Example 30 (step g) provided the title compound (60 mg, 74%) as a yellow solid: mp 285–288 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.9 (s, 1H), 8.32 (d, J = 8.8 Hz, 1H), 7.85 (d, J = 7.2 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.64 (d, J = 1.5 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.25 (d, J = 1.7 Hz, 1H), 7.14–7.11 (m, 2H), 4.65 (d, J = 12.1 Hz, 1H), 4.31 (dd, J = 14.2, 7.5 Hz, 1H), 3.81–3.74 (m, 1H), 3.71 (s, 3H), 3.55–3.45 (m, 1H), 3.26–3.15 (m, 2H), 2.98 (s, 3H), 2.72 (s, 3H); ESI MS m/z 386 [M + H]$^+$; HPLC (Method B) >99% (AUC), t_R = 9.4 min.

Example 65

Preparation of 4-(4-Fluoro-2-methoxyphenyl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

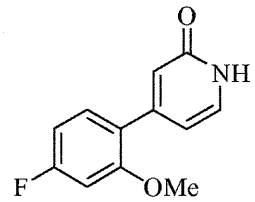
a) 4-(4-Fluoro-2-methoxyphenyl)pyridine 1-oxide



Chemical Formula: $C_{12}H_{10}FNO_2$
Exact Mass: 219.07
Molecular Weight: 219.21

4-Chloropyridine-*N*-oxide (305 mg, 2.35 mmol), 4-fluoro-2-methoxyphenylboronic acid (1.0 g, 8.8 mmol) were reacted according to the procedure of Example 39 (step a) to provide the title compound (450 mg, 87%) as a purple solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 7.2 Hz, 2H), 7.45 (d, J = 7.2 Hz, 2H), 7.31 (d, J = 6.5 Hz, 1H), 6.80–6.71 (m, 2H), 3.85 (s, 3H).

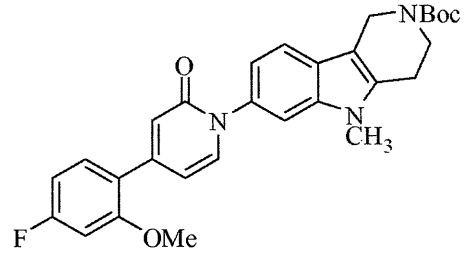
b) 4-(4-Fluoro-2-methoxyphenyl)pyridin-2(1*H*)-one



Chemical Formula: $C_{12}H_{10}FNO_2$
Exact Mass: 219.07
Molecular Weight: 219.21

4-(4-Fluoro-2-methoxyphenyl)pyridine 1-oxide (450 mg, 2.05 mmol) was reacted according to the procedure of Example 32 (step b) to provide the title compound (291 mg, 66%) as a brown solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.4 (br s, 1H), 7.39–7.31 (m, 2H), 7.03 (d, J = 10.2 Hz, 1H), 6.85 (overlapping dd, J = 7.4 Hz, 1H), 6.35 (s, 1H), 6.27 (d, J = 6.1 Hz, 1H), 3.80 (s, 3H).

c) *tert*-Butyl 7-(4-(4-fluoro-2-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate

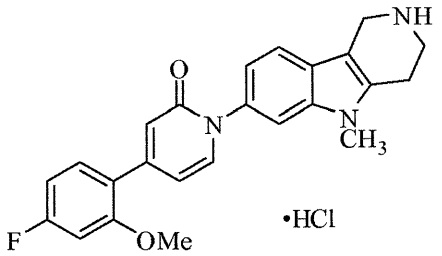


Chemical Formula: $C_{29}H_{30}FN_3O_4$
Exact Mass: 503.22
Molecular Weight: 503.56

4-(4-Fluoro-2-methoxyphenyl)pyridin-2(1*H*)-one (100 mg, 0.45 mmol) and *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (166 mg, 0.454 mmol) were reacted following the procedure of Example 30 (step g) to provide the

title compound (106 mg, 46%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 8.2 Hz, 1H), 7.41 (d, J = 7.1 Hz, 1H), 7.39–7.32 (m, 2H), 7.08 (d, J = 8.0 Hz, 1H), 6.80–6.70 (m, 3H), 6.46 (dd, J = 7.1, 1.9 Hz, 1H), 4.66 (br s, 2H), 3.87 (s, 3H), 3.86–3.78 (m, 2H), 3.64 (s, 3H), 2.83 (t, J = 6.1 Hz, 2H), 1.50 (s, 9H).

d) 4-(4-Fluoro-2-methoxyphenyl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

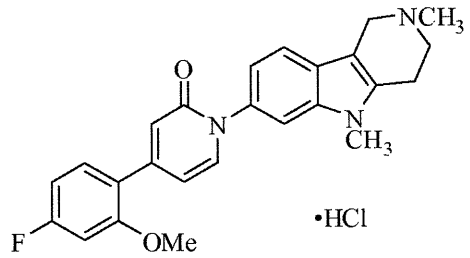


Chemical Formula: $C_{24}H_{23}ClFN_3O_2$
Exact Mass: 439.15
Molecular Weight: 439.91

tert-Butyl 7-(4-(4-fluoro-2-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (106 mg, 0.211 mmol) was deprotected according to the procedure of Example 30 (step e) to provide the free base (74 mg, 88%). The free-base (37 mg, 0.092 mmol) was converted to the hydrochloride salt according to the procedure of Example 30 (steps g) to provide the title compound (35 mg, 89%) as a yellow solid: mp 296–300 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.56 (br s, 2H), 7.64 (d, J = 7.1 Hz, 1H), 7.62–7.55 (m, 2H), 7.47 (dd, J = 8.4, 6.9 Hz, 1H), 7.12–7.06 (m, 2H), 6.90 (overlapping ddd, J = 8.4, 2.4 Hz, 1H), 6.55 (d, J = 1.6 Hz, 1H), 6.47 (dd, J = 7.1, 1.8 Hz, 1H), 4.37–4.30 (br m, 2H), 3.81 (s, 3H), 3.69 (s, 3H), 3.56–3.45 (br m, 2H), 3.10 (t, J = 5.5 Hz, 2H); ESI MS *m/z* 404 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 12.5 min.

Example 66

Preparation of 1-(2,5-Dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(4-fluoro-2-methoxyphenyl)pyridin-2(1*H*)-one hydrochloride



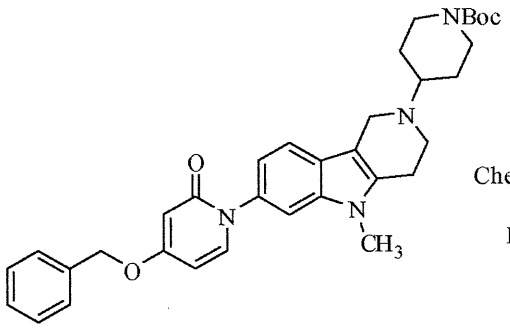
Chemical Formula: $C_{25}H_{25}ClFN_3O_2$
Exact Mass: 453.16
Molecular Weight: 453.94

4-(4-Fluoro-2-methoxyphenyl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (37 mg, 0.092 mmol) was reacted according to the procedure of Example 47 to provide the free-base. Conversion to the dihydrochloride salt using the procedure of Example 30 (step g) provided the title compound (21 mg, 52%) as a yellow solid: mp 294–298°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.83 (br s, 1H), 7.65 (d, J = 7.1 Hz, 1H), 7.61 (d, J = 1.4 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.46 (dd, J = 8.4, 6.9 Hz, 1H), 7.12–7.10 (m, 1H), 7.08 (d, J = 1.4 Hz, 1H), 6.91 (overlapping ddd, J = 8.4, 2.4 Hz, 1H), 6.55 (d, J = 1.6 Hz, 1H), 6.48 (dd, J = 7.1, 1.6 Hz, 1H), 4.62 (d, J = 12.2 Hz, 1H), 4.30 (dd, J = 14.2, 7.5 Hz, 1H), 3.86 (s, 3H), 3.80–3.76 (m, 1H), 3.75 (s, 3H), 3.52–3.42 (m, 1H), 3.24–3.15 (m, 2H), 2.79 (d, J = 4.6 Hz, 3H); ESI MS *m/z* 418 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 12.6 min.

Example 67

Preparation of 4-(Benzyloxy)-1-(5-methyl-2-(piperidin-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

a) *tert*-Butyl 4-(7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indol-2(5*H*)-yl)piperidine-1-carboxylate

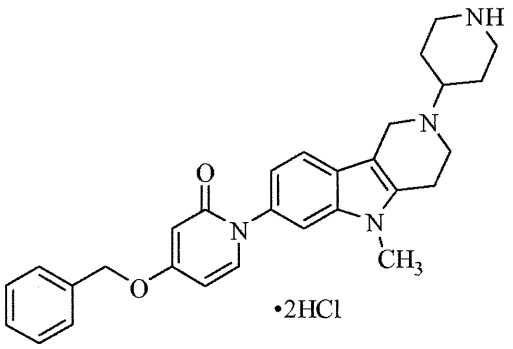


Chemical Formula: $C_{34}H_{40}N_4O_4$
Exact Mass: 568.30
Molecular Weight: 568.71

4-(Benzyloxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (100 mg, 0.26 mmol) and *tert*-butyl 4-oxopiperidine-1-carboxylate (27 mg, 0.26 mmol) were stirred in methylene chloride (1 mL) and AcOH (0.1 mL), and picoline borane complex (27 mg, 0.26 mmol) was added. After stirring for 16 h, the mixture was diluted with methylene chloride, washed with sodium carbonate solution and concentrated. The

obtained residue was purified by flash column chromatography (silica gel, (1:1 EtOAc/hexanes)/(10:1 methanol/ammonia), 10:0 to 9:1) to provide the title compound (90 mg, 61%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.36 (m, 5H), 7.32–7.30 (m, 1H), 7.32–7.27 (m, 2H), 6.99 (dd, J = 8.2, 1.6 Hz, 1H), 6.05–6.01 (m, 2H), 5.05 (s, 2H), 4.20 (s, 2H), 3.85 (s, 2H), 3.60 (s, 3H), 3.04–2.93 (m, 2H), 2.88–2.66 (m, 5H), 1.98–1.87 (m, 2H), 1.60–1.54 (m, 2H), 1.47 (s, 9H).

b) 4-(Benzyloxy)-1-(5-methyl-2-(piperidin-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

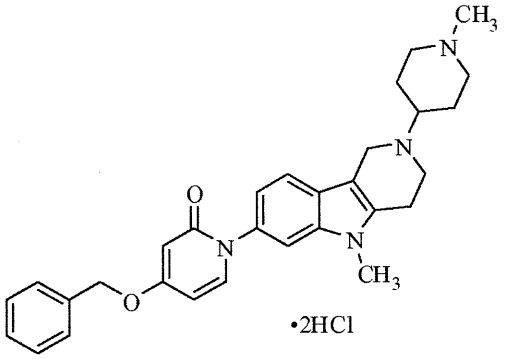


Chemical Formula: $C_{29}H_{34}Cl_2N_4O_2$
Exact Mass: 540.21
Molecular Weight: 541.51

tert-Butyl 4-(7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indol-2(5*H*)-yl)piperidine-1-carboxylate (90 mg, 0.16 mmol) was deprotected and converted to the dihydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (85 mg, 100%) as an orange solid: ^{1}H NMR (500 MHz, D_2O) δ 7.56–7.53 (m, 2H), 7.48–7.40 (m, 6H), 7.02 (dd, J = 8.4, 1.4 Hz, 1H), 6.33 (dd, J = 7.5, 2.4 Hz, 1H), 6.17 (d, J = 2.4 Hz, 1H), 5.16 (s, 2H), 4.63 (br s, 2H), 4.09–3.79 (br m, 2H), 3.69–3.53 (m, 6H), 3.26–3.23 (m, 2H), 3.14 (t, J = 12.8 Hz, 2H), 2.49 (d, J = 1.3 Hz, 2H), 2.16–2.04 (m, 2H); ESI MS *m/z* 469 $[M + H]^+$; HPLC (Method B) 98.1% (AUC), t_R = 11.4 min.

Example 68

Preparation of 4-(Benzyloxy)-1-(5-methyl-2-(1-methylpiperidin-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride



•2HCl

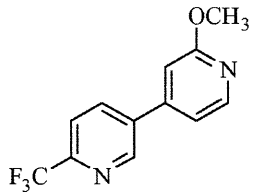
Chemical Formula: $C_{30}H_{36}Cl_2N_4O_2$
Exact Mass: 554.22
Molecular Weight: 555.54

4-(Benzyloxy)-1-(5-methyl-2-(piperidin-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (50 mg, 0.11 mmol) was methylated according to the procedure of Example 47 to provide the title compound (30 mg, 51%) as a white solid: ^{1}H NMR (500 MHz, D_2O) δ 7.56–7.52 (m, 2H), 7.48–7.38 (m, 6H), 7.02 (dd, J = 8.3, 1.6 Hz, 1H), 6.33 (dd, J = 7.5, 2.6 Hz, 1H), 6.16 (d, J = 2.5 Hz, 1H), 5.16 (s, 2H), 4.63 (s, 2H), 3.85–3.83 (m, 2H), 3.74–3.71 (m, 2H), 3.62 (s, 3H), 3.26–3.14 (m, 5H), 2.89 (s, 3H), 2.55–2.50 (m, 2H), 2.19–2.12 (m, 2H); ESI MS *m/z* 483 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 11.4 min.

Example 69

Preparation of 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2(1*H*)-one dihydrochloride

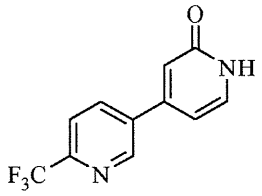
a) 2'-Methoxy-6-(trifluoromethyl)-3,4'-bipyridine



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

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 31 (step a) to provide the title compound (1.1 g, 81%) as a white solid: ESI MS *m/z* 255 [M + H].

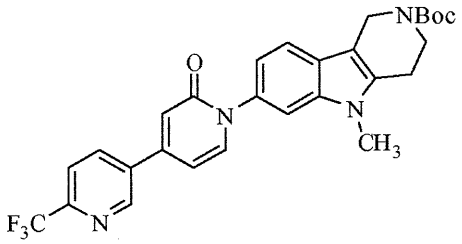
b) 4-(6-(Trifluoromethyl)pyridin-3-yl)pyridin-2(1*H*)-one



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

2'-Methoxy-6-(trifluoromethyl)-3,4'-bipyridine (1.1 g, 4.3 mmol) was reacted according to the procedure of Example 31 (step c) 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).

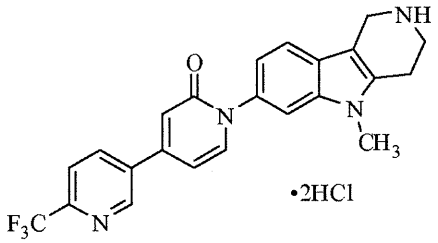
c) *tert*-Butyl 5-methyl-7-(2-oxo-4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{28}H_{27}F_3N_4O_3$
Exact Mass: 524.20
Molecular Weight: 524.53

4-(6-(Trifluoromethyl)pyridin-3-yl)pyridin-2(1*H*)-one (131 mg, 0.54 mmol) and *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (200 mg, 0.54 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (167 mg, 59%) as a green solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, J = 2.0 Hz, 1H), 8.10 (dd, J = 8.1, 1.8 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.60–7.54 (m, 2H), 7.32 (d, J = 1.9 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 1.8 Hz, 1H), 6.49 (dd, J = 7.1, 2.0 Hz, 1H), 4.66 (s, 2H), 3.85 (br m, 2H), 3.65 (s, 3H), 2.84 (s, 2H), 1.50 (s, 9H).

d) 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2(1*H*)-one dihydrochloride



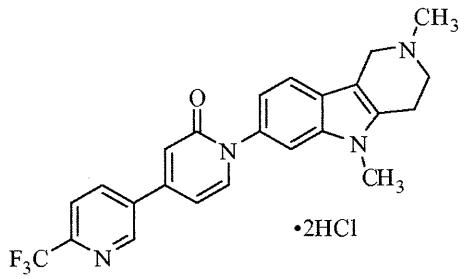
•2HCl

Chemical Formula: $C_{23}H_{21}Cl_2F_3N_4O$
Exact Mass: 496.10
Molecular Weight: 497.34

tert-Butyl 5-methyl-7-(2-oxo-4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (165 mg, 0.315 mmol) was deprotected and converted to the dihydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (40 mg, 26%) as a yellow solid: ^{1}H NMR (300 MHz, CD_3OD) δ 9.10 (d, J = 2.0 Hz, 1H), 8.41 (dd, J = 8.2, 1.7 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 7.2 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 1.6 Hz, 1H), 7.14 (dd, J = 8.3, 1.9 Hz, 1H), 7.02 (d, J = 1.6 Hz, 1H), 6.89 (dd, J = 7.1, 2.0 Hz, 1H), 4.49 (s, 2H), 3.76 (s, 3H), 3.68 (t, J = 6.2 Hz, 2H), 3.22 (t, J = 6.2 Hz, 2H); ESI MS m/z 425 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 12.3 min.

Example 70

Preparation of 1-(2,5-Dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2(1*H*)-one



•2HCl

Chemical Formula: $C_{24}H_{23}Cl_2F_3N_4O$
Exact Mass: 510.12
Molecular Weight: 511.37

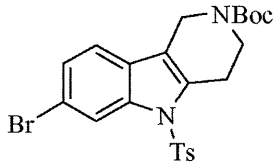
1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2(1*H*)-one (77 mg, 0.18 mmol) was reacted according to the procedure of Example 47 and converted to the dihydrochloride to provide the title compound (27 mg, 29%) as a yellow solid: mp 295–300 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 9.09 (d, J = 1.7 Hz, 1H), 8.42 (dd, J = 8.1, 2.0 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 7.1 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 1.5 Hz, 1H), 7.15 (dd, J

= 8.3, 1.8 Hz, 1H), 7.02 (d, J = 1.8 Hz, 1H), 6.89 (dd, J = 7.1, 2.0 Hz, 1H), 4.79–4.37 (br m, 2H), 3.90–3.60 (br m, 5H), 3.30 (br m, 2H), 3.14 (s, 3H); ESI MS m/z 439 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 12.4 min.

Example 71

Preparation of 1-(2,3,4,5-Tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one dihydrochloride

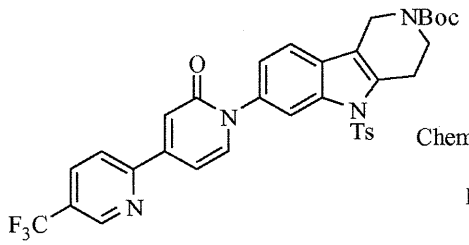
a) *tert*-Butyl 7-bromo-5-tosyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{23}H_{25}BrN_2O_4S$
Exact Mass: 504.07
Molecular Weight: 505.42

tert-Butyl 7-bromo-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (1.07 g, 3.04 mmol) was reacted according to the procedure of Example 87 (step a) to provide the title compound (1.39 g, 91%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.66 (d, J = 6.6 Hz, 2H), 7.35 (d, J = 8.2 Hz, 1H), 7.28–7.21 (m, 2H), 7.18 (d, J = 8.1 Hz, 1H), 4.47 (s, 2H), 3.77–3.65 (br m, 2H), 3.11–3.03 (br m, 2H), 2.36 (s, 3H), 1.48 (s, 9H).

b) *tert*-Butyl 7-(2-oxo-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-1(2*H*)-yl)-5-tosyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate

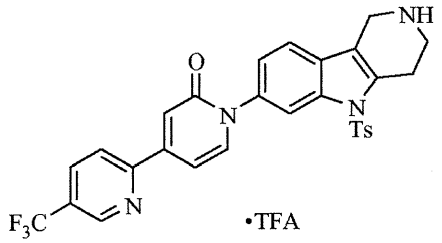


Chemical Formula: $C_{34}H_{31}F_3N_4O_5S$
Exact Mass: 664.20
Molecular Weight: 664.69

4-(5-(Trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one (131 mg, 0.545 mmol) and *tert*-butyl 7-bromo-5-tosyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (255 mg, 0.505 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (125 mg, 34%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.29 (d, J = 1.6 Hz, 1H), 8.08 (dd, J = 8.3, 1.9 Hz, 1H), 7.92 (d, J = 8.3 Hz, 1H), 7.74

(d, J = 8.3 Hz, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.33 (dd, J = 8.2, 1.6 Hz, 1H), 7.29–7.23 (m, 4H), 7.09 (dd, J = 7.2, 1.8 Hz, 1H), 4.52 (s, 2H), 3.80–3.73 (br m, 2H), 3.18–3.09 (br m, 2H), 2.35 (s, 3H), 1.50 (s, 9H).

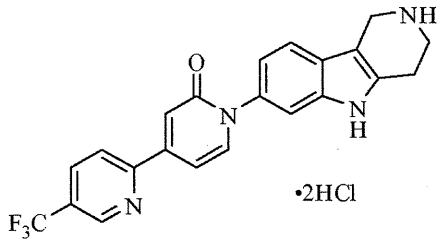
b) 1-(5-Tosyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one trifluoroacetic acid salt



Chemical Formula: $C_{31}H_{23}F_6N_4O_4S$
Exact Mass: 661.13
Molecular Weight: 661.59

tert-Butyl 7-(2-oxo-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-1(2*H*)-yl)-5-tosyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (165 mg, 0.248 mmol) was stirred in TFA (3 mL) and methylene chloride (1 mL) for 3 h. Concentration of the solution under reduced pressure provided the title compound (164 mg, 100%) as a yellow oil; ESI MS *m/z* 565 $[M + H]^+$.

c) 1-(2,3,4,5-Tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one dihydrochloride



Chemical Formula: $C_{22}H_{19}Cl_2F_3N_4O$
Exact Mass: 482.09
Molecular Weight: 483.31

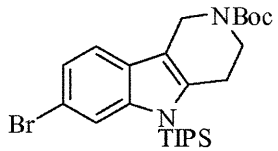
1-(5-Tosyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one trifluoroacetic acid salt (163 mg, 0.248 mmol) was deprotected and converted to the dihydrochloride salt according to the procedure of Example 106 (step b) to provide the title compound (30 mg, 25%) as an orange solid: mp 308–313 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 9.04 (s, 1H), 8.28 (dd, J = 8.3, 2.2 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 7.0 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.46 (d, J = 1.8 Hz, 1H), 7.38 (d, J = 1.8 Hz, 1H), 7.24 (dd, J = 7.1, 2.0 Hz, 1H), 7.11

(dd, J = 8.3, 2.0 Hz, 1H), 4.49 (s, 2H), 3.65 (t, J = 6.2 Hz, 2H), 3.21 (t, J = 6.2 Hz, 2H); ESI MS m/z 411 $[M + H]^+$; HPLC (Method B) 97.6% (AUC), t_R = 12.4 min.

Example 72

Preparation of 1-(2,3,4,5-Tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(6-(trifluoromethyl)pyridazin-3-yl)pyridin-2(1*H*)-one hydrochloride

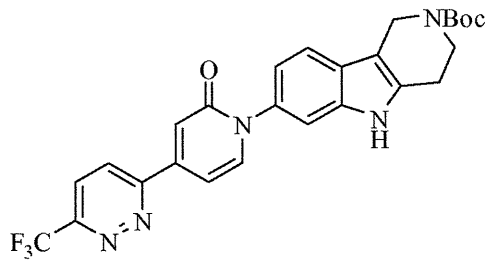
a) *tert*-Butyl 7-bromo-5-(triisopropylsilyl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{25}H_{39}BrN_2O_2Si$
Exact Mass: 506.20
Molecular Weight: 507.58

tert-Butyl 7-bromo-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (300 mg, 0.85 mmol) was dissolved in DMF (3 mL), and NaH (60% weight dispersion in mineral oil, 40 mg, 1.02 mmol) and TIPSCl (164 mg, 1.02 mmol) were added. After stirring for 1 h, the mixture was poured into water and extracted with EtOAc. Concentration of the organic extracts and purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes) provided the title compound (262 mg, 61%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.25 (d, J = 8.2 Hz, 1H), 7.19 (dd, J = 8.2, 1.4 Hz, 1H), 4.59 (s, 2H), 3.76–3.71 (br m, 2H), 2.96–2.90 (br m, 2H), 1.81–1.71 (m, 3H), 1.51 (s, 9H), 1.15 (d, J = 7.5 Hz, 18H).

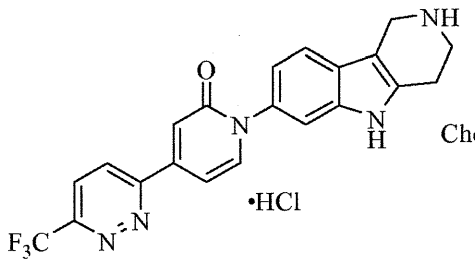
b) *tert*-Butyl 7-(2-oxo-4-(6-(trifluoromethyl)pyridazin-3-yl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{26}H_{24}F_3N_5O_3$
Exact Mass: 511.18
Molecular Weight: 511.50

tert-Butyl 7-bromo-5-(triisopropylsilyl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (260 mg, 0.51 mmol) and 4-(6-(trifluoromethyl)pyridazin-3-yl)pyridin-2(1*H*)-one (123 mg, 0.510 mmol) were reacted according to the procedure of Example 30 (step g) to provide the title compound (80 mg, 30%) as a yellow solid: ESI MS *m/z* 512 $[M + H]^+$.

c) 1-(2,3,4,5-Tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(6-(trifluoromethyl)pyridazin-3-yl)pyridin-2(1*H*)-one hydrochloride



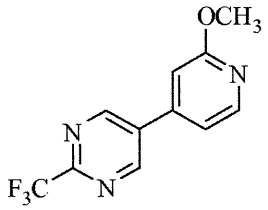
Chemical Formula: $C_{21}H_{17}ClF_3N_5O$
Exact Mass: 447.11
Molecular Weight: 447.84

tert-Butyl 7-(2-oxo-4-(6-(trifluoromethyl)pyridazin-3-yl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (80 mg, 0.15 mmol) was deprotected and converted to the hydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (30 mg, 44%) as an orange solid: mp 314–318 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 8.52 (d, J = 8.9 Hz, 1H), 8.28 (d, J = 8.9 Hz, 1H), 7.89 (d, J = 7.2 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.48 (d, J = 1.5 Hz, 1H), 7.43 (d, J = 1.5 Hz, 1H), 7.33 (dd, J = 7.2, 2.0 Hz, 1H), 7.14 (dd, J = 7.4, 2.0 Hz, 1H), 4.49 (s, 2H), 3.65 (t, J = 6.2 Hz, 2H), 3.21 (t, J = 6.2 Hz, 2H); ESI MS *m/z* 412 $[M + H]^+$; HPLC (Method B) 96.0% (AUC), t_R = 11.6 min.

Example 73

Preparation of 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)pyridin-2(1*H*)-one hydrochloride

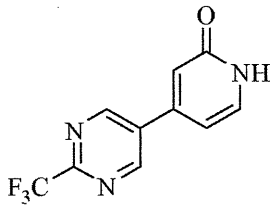
a) 5-(2-Methoxypyridin-4-yl)-2-(trifluoromethyl)pyrimidine



Chemical Formula: $C_{11}H_8F_3N_3O$
Exact Mass: 255.06
Molecular Weight: 255.20

2-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (2.0 g, 8.5 mmol) and 5-chloro-2-(trifluoromethyl)pyrimidine (2.3 g, 13 mmol) were reacted according to the procedure of Example 31 (step a) to provide the title compound (1.0 g, 46 %) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (s, 2H), 8.35 (d, J = 5.5 Hz, 1H), 7.11 (dd, J = 5.5, 1.6 Hz, 1H), 6.98 (d, J = 1.6 Hz, 1H), 4.02 (s, 3H).

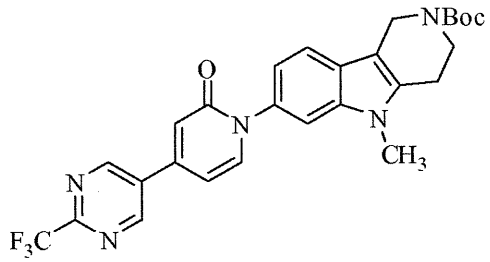
b) 4-(2-(Trifluoromethyl)pyrimidin-5-yl)pyridin-2(1*H*)-one



Chemical Formula: $C_{10}H_6F_3N_3O$
Exact Mass: 241.05
Molecular Weight: 241.17

5-(2-Methoxypyridin-4-yl)-2-(trifluoromethyl)pyrimidine (900 mg, 3.5 mmol) was reacted according to the procedure of Example 31 (step c) to provide the title compound (470 mg, 56%) as an orange solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.6 (br s, 1H), 9.41 (s, 2H), 7.61 (d, J = 6.8 Hz, 1H), 6.91 (s, 1H), 6.68 (dd, J = 6.8, 1.6 Hz, 1H).

c) *tert*-Butyl 5-methyl-7-(2-oxo-4-(2-(trifluoromethyl)pyrimidin-5-yl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate

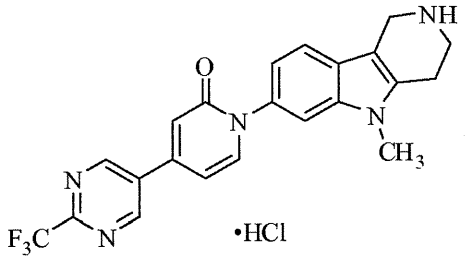


Chemical Formula: $C_{27}H_{26}F_3N_5O_3$
Exact Mass: 525.20
Molecular Weight: 525.52

4-(2-(Trifluoromethyl)pyrimidin-5-yl)pyridin-2(1*H*)-one (100 mg, 0.42 mmol) and *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (116

mg, 0.32 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (41 mg, 24%) as a yellow oil: ESI MS *m/z* 526 $[M + H]^+$.

d) 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)pyridin-2(1*H*)-one hydrochloride



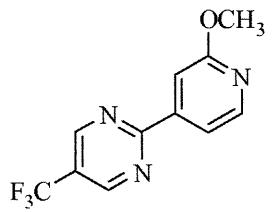
Chemical Formula: $C_{22}H_{19}ClF_3N_5O$
Exact Mass: 461.12
Molecular Weight: 461.87

tert-Butyl 5-methyl-7-(2-oxo-4-(2-(trifluoromethyl)pyrimidin-5-yl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (41 mg, 0.078 mmol) was deprotected and converted to the hydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (29 mg, 80%) as a yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.51 (s, 2H), 9.37 (br s, 2H), 7.90 (d, J = 7.2 Hz, 1H), 7.62–7.60 (m, 2H), 7.13 (d, J = 1.9 Hz, 1H), 7.10 (dd, J = 8.3, 1.7 Hz, 1H), 6.88 (dd, J = 7.1, 2.0 Hz, 1H), 4.38–4.34 (br m, 2H), 3.70 (s, 3H), 3.56–3.50 (br m, 2H), 3.11 (t, J = 5.8 Hz, 2H); ESI MS *m/z* 426 $[M + H]^+$; HPLC (Method B) >100% (AUC), t_R = 12.2 min.

Example 74

Preparation of 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyrimidin-2-yl)pyridin-2(1*H*)-one hydrochloride

a) 2-(2-Methoxypyridin-4-yl)-5-(trifluoromethyl)pyrimidine

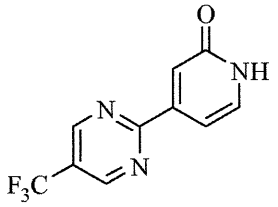


Chemical Formula: $C_{11}H_8F_3N_3O$
Exact Mass: 255.06
Molecular Weight: 255.20

2-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.66 g, 7.06 mmol) and 2-chloro-5-(trifluoromethyl)pyrimidine (1.3 g, 7.1 mmol) were reacted

according to the procedure of Example 31 (step a) to provide the title compound (307 mg, 16%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (s, 2H), 8.34 (d, J = 5.3 Hz, 1H), 7.89 (dd, J = 5.3, 1.4 Hz, 1H), 7.81 (s, 1H), 4.01 (s, 3H).

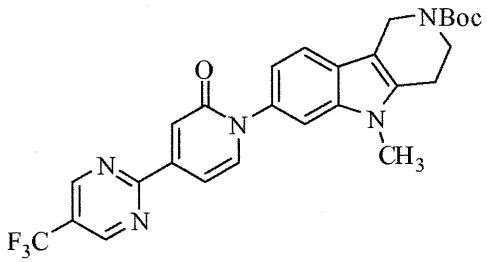
b) 4-(5-(Trifluoromethyl)pyrimidin-2-yl)pyridin-2(1*H*)-one



Chemical Formula: $C_{10}H_6F_3N_3O$
Exact Mass: 241.05
Molecular Weight: 241.17

2-(2-Methoxypyridin-4-yl)-5-(trifluoromethyl)pyrimidine (400 mg, 1.56 mmol) was reacted according to the procedure of Example 31 (step c) to provide the title compound (200 mg, 63 %) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.9 (br s, 1H), 9.43 (s, 2H), 7.58 (d, J = 6.8 Hz, 1H), 7.34 (s, 1H), 7.06 (dd, J = 6.8, 1.7 Hz, 1H).

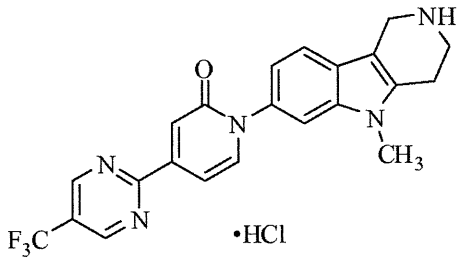
c) *tert*-Butyl 5-methyl-7-(2-oxo-4-(5-(trifluoromethyl)pyrimidin-2-yl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{27}H_{26}F_3N_5O_3$
Exact Mass: 525.20
Molecular Weight: 525.52

4-(5-(Trifluoromethyl)pyrimidin-2-yl)pyridin-2(1*H*)-one (100 mg, 0.34 mmol) and *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5H)-carboxylate (124 mg, 0.339 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (70 mg, 39%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.11 (s, 2H), 7.86 (s, 1H), 7.59–7.53 (m, 2H), 7.38 (s, 1H), 7.28–7.26 (m, 1H), 7.08 (d, J = 8.4 Hz, 1H), 4.89–4.63 (br m, 2H), 3.90–3.80 (br m, 2H), 3.65 (s, 3H), 2.88–2.79 (br m, 2H), 1.50 (s, 9H).

d) 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyrimidin-2-yl)pyridin-2(1*H*)-one hydrochloride



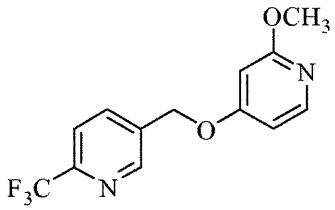
Chemical Formula: $C_{22}H_{19}ClF_3N_5O$
Exact Mass: 461.12
Molecular Weight: 461.87

tert-Butyl 5-methyl-7-(2-oxo-4-(5-(trifluoromethyl)pyrimidin-2-yl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (70 mg, 0.13 mmol) was deprotected and converted to the hydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (51 mg, 87%) as a yellow solid: mp 301–309 °C; ^{1}H NMR (500 MHz, DMSO–d_6) δ 9.48 (s, 2H), 9.37 (br s, 2H), 7.89 (d, J = 7.2 Hz, 1H), 7.65 (d, J = 1.6 Hz, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.50 (d, J = 1.6 Hz, 1H), 7.21 (dd, J = 7.6, 1.9 Hz, 1H), 7.12 (dd, J = 8.3, 1.8 Hz, 1H), 4.41–4.31 (br m, 2H), 3.71 (s, 3H), 3.51–3.48 (br m, 2H), 3.10 (t, J = 5.6 Hz, 2H); ESI MS *m/z* 426 $[M + H]^+$; HPLC (Method B) 97.9% (AUC), t_R = 12.6 min.

Example 75

Preparation of 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-((6-(trifluoromethyl)pyridin-3-yl)methoxy)pyridin-2(1*H*)-one hydrochloride

a) 2-Methoxy-4-((6-(trifluoromethyl)pyridin-3-yl)methoxy)pyridine

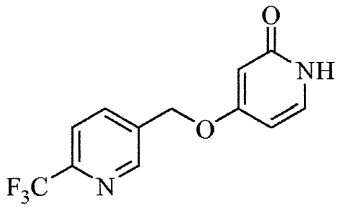


Chemical Formula: $C_{13}H_{11}F_3N_2O_2$
Exact Mass: 284.08
Molecular Weight: 284.23

4-BromoBromo-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).

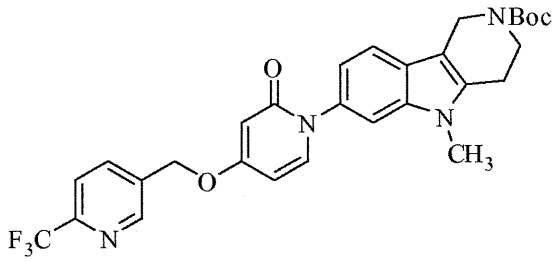
b) 4-((6-(Trifluoromethyl)pyridin-3-yl)methoxy)pyridin-2(1*H*)-one



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

2-Methoxy-4-((6-(trifluoromethyl)pyridin-3-yl)methoxy)pyridine (3.19 g, 11.2 mmol) was reacted according to the procedure of Example 31 (step c) 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) *tert*-Butyl 5-methyl-7-(2-oxo-4-((6-(trifluoromethyl)pyridin-3-yl)methoxy)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate

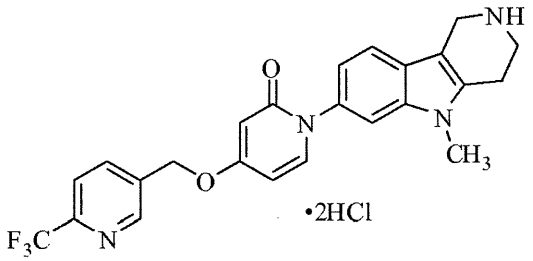


Chemical Formula: $C_{29}H_{29}F_3N_4O_4$
Exact Mass: 554.21
Molecular Weight: 554.56

4-((6-(Trifluoromethyl)pyridin-3-yl)methoxy)pyridin-2(1*H*)-one (177 mg, 0.655 mmol) and *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(*5H*)-carboxylate (200 mg, 0.54 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (120 mg, 40%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.28 (m, 1H), 7.01 (d, J = 8.1 Hz, 1H), 6.06–6.04 (m,

2H), 5.16 (s, 2H), 4.65–4.60 (br m, 2H), 3.89–3.79 (br m, 2H), 3.63 (s, 3H), 2.87–2.78 (br m, 2H), 1.50 (s, 9H).

d) 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-((6-(trifluoromethyl)pyridin-3-yl)methoxy)pyridin-2(1*H*)-one dihydrochloride



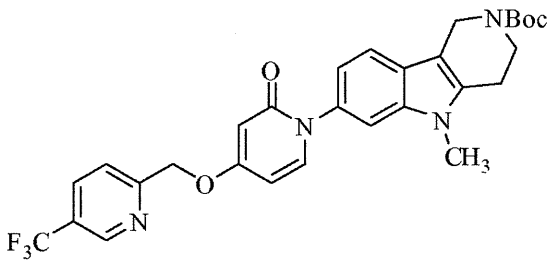
Chemical Formula: $C_{24}H_{23}Cl_2F_3N_4O_2$
Exact Mass: 526.12
Molecular Weight: 527.37

tert-Butyl 5-methyl-7-(2-oxo-4-((6-(trifluoromethyl)pyridin-3-yl)methoxy)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (120 mg, 0.21 mmol) was deprotected and converted to the dihydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (90 mg, 81%) as a white solid: mp 286–291 °C; ^{1}H NMR (500 MHz, DMSO–d_6) δ 9.54 (br s, 2H), 8.89 (s, 1H), 8.19 (dd, J = 7.9, 1.4 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.50 (d, J = 1.7 Hz, 1H), 6.98 (dd, J = 8.3, 1.8 Hz, 1H), 6.15 (dd, J = 7.5, 2.7 Hz, 1H), 6.02 (d, J = 2.7 Hz, 1H), 5.35 (s, 2H), 4.35–4.30 (br m, 2H), 3.67 (s, 3H), 3.53–3.47 (br m, 2H), 3.09 (t, J = 5.8 Hz, 2H); ESI MS *m/z* 455 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 12.7 min.

Example 76

Preparation of 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-((5-(trifluoromethyl)pyridin-2-yl)methoxy)pyridin-2(1*H*)-one

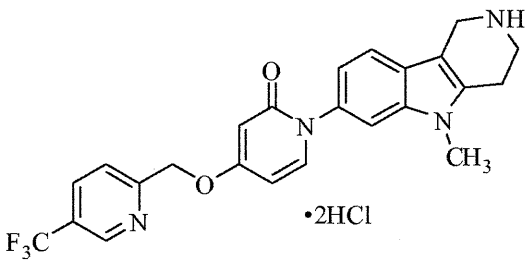
a) *tert*-Butyl 5-methyl-7-(2-oxo-4-((5-(trifluoromethyl)pyridin-2-yl)methoxy)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{29}H_{29}F_3N_4O_4$
Exact Mass: 554.21
Molecular Weight: 554.56

2-(Bromomethyl)-5-(trifluoromethyl)pyridine (140 mg, 0.58 mmol), *tert*-butyl 7-(4-hydroxy-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (230 mg, 0.58 mmol) and K_2CO_3 (160 mg, 1.16 mmol) were stirred in acetonitrile/DMF (3 mL/0.5mL) for 72 h. The mixture was diluted with methylene chloride, washed with water and concentrated to provide the title compound (96 mg, 29%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.00 (dd, J = 8.2, 2.0 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.51 (d, J = 8.2 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.28–7.26 (m, 1H), 7.00 (d, J = 7.7 Hz, 1H), 6.12 (dd, J = 7.6, 2.7 Hz, 1H), 6.04 (d, J = 2.7 Hz, 1H), 5.26 (s, 2H), 4.63–4.58 (br m, 2H), 3.87–3.76 (br m, 2H), 3.63 (s, 3H), 2.86–2.76 (br m, 2H), 1.50 (s, 9H).

b) 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-((5-(trifluoromethyl)pyridin-2-yl)methoxy)pyridin-2(1*H*)-one dihydrochloride



Chemical Formula: $C_{24}H_{23}Cl_2F_3N_4O_2$
Exact Mass: 526.12
Molecular Weight: 527.37

tert-Butyl 5-methyl-7-(2-oxo-4-((5-(trifluoromethyl)pyridin-2-yl)methoxy)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (90 mg, 0.16 mmol) was deprotected and converted to the dihydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (76 mg, 90%) as a white solid: mp 296–300 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 8.93 (s, 1H), 8.23 (dd, J = 8.2, 2.1 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 1.7 Hz, 1H), 7.06 (dd, J = 8.3, 1.8 Hz, 1H), 6.47 (dd, J = 7.5, 2.7 Hz, 1H), 6.20 (d, J =

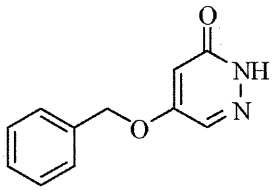
2.6 Hz, 1H), 5.42 (s, 2H), 4.48 (s, 2H), 3.73 (s, 3H), 3.67 (t, J = 6.1 Hz, 2H), 3.20 (t, J = 6.1 Hz, 2H); ESI MS *m/z* 455 $[M + H]^+$; HPLC (Method B) 97.6% (AUC), t_R = 12.6 min.

Example 77

Preparation of 5-(Benzyloxy)-2-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridazin-3(2*H*)-one hydrochloride

a) 5-(Benzyloxy)pyridazin-3(2*H*)-one

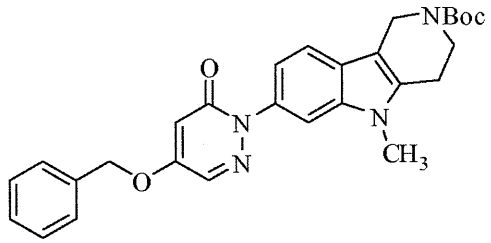
CAS Registry Number 1008517-73-4



Chemical Formula: $C_{11}H_{10}N_2O_2$
Exact Mass: 202.07
Molecular Weight: 202.21

This compound was prepared in accordance with the procedure of Stenkamp et al., WO 2008/022979.

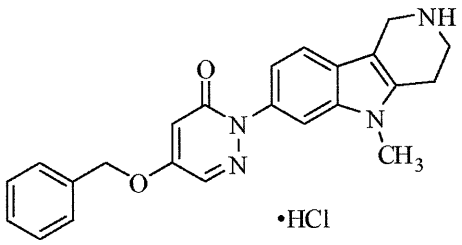
b) *tert*-Butyl 7-(4-(benzyloxy)-6-oxopyridazin-1(6*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{28}H_{30}N_4O_4$
Exact Mass: 486.23
Molecular Weight: 486.56

5-(Benzyloxy)pyridazin-3(2*H*)-one (100 mg, 0.5 mmol) and *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (180 mg, 0.5 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (106 mg, 43%) as a solid: ESI MS *m/z* 487 $[M + H]^+$.

c) 5-(Benzyloxy)-2-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridazin-3(2*H*)-one hydrochloride



Chemical Formula: $C_{23}H_{23}ClN_4O_2$
Exact Mass: 422.15
Molecular Weight: 422.91

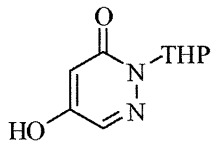
tert-Butyl 7-(4-(benzyloxy)-6-oxopyridazin-1(6*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (100 mg, 0.2 mmol) was deprotected and converted to the hydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (30 mg, 35%) as a white solid: mp 261–265 °C; ^{1}H NMR (500 MHz, DMSO–d_6) δ 9.23 (s, 2H), 7.96 (d, J = 2.8 Hz, 1H), 7.59 (d, J = 1.6 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.51–7.48 (m, 2H), 7.46–7.42 (m, 2H), 7.40 (d, J = 7.5 Hz, 1H), 7.13 (dd, J = 8.4, 1.7 Hz, 1H), 6.51 (d, J = 2.8 Hz, 1H), 5.22 (s, 2H), 4.34 (s, 2H), 3.69 (s, 3H), 3.52 (t, J = 5.8 Hz, 2H), 3.09 (t, J = 5.8 Hz, 2H); ESI MS *m/z* 387 $[M + H]^+$; HPLC (Method B) 97.7% (AUC), t_R = 12.8 min.

Example 78

Preparation of 2-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-5-(4-(trifluoromethyl)phenyl)pyridazin-3(2*H*)-one hydrochloride

a) 5-Hydroxy-2-(tetrahydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one

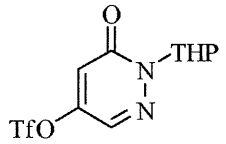
CAS Registry Number 1008517-74-5



Chemical Formula: $C_9H_{12}N_2O_3$
Exact Mass: 196.08
Molecular Weight: 196.20

This compound was prepared in accordance with the procedure of Stenkamp et al., WO 2008/022979.

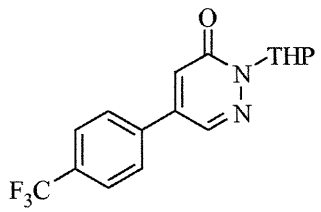
b) 6-Oxo-1-(tetrahydro-2*H*-pyran-2-yl)-1,6-dihydropyridazin-4-yl trifluoromethanesulfonate



Chemical Formula: $C_{10}H_{11}F_3N_2O_5S$
Exact Mass: 328.03
Molecular Weight: 328.26

5-Hydroxy-2-(tetrahydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one (2.4 g, 13 mmol) dissolved in methylene chloride (75 mL) and cooled to 0 °C. Triethylamine (3.5 mL, 25 mmol) and Tf_2O (2.3 mL, 14 mmol) were added and the mixture stirred for a further 2.5 h. Saturated $NaHCO_3$ solution was added and the organic phase removed, dried over Na_2SO_4 and concentrated. Purification by flash column chromaotgraphy (silica gel, EtOAc/hexanes) provided the title compound (2.47 g, 60%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 2.8 Hz, 1H), 6.86 (d, J = 2.7 Hz, 1H), 6.01 (dd, J = 10.2, 2.2 Hz, 1H), 4.15–4.12 (m, 1H), 3.75 (dt, J = 11.6, 2.5 Hz, 1H), 2.18–2.02 (m, 2H), 1.78–1.66 (m, 3H), 1.62–1.55 (m, 1H).

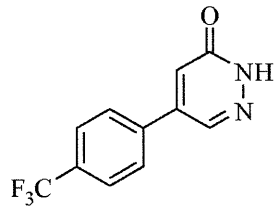
c) 2-(Tetrahydro-2*H*-pyran-2-yl)-5-(4-(trifluoromethyl)phenyl)pyridazin-3(2*H*)-one



Chemical Formula: $C_{16}H_{15}F_3N_2O_2$
Exact Mass: 324.11
Molecular Weight: 324.30

6-Oxo-1-(tetrahydro-2*H*-pyran-2-yl)-1,6-dihydropyridazin-4-yl trifluoromethanesulfonate (2.47 g, 7.5 mmol) and 4-trifluoromethylphenylboronic acid (2.56 g, 15 mmol) were reacted according to the procedure of Example 31 (step a) to provide the title compound (500 mg, 20%) as a white solid: ESI MS *m/z* 325 $[M + H]^+$.

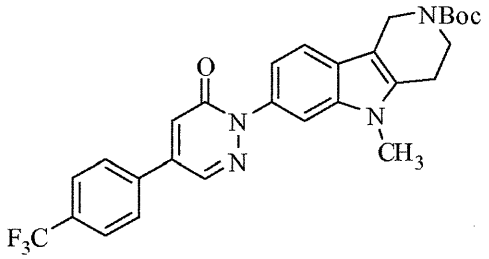
d) 5-(4-(Trifluoromethyl)phenyl)pyridazin-3(2*H*)-one



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

2-(Tetrahydro-2*H*-pyran-2-yl)-5-(4-(trifluoromethyl)phenyl)pyridazin-3(2*H*)-one (500 mg, 1.54 mmol) was reacted according to the procedure of Example 31 (step c) to provide the title compound (100 mg, 27%) as a solid: ESI MS *m/z* 241 $[M + H]^+$.

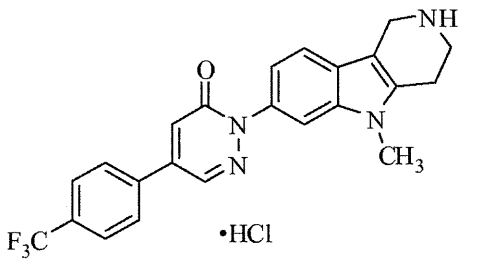
e) *tert*-Butyl 5-methyl-7-(6-oxo-4-(4-(trifluoromethyl)phenyl)pyridazin-1(6*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{28}H_{27}F_3N_4O_3$
Exact Mass: 524.20
Molecular Weight: 524.53

5-(4-(Trifluoromethyl)phenyl)pyridazin-3(2*H*)-one (100 mg, 0.41 mmol) and *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (151 mg, 0.41 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (65 mg, 30%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 1.6 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 6.9 Hz, 1H), 7.26–7.24 (m, 1H), 4.62 (s, 2H), 3.89–3.80 (br m, 2H), 3.66 (s, 3H), 2.84 (br m, 2H), 1.51 (s, 9H).

f) 2-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-5-(4-(trifluoromethyl)phenyl)pyridazin-3(2*H*)-one hydrochloride



Chemical Formula: $C_{23}H_{20}ClF_3N_4O$
Exact Mass: 460.13
Molecular Weight: 460.88

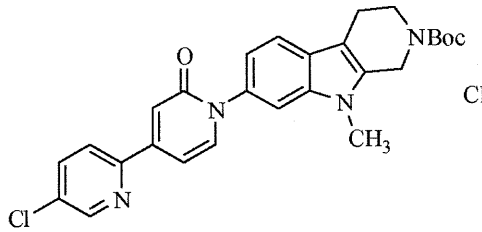
tert-Butyl 5-methyl-7-(6-oxo-4-(4-(trifluoromethyl)phenyl)pyridazin-1(6*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (65 mg, 0.12 mmol) was deprotected and converted to the hydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (47 mg, 80%) as an orange solid: mp

315–320 °C; ^{1}H NMR (300 MHz, DMSO–d_6) δ 9.37 (s, 2H), 8.56 (d, J = 2.2 Hz, 1H), 8.13 (d, J = Hz, 2H), 7.93 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 1.6 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.4, 1.8 Hz, 1H), 4.36 (s, 2H), 3.70 (s, 3H), 3.58–3.48 (br m, 2H), 3.11 (t, J = 5.7 Hz, 2H); ESI MS m/z 425 $[M + H]^+$; HPLC (Method A) 96.6% (AUC), t_R = 15.7 min.

Example 79

Preparation of 4-(5-Chloropyridin-2-yl)-1-(9-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride:

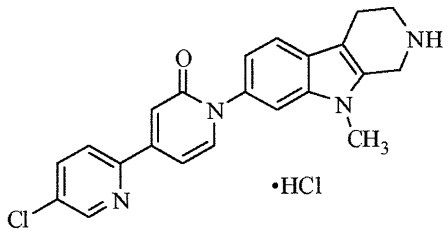
a) *tert*-Butyl 7-(4-(5-chloropyridin-2-yl)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{27}H_{27}ClN_4O_3$
Exact Mass: 490.18
Molecular Weight: 490.98

tert-Butyl 7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (200 mg, 0.549 mmol) and 4-(5-chloropyridin-2-yl)pyridin-2(1*H*)-one (87 mg, 0.42 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (97 mg, 47%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, J = 2.0 Hz, 1H), 7.80 (dd, J = 8.5, 2.3 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.55 (overlapping dd, J = 7.4 Hz, 2H), 7.36 (s, 1H), 7.18 (d, J = 1.7 Hz, 1H), 7.08 (dd, J = 8.3, 1.6 Hz, 1H), 7.00 (dd, J = 7.1, 1.8 Hz, 1H), 4.65 (s, 2H), 3.76 (br m, 2H), 3.65 (s, 3H), 2.82 (br m, 2H), 1.52 (s, 9H).

b) 4-(5-Chloropyridin-2-yl)-1-(9-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

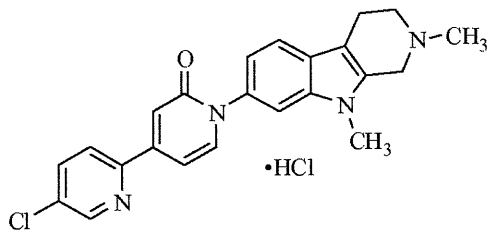


Chemical Formula: $C_{22}H_{20}Cl_2N_4O$
Exact Mass: 426.10
Molecular Weight: 427.33

tert-Butyl 7-(4-(5-chloropyridin-2-yl)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(5*H*)-carboxylate (97 mg, 0.20 mmol) was deprotected and converted to the hydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound as a orange solid (68 mg, 88%): mp 310–320 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.73 (dd, J = 2.4, 0.6 Hz, 1H), 8.03 (dd, J = 8.5, 0.5 Hz, 1H), 8.00 (dd, J = 8.5, 2.4 Hz, 1H), 7.80 (d, J = 7.1 Hz, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 1.7 Hz, 1H), 7.31 (d, J = 1.7 Hz, 1H), 7.19 (dd, J = 7.1, 2.0 Hz, 1H), 7.14 (dd, J = 8.4, 1.8 Hz, 1H), 4.56 (s, 2H), 3.74 (s, 3H), 3.61 (t, J = 6.1 Hz, 2H), 3.14 (t, J = 6.1 Hz, 2H); ESI MS *m/z* 391 $[M + H]^+$; HPLC (Method A) >99% (AUC), t_R = 11.9 min.

Example 80

Preparation of 1-(2,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(5-chloropyridin-2-yl)pyridin-2(1*H*)-one hydrochloride



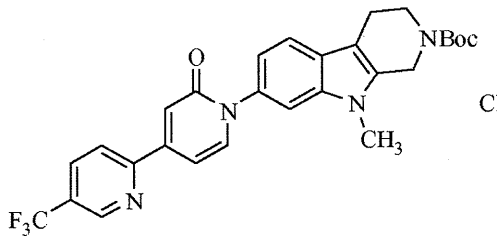
Chemical Formula: $C_{23}H_{22}Cl_2N_4O$
Exact Mass: 440.12
Molecular Weight: 441.35

4-(5-Chloropyridin-2-yl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one (104 mg, 0.266 mmol) was reacted following the procedure of Example 47 to provide the title compound (75 mg, 70%) as a yellow solid: mp 283–295°C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.73 (d, J = 2.3 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H) 7.99 (dd, J = 8.5, 2.3 Hz, 1H), 7.79 (d, J = 7.2 Hz, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.57 (s, 1H), 7.31 (d, J = 1.6 Hz, 1H), 7.19 (dd, J = 7.1, 1.8 Hz, 1H), 7.15 (dd, J = 8.3, 1.7 Hz, 1H), 4.65 (br s, 2H), 3.74 (m, 5H), 3.21 (t, J = 5.7 Hz, 2H), 3.17 (s, 3H); ESI MS *m/z* 405 $[M + H]^+$; HPLC (Method B) 98.7% (AUC), t_R = 12.1 min.

Example 81

Preparation of 4-(5-(Trifluoromethyl)pyridin-2-yl)-1-(9-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride:

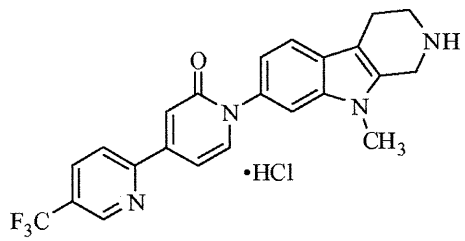
a) *tert*-Butyl 9-methyl-7-(2-oxo-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{28}H_{27}F_3N_4O_3$
Exact Mass: 524.20
Molecular Weight: 524.53

tert-Butyl 7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (100 mg, 0.417 mmol) and 4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1H)-one (197 mg, 0.542 mmol), were reacted following the procedure of Example 30 (step g) to provide the title compound (168 mg, 66%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.07 (dd, J = 8.3, 1.9 Hz, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.58 (overlapping dd, J = 7.1 Hz, 2H), 7.37 (s, 1H), 7.26 (d, 1H under solvent), 7.08 (dd, J = 8.3, 1.7 Hz, 1H), 7.03 (dd, J = 7.1, 1.9 Hz, 1H), 4.66 (s, 2H), 3.76 (br m, 2H), 3.65 (s, 3H), 2.82 (br m, 2H), 1.52 (s, 9H).

b) 4-(5-(Trifluoromethyl)pyridin-2-yl)-1-(9-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



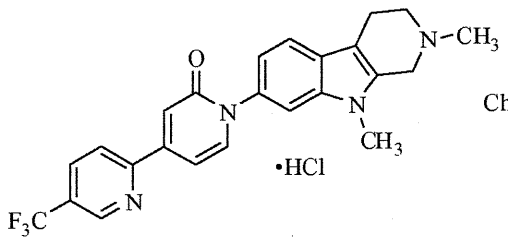
Chemical Formula: $C_{23}H_{20}ClF_3N_4O$
Exact Mass: 460.13
Molecular Weight: 460.88

tert-Butyl 9-methyl-7-(2-oxo-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (168 mg, 0.321 mmol) was deprotected and converted to the hydrochloride salt according to the procedure of Example

30 (steps e and g) to provide the title compound as an orange solid (73 mg, 54%): mp 305–315 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 9.05 (s, 1H), 8.28 (dd, J = 8.3, 2.2 Hz, 1H), 8.22 (d, J = 8.3, Hz, 1H), 7.84 (d, J = 7.1 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 1.8 Hz, 1H), 7.40 (d, J = 1.8 Hz, 1H), 7.25 (dd, J = 7.2, 2.0 Hz, 1H), 7.15 (dd, J = 8.4, 1.8 Hz, 1H), 4.57 (s, 2H), 3.74 (s, 3H), 3.62 (t, J = 6.1 Hz, 2H), 3.15 (t, J = 5.9 Hz, 2H); ESI MS m/z 425 $[M + H]^+$; HPLC (Method A) 96.4% (AUC), t_R = 12.6 min.

Example 82

Preparation of 1-(2,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(5-(trifluoromethyl) pyridin-2-yl)pyridin-2(1*H*)-one hydrochloride:



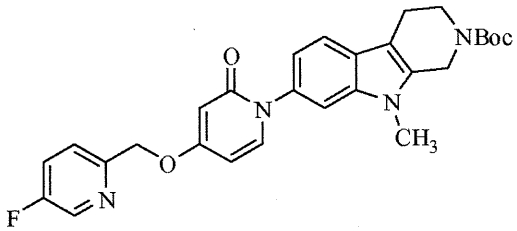
Chemical Formula: $C_{24}H_{22}ClF_3N_4O$
Exact Mass: 474.14
Molecular Weight: 474.91

4-(5-(Trifluoromethyl)pyridin-2-yl)-1-(9-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one (125 mg, 0.294 mmol) was reacted following the procedure of Example 47 to provide the title compound (97.9 g, 78%) as a yellow solid: mp 280–290°C; ^{1}H NMR (500 MHz, CD_3OD) δ 9.05 (s, 1H), 8.28 (dd, J = 8.3, 2.1 Hz, 1H) 8.22 (d, J = 8.4, Hz, 1H), 7.84 (d, J = 7.1 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.59 (d, J = 1.6, 1H), 7.40 (d, J = 1.7 Hz, 1H), 7.25 (dd, J = 7.2, 1.9 Hz, 1H), 7.16 (dd, J = 8.3, 1.8 Hz, 1H), 4.87 (s, 1H), 4.51 (s, 1H), 3.87 (s, 1H), 3.75 (br s, 3H), 3.55 (br s, 1H), 3.21–3.17 (m, 5H); ESI MS m/z 439 $[M + H]^+$; HPLC (Method B) 98.3% (AUC), t_R = 12.8 min.

Example 84

Preparation of 4-((5-Fluoropyridin-2-yl)methoxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride:

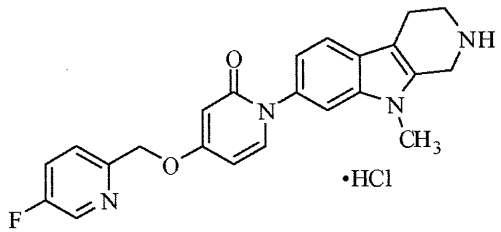
a) *tert*-Butyl 7-(4-((5-fluoropyridin-2-yl)methoxy)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{28}H_{29}FN_4O_4$
Exact Mass: 504.22
Molecular Weight: 504.55

tert-Butyl 7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (306 mg, 0.840 mmol) and 4-(4-fluorobenzyloxy)pyridin-2(1*H*)-one (142 mg, 0.640 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (157 mg, 49%) as a yellow/green solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, J = 2.0 Hz, 1H), 7.54–7.46 (m, 3H), 7.34–7.28 (m, 2H), 7.01 (dd, J = 8.2, 1.8 Hz, 1H), 6.10 (d, J = 2.7 Hz, 1H), 6.07 (s, 1H), 5.17 (s, 2H), 4.63 (br m, 2H), 3.74 (br m, 2H), 3.62 (s, 3H), 2.80 (br m, 2H), 1.51 (s, 9H).

b) 4-((5-Fluoropyridin-2-yl)methoxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

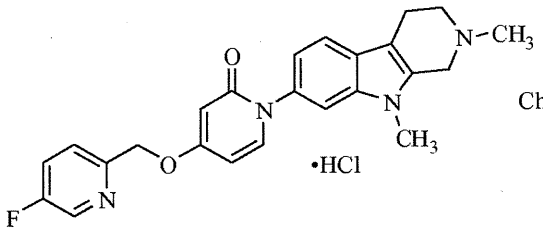


Chemical Formula: $C_{23}H_{22}ClFN_4O_2$
Exact Mass: 440.14
Molecular Weight: 440.90

tert-Butyl 7-(4-((5-fluoropyridin-2-yl)methoxy)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (157 mg, 0.312 mmol) was deprotected and converted to the hydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound as a yellow solid (72.7 mg, 54%): mp 285–295 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.51 (s, 1H), 7.72–7.59 (m, 4H), 7.46 (d, J = 1.0 Hz, 1H), 7.05 (dd, J = 8.3, 1.5 Hz, 1H), 6.32 (dd, J = 7.6, 2.6 Hz, 1H), 7.05 (d, J = 2.6 Hz, 1H), 5.26 (s, 2H), 4.54 (s, 2H), 3.71 (s, 3H), 3.60 (t, J = 6.0 Hz, 2H), 3.12 (t, J = 5.8 Hz, 2H); ESI MS m/z 405 $[M + H]^+$; HPLC (Method B) 98.3% (AUC), t_R = 12.0 min.

Example 85

Preparation of 1-(2,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-((5-fluoropyridin-2-yl)methoxy)pyridin-2(1*H*)-one hydrochloride



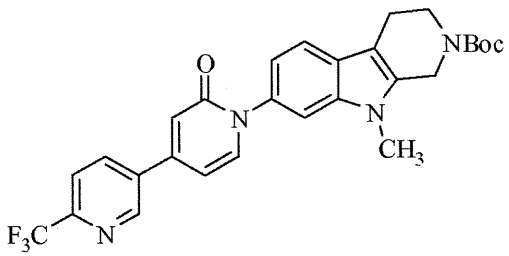
Chemical Formula: $C_{24}H_{24}ClFN_4O_2$
Exact Mass: 454.16
Molecular Weight: 454.92

4-((5-Fluoropyridin-2-yl)methoxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one (76 mg, 0.19 mmol) was reacted following the procedure of Example 47 to provide the title compound (61 mg, 79%) as a yellow solid: mp 287–300 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.51 (d, J = 2.6 Hz, 1H), 7.72–7.59 (m, 4H), 7.47 (s, 1H), 7.06 (dd, J = 8.3, 1.7 Hz, 1H), 6.32 (dd, J = 7.6, 2.6 Hz, 1H), 6.13 (d, J = 2.6 Hz, 1H), 5.26 (s, 2H), 4.68 (m, 2H), 3.71 (m, 5H), 3.18 (t, J = 5.9 Hz, 2H), 3.15 (s, 3H); ESI MS *m/z* 419 $[M + H]^+$; HPLC (Method B) 98.4% (AUC), t_R = 11.1 min.

Example 86

Preparation of 1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2(1*H*)-one hydrochloride

a) *tert*-Butyl 9-methyl-7-(2-oxo-4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate

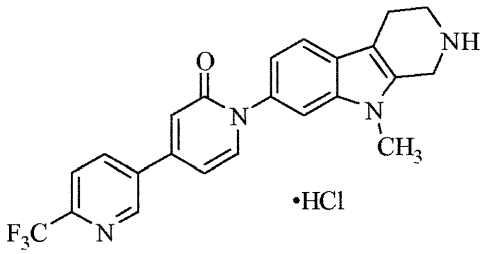


Chemical Formula: $C_{28}H_{27}F_3N_4O_3$
Exact Mass: 524.20
Molecular Weight: 524.53

4-(6-(Trifluoromethyl)pyridin-3-yl)pyridin-2(1*H*)-one (145 mg, 0.604 mmol) and *tert*-butyl 7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (200 mg, 0.549 mmol) were coupled following the procedure of Example 30 (step g) to provide the title compound (129 mg, 45%) as a yellow/green solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ

9.00 (s, 1H), 8.10 (dd, J = 8.1, 2.0 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.60–7.57 (m, 2H), 7.36 (s, 1H), 7.08 (dd, J = 8.3, 1.8 Hz, 1H), 6.93 (d, J = 1.8 Hz, 1H), 6.49 (dd, J = 7.1, 2.0 Hz, 1H), 4.66 (br m, 2H), 3.76 (br m, 2H), 3.66 (s, 3H), 2.82 (br m, 2H), 1.52 (s, 9H).

b) 1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2(1*H*)-one hydrochloride



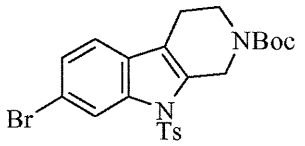
Chemical Formula: $C_{23}H_{20}ClF_3N_4O$
Exact Mass: 460.13
Molecular Weight: 460.88

tert-Butyl 9-methyl-7-(2-oxo-4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (129 mg, 0.25 mmol) was deprotected and converted to the hydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (67 mg, 58%) as a yellow/brown solid: mp 315–320 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 9.10 (d, J = 1.9 Hz, 1H), 8.41 (dd, J = 8.2, 2.2 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H), 7.85 (d, J = 7.0 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.57 (d, J = 1.7 Hz, 1H), 7.15 (dd, J = 8.3, 1.8 Hz, 1H), 7.03 (d, J = 1.8 Hz, 1H), 6.89 (dd, J = 7.1, 2.0 Hz, 1H), 4.57 (br m, 2H), 3.75 (s, 3H), 3.62 (br m, 2H), 3.15 (br m, 2H); ESI MS m/z 425 $[M + H]^+$; HPLC (Method B) 97.4% (AUC), t_R = 12.3 min.

Example 87

Preparation of 1-(2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one hydrochloride

a) *tert*-Butyl 7-bromo-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate

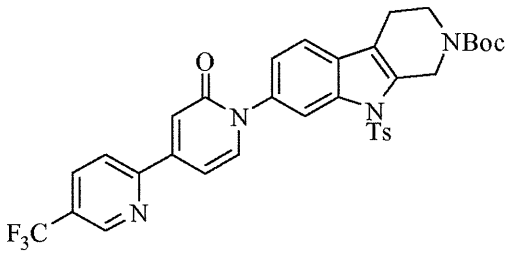


Chemical Formula: $C_{23}H_{25}BrN_2O_4S$
Exact Mass: 504.07
Molecular Weight: 505.42

6 N NaOH solution (6 mL), $(Bu_4N)_2SO_4$ (50% wt. solution in H_2O, 0.20 mL), and TsCl (646 mg, 3.39 mmol) were added to a suspension of *tert*-butyl 7-bromo-3,4-dihydro-

1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (991 mg, 2.82 mmol) in toluene (20 mL) and the resulting suspension was stirred at 25 °C for 1.5 h. H_2O and EtOAc were added to the suspension and the phases were separated. The organic phase was washed with H_2O, dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound (1.285 g, 90%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, J = 1.5 Hz, 1H), 7.78–7.66 (m, 2H), 7.36 (dd, J = 8.4, 1.5 Hz, 1H), 7.25–7.21 (m, 2H), 7.21–7.13 (m, 1H), 4.92–4.81 (m, 2H), 3.74–3.63 (m, 2H), 2.70–2.61 (m, 2H), 2.37 (s, 3H), 1.50 (s, 9H).

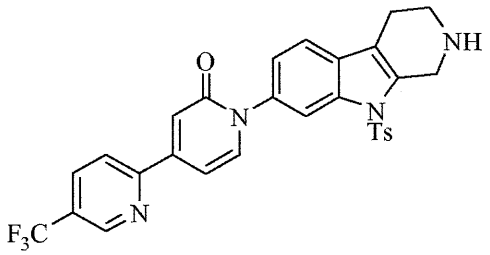
b) *tert*-Butyl 7-(2-oxo-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-1(2*H*)-yl)-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{34}H_{31}F_3N_4O_5S$
Exact Mass: 664.20
Molecular Weight: 664.69

4-(5-(Trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one (200 mg, 0.830 mmol) and *tert*-butyl 7-bromo-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (419 mg, 0.830 mmol) were coupled following the procedure of Example 30 (step g) to provide the title compound (222 mg, 40%) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.26 (s, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.80 (br s, 2H), 7.57 (d, J = 7.2 Hz, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.27 (3H, under solvent peak), 7.07 (d, J = 6.8 Hz, 1H), 4.91 (br m, 2H), 3.71 (br m, 2H), 2.71 (br m, 2H), 2.36 (s, 3H), 1.52 (s, 9H).

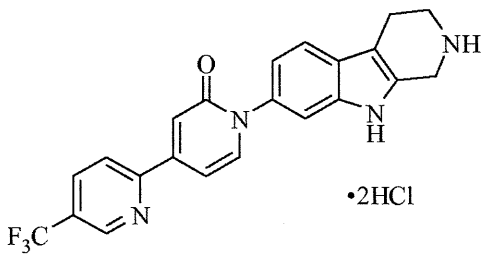
c) 1-(9-Tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one



Chemical Formula: $C_{29}H_{23}F_3N_4O_3S$
Exact Mass: 564.14
Molecular Weight: 564.58

tert-Butyl 7-(2-oxo-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-1(2*H*)-yl)-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (222 mg, 0.334 mmol) was deprotected according to the procedure of Example 30 (step e) to provide the title compound (131 mg, 58%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.25 (d, J = 1.6 Hz, 1H), 8.08 (dd, J = 8.3, 1.9 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 7.2 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.32 (dd, J = 8.3, 1.8 Hz, 1H), 7.28–7.24 (3H, under solvent peak), 7.08 (dd, J = 7.2, 2.0 Hz, 1H), 4.30 (br s, 2H), 3.13 (t, J = 5.6 Hz, 2H), 3.61 (br m, 2H), 2.36 (s, 3H).

d) 1-(2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one dihydrochloride



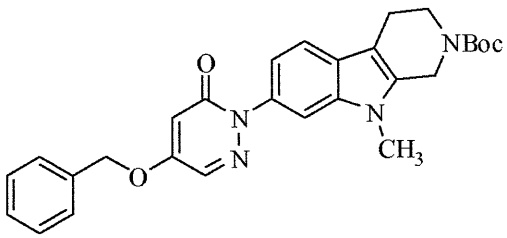
Chemical Formula: $C_{22}H_{19}Cl_2F_3N_4O$
Exact Mass: 482.09
Molecular Weight: 483.31

1-(9-Tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one (130 mg, 0.23 mmol) was deprotected according to the procedure of Example 106 (step b) to provide the title compound (39.5 mg, 36%) as a yellow solid: mp 320–330 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 9.05 (s, 1H), 8.28 (dd, J = 8.4, 2.1 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 7.2 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 7.1 Hz, 1H), 7.39 (d, J = 1.7 Hz, 1H), 7.24 (dd, J = 7.2, 1.9 Hz, 1H), 7.13 (dd, J = 8.4, 1.8 Hz, 1H), 4.50 (s, 2H), 3.63 (t, J = 6.1 Hz, 2H), 3.14 (t, J = 6.1 Hz, 2H); ESI MS *m/z* 411 $[M + H]^+$; HPLC (Method B) 98.4% (AUC), t_R = 12.6 min.

Example 88

Preparation of 5-(Benzyloxy)-2-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridazin-3(2*H*)-one hydrochloride

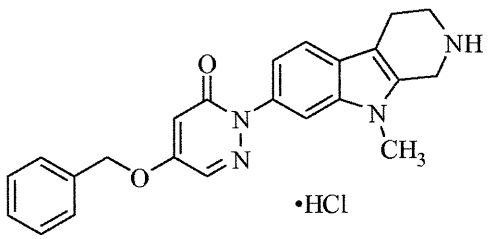
a) *tert*-Butyl 7-(4-(benzyloxy)-6-oxopyridazin-1(6*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{28}H_{30}N_4O_4$
Exact Mass: 486.23
Molecular Weight: 486.56

5-(Benzyloxy)pyridazin-3(2*H*)-one (197 mg, 0.974 mmol) and *tert*-butyl 7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (353 mg, 0.966 mmol) were coupled following the procedure of Example 30 (step g) to provide the title compound (130 mg, 28%) as a yellow/green solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 2.7 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.45–7.40 (m, 7H), 7.21 (dd, J = 8.4, 1.5 Hz, 1H), 5.08 (s, 2H), 4.64 (br m, 2H), 3.75 (br m, 2H), 3.63 (s, 3H), 2.80 (br m, 2H), 1.52 (s, 9H).

b) 5-(Benzyloxy)-2-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridazin-3(2*H*)-one hydrochloride



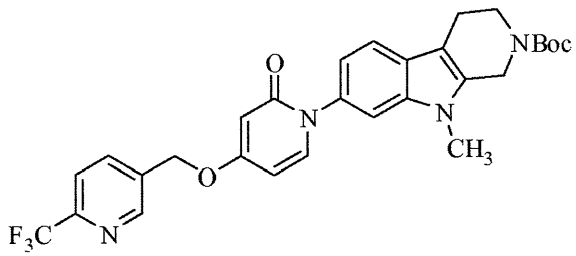
Chemical Formula: $C_{23}H_{23}ClN_4O_2$
Exact Mass: 422.15
Molecular Weight: 422.91

tert-Butyl 7-(4-(benzyloxy)-6-oxopyridazin-1(6*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (130 mg, 0.27 mmol) was deprotected and converted to the hydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (55.7, 48%) as a yellow solid: mp 235–245 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.93 (d, J = 2.7 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 1.5 Hz, 1H), 7.50–7.48 (m, 2H), 7.43 (overlapping dd, J = 7.8 Hz, 2H), 7.39 (d, J = 1.7 Hz, 1H), 7.18 (dd, J = 8.4, 1.7 Hz, 1H), 6.48 (d, J = 2.7 Hz, 1H), 5.22 (s, 2H), 4.54 (s, 2H), 3.71 (s, 3H), 3.59 (t, J = 5.6 Hz, 2H), 3.12 (t, J = 5.9 Hz, 2H); ESI MS m/z 387 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 11.7 min.

Example 89

Preparation of 1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-((6-(trifluoromethyl)pyridin-3-yl)methoxy)pyridin-2(1*H*)-one hydrochloride

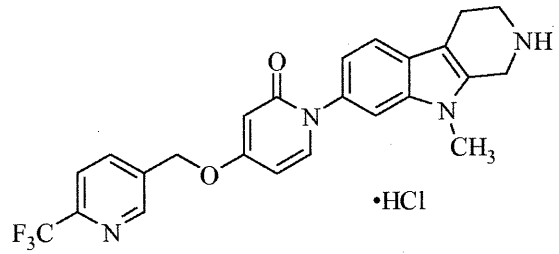
a) *tert*-Butyl 9-methyl-7-(2-oxo-4-((6-(trifluoromethyl)pyridin-3-yl)methoxy)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{29}H_{29}F_3N_4O_4$
Exact Mass: 554.21
Molecular Weight: 554.56

4-((6-(Trifluoromethyl)pyridin-3-yl)methoxy)pyridin-2(1*H*)-one (100 mg, 0.37 mmol) and *tert*-butyl 7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (135 mg, 0.370 mmol) were coupled following the procedure of Example 30 (step g) to provide the title compound (44 mg, 21%) as a yellow/brown solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.96 (d, J = 8.6 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.37–7.34 (m, 1H), 7.27 (1H, under solvent peak), 7.02 (dd, J = 8.3, 1.7 Hz, 1H), 6.07–6.04 (m, 2H), 5.16 (s, 2H), 4.64 (br m, 2H), 3.75 (br m, 2H), 3.63 (s, 3H), 2.80 (br m, 2H), 1.52 (s, 9H).

b) 1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-((6-(trifluoromethyl)pyridin-3-yl)methoxy)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{24}H_{22}ClF_3N_4O_2$
Exact Mass: 490.14
Molecular Weight: 490.91

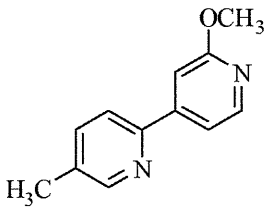
tert-Butyl 9-methyl-7-(2-oxo-4-((6-(trifluoromethyl)pyridin-3-yl)methoxy)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (44 mg, 0.079 mmol) was deprotected and converted to the hydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (28 mg, 65%) as a yellow solid:

mp 285–295 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.75 (s, 1H), 8.08 (d, J = 7.9 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.53 (dd, J = 7.9, 2.0 Hz, 2H), 7.38 (d, J = 1.7 Hz, 1H), 6.97 (dd, J = 8.4, 1.8 Hz, 1H), 6.25 (dd, J = 7.6, 2.7 Hz, 1H), 6.08 (d, J = 2.6 Hz, 1H), 5.26 (s, 2H), 4.46 (s, 2H), 3.63 (s, 3H), 3.51 (t, J = 6.1 Hz, 2H), 3.03 (t, J = 6.1 Hz, 2H); ESI MS *m/z* 455 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 12.8 min.

Example 90

Preparation of 1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(5-methylpyridin-2-yl)pyridin-2(1*H*)-one dihydrochloride

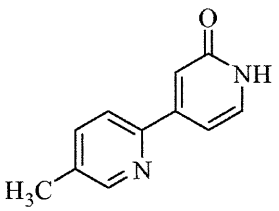
a) 2'-Methoxy-5-methyl-2,4'-bipyridine



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

2-Bromo-5-methylpyridine (2.93 g, 17.0 mmol) and 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (3.34 g, 14.2 mmol) were reacted according to Example 31 (step a) to provide the title compound (1.2 g, 42%) as a brown solid: ESI MS *m/z* 201 $[M + H]^+$.

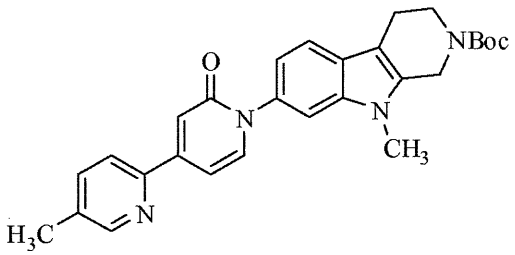
b) 4-(5-Methylpyridin-2-yl)pyridin-2(1*H*)-one



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

2'-Methoxy-5-methyl-2,4'-bipyridine (1.2 g, 6.0 mmol) was reacted according to Example 31 (step c) to provide the title compound (301 mg, 27%) as a white solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.58 (s, 1H) 8.53 (s, 1H), 7.88 (overlapping dd, J = 8.2 Hz, 1H), 7.71 (d, J = 6.0 Hz, 1H), 7.43 (d, J = 7.7, 1H), 6.95 (d, J = 1.5 Hz, 1H), 6.84 (dd, J = 6.9, 1.7 Hz, 1H), 2.34 (s, 3H).

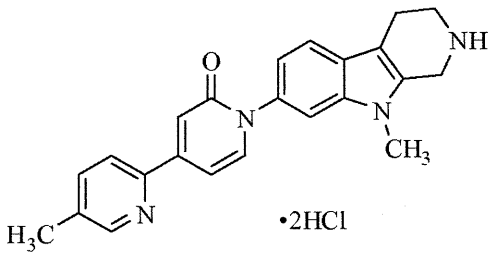
c) *tert*-Butyl 9-methyl-7-(4-(5-methylpyridin-2-yl)-2-oxopyridin-1(2*H*)-yl)-3,4-dihydro-1H-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{28}H_{30}N_4O_3$
Exact Mass: 470.23
Molecular Weight: 470.56

4-(5-methylpyridin-2-yl)pyridin-2(1*H*)-one (150 mg, 0.81 mmol) and *tert*-butyl 7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (294 mg, 0.805 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (138 mg, 36%) as a yellow/green solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.63–7.61 (m, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 7.2 Hz, 1H), 7.37 (s, 1H), 7.17 (d, J = 1.6 Hz, 1H), 7.09 (dd, J = 8.3, 1.7 Hz, 1H), 7.04 (dd, J = 7.2, 1.9 Hz, 1H), 4.65 (br m, 2H), 3.76 (br m, 2H), 3.65 (s, 3H), 2.82 (br m, 2H), 2.42 (s, 3H), 1.51 (s, 9H).

d) 1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(5-methylpyridin-2-yl)pyridin-2(1*H*)-one dihydrochloride



Chemical Formula: $C_{23}H_{24}Cl_2N_4O$
Exact Mass: 442.13
Molecular Weight: 443.37

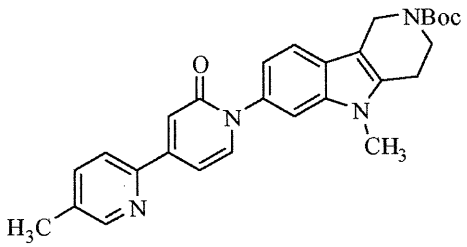
tert-Butyl 9-methyl-7-(4-(5-methylpyridin-2-yl)-2-oxopyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (138 mg, 0.27 mmol) was deprotected and converted to the dihydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (18 mg, 15%) as a yellow solid: mp 303–310 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.59 (s, 1H), 7.95 (d, J = 8.1Hz, 1H), 7.87 (d, J = 6.5 Hz, 1H), 7.80 (d, J = 7.0 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 1.4 Hz, 1H), 7.24 (d, J

= 1.6 Hz, 1H), 7.15–7.12 (m, 2H), 4.57 (s, 2H), 3.74 (s, 3H), 3.61 (t, J = 6.0 Hz, 2H), 3.14 (t, J = 6.1 Hz, 2H), 2.46 (s, 3H); ESI MS *m/z* 371 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 11.0 min.

Example 91

Preparation of 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-methylpyridin-2-yl)pyridin-2(1*H*)-one dihydrochloride

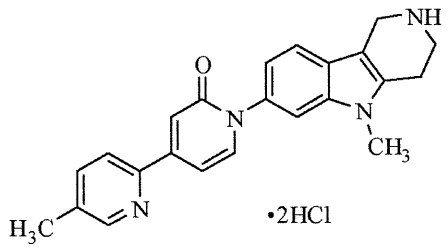
a) *tert*-Butyl 5-methyl-7-(4-(5-methylpyridin-2-yl)-2-oxopyridin-1(2*H*)-yl)-3,4-dihydro-1H-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{28}H_{30}N_4O_3$
Exact Mass: 470.23
Molecular Weight: 470.56

4-(5-Methylpyridin-2-yl)pyridin-2(1*H*)-one (150 mg, 0.81 mmol) and *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (294 mg, 0.805 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (245 mg, 64%) as a yellow/green solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, J = 2.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.64–7.60 (m, 1H), 7.55–7.51 (m, 2H), 7.37 (d, J = 1.6 Hz, 1H), 7.17 (d, J = 1.6 Hz, 1H), 7.10–7.03 (m, 2H), 4.66 (br m, 2H), 3.85 (br m, 2H), 3.65 (s, 3H), 2.84 (br m, 2H), 2.42 (s, 3H), 1.51 (s, 9H).

b) 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-methylpyridin-2-yl)pyridin-2(1*H*)-one dihydrochloride



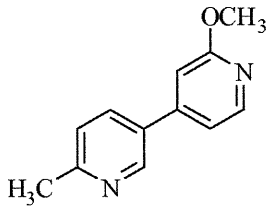
Chemical Formula: $C_{23}H_{24}Cl_2N_4O$
Exact Mass: 442.13
Molecular Weight: 443.37

tert-Butyl 5-methyl-7-(4-(5-methylpyridin-2-yl)-2-oxopyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (245 mg, 0.520 mmol) was deprotected and converted to the dihydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (57 mg, 30%) as a yellow solid: mp 295–305 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.76 (d, J = 1.8 Hz, 1H), 8.34 (d, J = 6.9 Hz, 1H), 8.24 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 7.2 Hz, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.61 (d, J = 1.7 Hz, 1H), 7.23 (d, J = 1.8 Hz, 1H), 7.17 (dd, J = 8.3, 1.8 Hz, 1H), 7.04 (dd, J = 7.1, 2.1 Hz, 1H), 4.53 (s, 2H), 3.79 (s, 3H), 3.71 (t, J = 6.2 Hz, 2H), 3.25 (t, J = 6.2 Hz, 2H), 2.61 (s, 3H); ESI MS *m/z* 371 $[M + H]^+$; HPLC (Method B) 97.3% (AUC), t_R = 10.9 min.

Example 92

Preparation of 1-(5-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(6-methylpyridin-3-yl)pyridin-2(1*H*)-one dihydrochloride

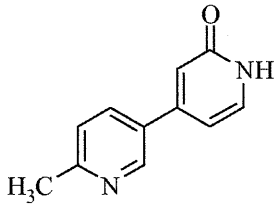
a) 2'-Methoxy-6-methyl-3,4'-bipyridine



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

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 31 (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).

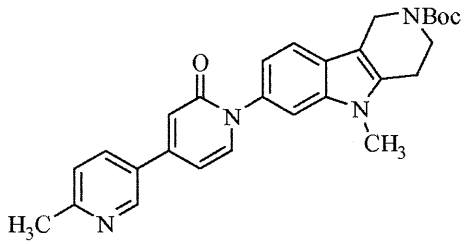
b) 4-(6-Methylpyridin-3-yl)pyridin-2(1*H*)-one



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

2'-Methoxy-6-methyl-3,4'-bipyridine (2.1 g, 10.4 mmol) was reacted according to Example 31 (step c) 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).

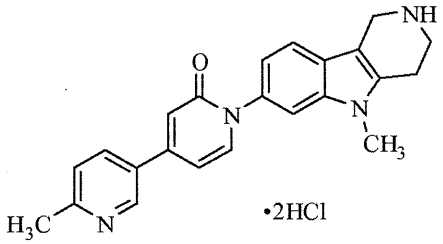
c) *tert*-Butyl 5-methyl-7-(4-(6-methylpyridin-3-yl)-2-oxopyridin-1(2*H*)-yl)-3,4-dihydro-1H-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{28}H_{30}N_4O_3$
Exact Mass: 470.23
Molecular Weight: 470.56

4-(6-Methylpyridin-3-yl)pyridin-2(1*H*)-one (150 mg, 0.81 mmol) and *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (294 mg, 0.805 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (220 mg, 58%) as a yellow/green solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (d, J = 8.2 Hz, 1H), 7.83 (dd, J = 8.1, 2.4 Hz, 1H), 7.56–7.51 (m, 2H), 7.37 (d, J = 1.4 Hz, 1H), 7.30 (1H, partially under solvent), 7.08 (d, J = 8.7 Hz, 1H), 6.90 (d, J = 1.6 Hz, 1H), 6.50 (dd, J = 7.1, 1.9 Hz, 1H), 4.66 (br s, 2H), 3.85 (br m, 2H), 3.65 (s, 3H), 2.84 (br m, 2H), 2.64 (s, 3H), 1.51 (s, 9H).

d) 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(6-methylpyridin-3-yl)pyridin-2(1*H*)-one dihydrochloride



•2HCl

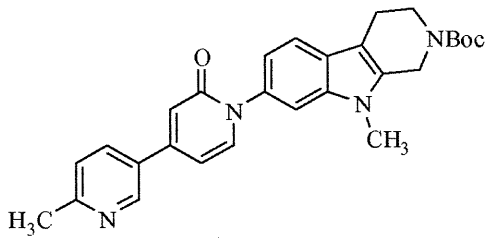
Chemical Formula: $C_{23}H_{24}Cl_2N_4O$
Exact Mass: 442.13
Molecular Weight: 443.37

tert-Butyl 5-methyl-7-(4-(6-methylpyridin-3-yl)-2-oxopyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (220 mg, 0.47 mmol) was deprotected and converted to the dihydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (50.2 mg, 29%) as a yellow solid: mp 295–305 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.80 (d, J = 2.2 Hz, 1H), 8.12 (dd, J = 8.1, 2.5 Hz, 1H), 7.79 (d, J = 7.0 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 1.7 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.10 (dd, J = 8.3, 1.9 Hz, 1H), 6.93 (d, J = 1.8 Hz, 1H), 6.85 (dd, J = 7.1, 2.0 Hz, 1H), 4.34 (s, 2H), 3.73 (s, 3H), 3.52 (t, J = 6.1 Hz, 2H), 3.10 (t, J = 6.1 Hz, 2H), 2.62 (s, 3H); ESI MS *m/z* 371 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 8.7 min.

Example 93

Preparation of 1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(6-methylpyridin-3-yl)pyridin-2(1*H*)-one dihydrochloride

a) *tert*-Butyl 9-methyl-7-(4-(6-methylpyridin-3-yl)-2-oxopyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate

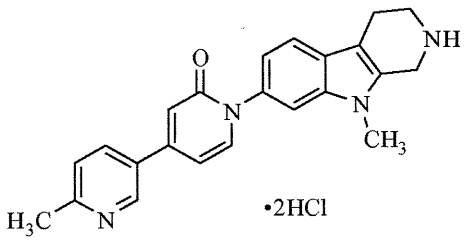


Chemical Formula: $C_{28}H_{30}N_4O_3$
Exact Mass: 470.23
Molecular Weight: 470.56

4-(6-Methylpyridin-3-yl)pyridin-2(1*H*)-one (150 mg, 0.81 mmol) and *tert*-butyl 7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (294 mg, 0.805 mmol) were reacted following the procedure of Example 30 (step g) to provide the title compound (208 mg, 55%) as a yellow/green solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (d, J = 8.2 Hz, 1H), 7.83 (dd, J = 8.0, 2.3 Hz, 1H), 7.58–7.51 (m, 2H), 7.36 (s, 1H), 7.30 (1H,

partially under solvent), 7.08 (dd, J = 8.3, 1.8 Hz, 1H), 6.90 (d, J = 1.7 Hz, 1H), 6.50 (dd, J = 7.1, 2.0 Hz, 1H), 4.65 (br s, 2H), 3.76 (br m, 2H), 3.65 (s, 3H), 2.82 (br m, 2H), 2.64 (s, 3H), 1.52 (s, 9H).

b) 1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(6-methylpyridin-3-yl)pyridin-2(1*H*)-one dihydrochloride



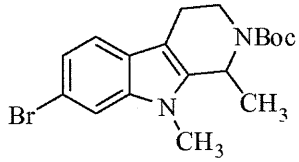
Chemical Formula: $C_{23}H_{24}Cl_2N_4O$
Exact Mass: 442.13
Molecular Weight: 443.37

tert-Butyl 9-methyl-7-(4-(6-methylpyridin-3-yl)-2-oxopyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (208 mg, 0.442 mmol) was deprotected and converted to the dihydrochloride salt according to the procedure of Example 30 (steps e and g) to provide the title compound (40.6 mg, 23%) as a yellow solid: mp 305–313 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.80 (d, J = 8.1Hz, 1H), 8.11 (dd, J = 8.2, 2.5 Hz, 1H), 7.79 (d, J = 7.0 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 1.7 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.11 (dd, J = 8.3, 1.8 Hz, 1H), 6.93 (d, J = 1.9 Hz, 1H), 6.85 (dd, J = 7.1, 2.0 Hz, 1H), 4.40 (s, 2H), 3.71 (s, 3H), 3.46 (t, J = 5.9 Hz, 2H), 3.04 (t, J = 5.9 Hz, 2H), 2.62 (s, 3H); ESI MS *m/z* 371 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 8.9 min.

Example 94

Preparation of 4-(Benzyloxy)-1-(1,9-dimethyl-2,3,4,9-tetrahydro-*1H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(*1H*)-one hydrochloride

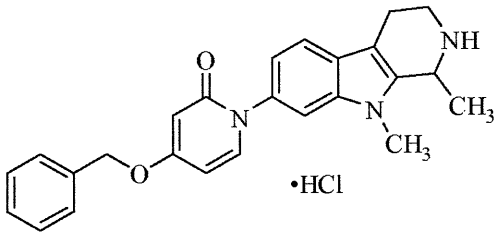
a) *tert*-Butyl 7-bromo-1,9-dimethyl-3,4-dihydro-1*H*-pyrido[4,3-b]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{18}H_{23}BrN_2O_2$
Exact Mass: 378.0943
Molecular Weight: 379.2914

To a solution of 2-(6-bromo-1*H*-indol-3-yl)ethanamine (1.9 g, 8.0 mmol) in THF (30 mL) at 0 °C was added saturated aqueous $NaHCO_3$ (30 mL) and acetyl chloride (0.56 mL, 7.95 mmol). The reaction was warmed up to room temperature and stirred at room temperature until complete. The solution was concentrated, and the residue was dissolved in CH_2Cl_2, washed with H_2O and brine and dried with Na_2SO_4. The organic solution was filtered and concentrated to give a pale yellow foam. The foam was suspended in benzene (70 mL) and treated with $POCl_3$ (3.52 mL, 38.4 mmol). The reaction was heated and stirred at 85 °C for one hour. After the solution was concentrated, the residue was purified by flash column chromatography (silica gel, 10% CH_3OH in CH_2Cl_2) to give a brown solid (1.83 g 91%). The solid was suspended in EtOH (20 mL) and $CHCl_3$ (20 mL) and cooled to 0 °C. $NaBH_4$ (0.26 g, 6.95 mmol) was added, and the reaction was stirred from 0 °C to room temperature for one hour. The reaction was quenched with H_2O, extracted with CH_2Cl_2, washed with H_2O and brine and dried over Na_2SO_4. The organic solution was filtered and concentrated to give a yellow foam (1.44 g, 78%). The foam was dissolved in *i*-PrOH (15 mL) and H_2O (10 mL) and treated with Boc_2O (1.36 g, 6.24 mmol) and K_2CO_3 (0.86 g, 6.2 mmol). The reaction was stirred at room temperature for one hour and then concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2, washed with H_2O and brine and dried over Na_2SO_4. After filtration and concentration, the residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 4:1) to give a yellow foam (0.92 g, 46 %). The foam was dissolved in DMF (6 mL) and cooled to 0 °C. The solution was treated with NaH (60% weight dispersion in mineral oil, 108 mg, 2.68 mmol) followed by CH_3I (0.17 mL, 0.69 mmol). The reaction was stirred at 0 °C until complete. The reaction was quenched with H_2O, extracted with CH_2Cl_2, washed with H_2O and brine and dried over Na_2SO_4. The organic solution was filtered and concentrated, and the residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 4:1) to give the title compound as a white foam (0.82 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 5.43–5.20 (m, 1H), 4.48–4.26 (m, 1H), 3.62 (s, 3H), 3.24–3.13 (m, 1H), 2.78–2.66 (m, 2H), 1.49 (s, 9H), 1.47 (d, J = 6.5 Hz, 3H); MS (ESI) *m/z* 380 $[M + H]^+$.

b) 4-(Benzyloxy)-1-(1,9-dimethyl-2,3,4,9-tetrahydro-*1H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(*1H*)-one hydrochloride

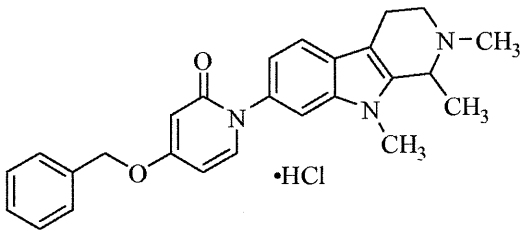


Chemical Formula: $C_{25}H_{26}ClN_3O_2$
Exact Mass: 435.17
Molecular Weight: 435.95

To a mixture of *tert*-butyl 7-bromo-1,9-dimethyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(9*H*)-carboxylate (0.57g, 1.6 mmol), 4-(benzyloxy)pyridin-2(1*H*)-one (0.32 g, 1.6 mmol), 8-hydroxyquilinine (46 mg, 0.32 mmol), K_2CO_3 (0.26 g, 1.9 mmol) and CuI (0.15 g, 0.79 mmol) was added DMSO (4 mL). The reaction mixture was degassed and back-filled with N_2. The reaction 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, 5% CH_3OH in CH_2Cl_2) to give a yellow solid (0.5 g, 64%). The solid was dissolved in CH_3OH (8 mL) and treated with 1 N HCl in Et_2O (5 mL). The reaction was stirred at room temperature until complete. The solvent was removed under reduced pressure and the resulting solid was dried under vacumn to give the title compound (0.44 g, 100%) as a yellow powder: ^{1}H NMR (500 MHz, CD_3OD) δ 7.79 (d, J = 7.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.53 (s, 1H), 7.48–7.36 (m, 5H), 7.10 (d, J = 8.5 Hz, 1H), 6.55 (d, J = 6.5 Hz, 1H), 6.33 (s, 1H), 5.27 (s, 2H), 4.98 (q, J = 6.5 Hz, 1H), 3.76 (s, 3H), 3.67–3.59 (m, 2H), 3.13–3.08 (m, 2H), 1.76 (d, J = 7.0 Hz, 3H); ESI MS *m/z* 400 $[M + H]^+$; HPLC (Method A) >99 % (AUC), t_R = 12.9 min.

Example 95

Preparation of 4-(Benzyloxy)-1-(1,2,9-trimethyl-2,3,4,9-tetrahydro-*1H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(*1H*)-one hydrochloride



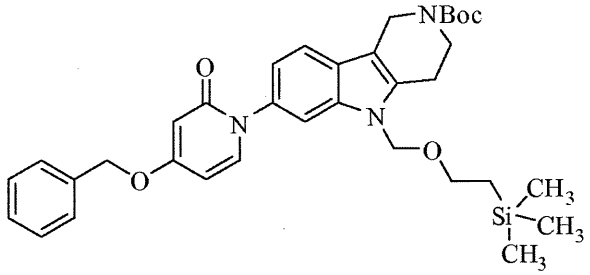
Chemical Formula: $C_{26}H_{28}ClN_3O_2$
Exact Mass: 449.19
Molecular Weight: 449.97

To a solution of 4-(benzyloxy)-1-(1,9-dimethyl-2,3,4,9-tetrahydro-*1H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(*1H*)-one hydrochloride (205 mg, 0.470 mmol) in CH_3OH (8 mL) was added formaldehyde (53 μL, 0.71 mmol) and $NaBH(OAc)_3$ (200 mg, 0.94 mmol). The reaction was stirred at room temperature until complete and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and 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 4-(benzyloxy)-1-(1,2,9-trimethyl-2,3,4,9-tetrahydro-*1H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(*1H*)-one as a white solid (0.15 g, 77 %). The free base was converted to the HCl salt to give the title compound (147 mg, 90 %) as an off-white powder: ^{1}H NMR (500 MHz, CD_3OD) δ 7.58–7.55 (m, 2H), 7.47–7.34 (m, 6H), 6.99 (d, J = 8.5, 1.0 Hz, 1H), 6.28 (dd, J = 7.5, 2.5 Hz, 1H), 6.11 (d, J = 2.5 Hz, 1H), 5.18 (s, 2H), 4.27 (q, J = 6.5 Hz, 1H), 3.69 (s, 3H), 3.36–3.33 (m, 1H), 3.10–2.96 (m, 2H), 2.84–2.80 (m, 1H), 2.65 (s, 3H), 1.51 (d, J = 6.5 Hz, 3H); ESI MS *m/z* 414 $[M + H]^+$; HPLC (Method A) >99 % (AUC), t_R = 13.0 min.

Example 96

Preparation of 4-(Benzyloxy)-1-(5-(ethoxymethyl)-2,3,4,5-tetrahydro-*1H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(*1H*)-one hydrochloride

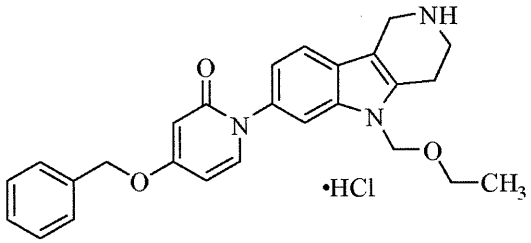
a) *tert*-Butyl 7-(4-(benzyloxy)-2-oxopyridin-1(*2H*)-yl)-5-(ethoxymethyl)-3,4-dihydro-*1H*-pyrido[4,3-*b*]indole-2(*5H*)-carboxylate



Chemical Formula: $C_{34}H_{43}N_3O_5Si$
Exact Mass: 601.30
Molecular Weight: 601.81

To a solution of *tert*-butyl 7-bromo-3,4-dihydro-*1H*-pyrido[4,3-*b*]indole-2(*5H*)-carboxylate (0.66 g, 1.9 mmol) in DMF (8 mL) was added NaH (60% weight dispersion in mineral oil, 113 mg, 2.82 mmol) followed by SEMCl (0.50 mL, 2.8 mmol). The reaction was stirred at room temperature until complete. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2. The organic phase was washed with H_2O and brine and dried over Na_2SO_4. After filtration and concentration, the residue was dried under vacuum to give *tert*-butyl 7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydro-*1H*-pyrido[4,3-*b*]indole-2(*5H*)-carboxylate, which and used directly in the next step. To a mixture of *tert*-butyl 7-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydro-*1H*-pyrido[4,3-*b*]indole-2(*5H*)-carboxylate (0.75 g, 1.6 mmol), 4-benzyloxypyridone (0.31 g, 1.6 mmol), 8-hydroxyquilinine (34 mg, 0.23 mmol), K_2CO_3 (0.26 g, 1.9 mmol) and CuI (45 mg, 0.23 mmol) was added DMSO (6 mL). The reaction mixture was degassed and back-filled with N_2. The reaction 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, and the residue was purified by flash column chromatography (silica gel, 5% CH_3OH in CH_2Cl_2) to give the title compound as a yellow oil (0.12 g, 13%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 8.5 Hz, 1H), 7.44–7.37 (m, 6H), 7.31 (d, J = 7.5 Hz, 1H), 7.09 (m, 1H), 6.12 (s, 1H), 6.07 (d, J = 6.5 Hz, 1H), 5.40 (s, 2H), 5.07 (s, 2H), 4.65 (m, 2H), 3.86 (m, 2H), 3.51 (t, J = 8.0 Hz, 2H), 2.73 (m, 2H), 1.53 (s, 9H), 0.89 (t, J = 8.0 Hz, 2H), -0.04 (s, 9H); ESI MS *m/z* 602 $[M + H]^+$.

b) 4-(Benzyloxy)-1-(5-(ethoxymethyl)-2,3,4,5-tetrahydro-*1H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(*1H*)-one hydrochloride



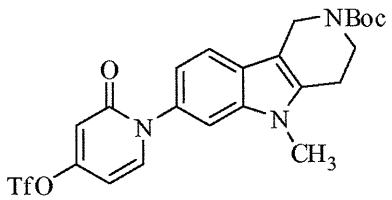
Chemical Formula: $C_{26}H_{28}ClN_3O_3$
Exact Mass: 465.18
Molecular Weight: 465.97

To a solution of *tert*-butyl 7-(4-(benzyloxy)-2-oxopyridin-1(*2H*)-yl)-5-(ethoxymethyl)-3,4-dihydro-*1H*-pyrido[4,3-*b*]indole-2(*5H*)-carboxylate (120 mg, 0.20 mmol) in EtOH (2 mL) was added 1 N HCl in Et_2O (1 mL). The reaction was stirred at 60 °C until complete. The solvent was concentrated and the residue was purified by preparative HPLC (Phenomenex Luna C18 (2), 250 × 50 mm, 15 micron, H_2O with 0.05% TFA and CH_3CN with 0.05% TFA) to give 4-(benzyloxy)-1-(5-(ethoxymethyl)-2,3,4,5-tetrahydro-*1H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(*1H*)-one as a white solid (54 mg, 73 %). The free base was converted to the HCl salt to give the title compound (35 mg, 65 %) as a white powder: mp 148–149 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.12 (s, 2H), 7.66 (d, J = 2.0 Hz, 1H), 7.59–7.56 (m, 2H), 7.49–7.37 (m, 5H), 7.08–7.05 (m, 1H), 6.14–6.12 (m, 1H), 5.99 (d, J = 2.5 Hz, 1H), 5.57 (s, 2H), 5.17 (s, 2H), 4.38 (m, 2H), 3.55 (m, 2H), 3.45–3.40 (m, 2H), 3.13 (m, 2H), 1.08–1.05 (m, 3H); ESI MS *m/z* 430 $[M + H]^+$; HPLC (Method A) >99 % (AUC), t_R = 12.8 min.

Example 97

Preparation of 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-phenylpyridin-2(1*H*)-one hydrochloride

a) *tert*-Butyl 5-methyl-7-(2-oxo-4-(trifluoromethylsulfonyloxy)pyridine-1(2*H*)-yl)3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate

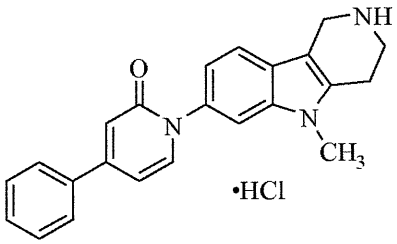


Chemical Formula: $C_{23}H_{24}F_3N_3O_6S$
Exact Mass: 527.13
Molecular Weight: 527.51

To a solution of *tert*-butyl 7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (0.98 g, 2.0 mmol) in CH_3OH (30 mL)

was added 5% Pd/C (0.3 g) and ammonium formate (0.32 g, 5.1 mmol) under an atmosphere of argon. The reaction was stirred at 90 °C until complete. The reaction mixture was cooled and filtered through a layer of Celite. The solvent was removed under reduced pressure to give *tert*-butyl 7-(4-hydroxy-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate, which was used directly in the next step. To a solution of *tert*-butyl 7-(4-hydroxy-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (800 mg, 2.02 mmol) in THF (10 mL) was added $LiN(SiMe_3)_2$ (1.0 M in THF, 2.6 mL, 2.6 mmol) followed by $PhN(Tf)_2$ (0.94 g, 2.6 mmol) under an atmosphere of argon. The reaction was stirred at room temperature until complete. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 1:1) to give the title compound (0.42g, 40% yield) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.53 (m, 2H), 7.30 (d, J = 1.5 Hz, 1H), 7.02–6.99 (m, 1H), 6.60 (d, J = 2.7 Hz, 1H), 6.27 (dd, J = 7.8, 2.7 Hz, 1H), 4.65 (s, 2H), 3.85 (m, 2H), 3.65 (s, 3H), 2.84 (m, 2H), 1.51 (s, 9H); ESI MS *m/z* 528 $[M + H]^+$.

b) 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-phenylpyridin-2(1*H*)-one hydrochloride

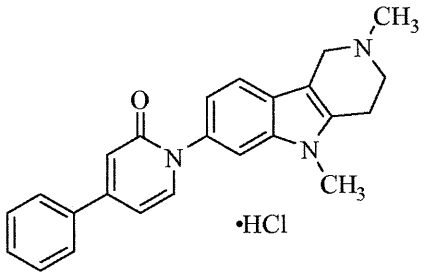


Chemical Formula: $C_{23}H_{22}ClN_3O$
Exact Mass: 391.15
Molecular Weight: 391.89

Following the procedure of Example 25 (step b), but substituting phenylboronic acid for 4-fluorophenylboronic acid and eliminating the methylation step, the title compound (37 mg, 46%) was obtained as a yellow solid: mp 275–280 °C (decompose); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.26 (s, 2H), 7.79 (dd, J = 8.0, 1.5 Hz, 2H), 7.75 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 1.5 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.55–7.50 (m, 3H), 7.10 (dd, J = 8.5, 2.0 Hz, 1H), 6.78 (d, J = 1.5 Hz, 1H), 6.70 (dd, J = 7.0, 2.0 Hz, 1H), 4.37 (m, 2H), 3.71 (s, 3H), 3.54–3.53 (m, 2H), 3.10 (t, J = 6.0 Hz, 2H); ESI MS *m/z* 356 $[M + H]^+$; HPLC (Method A) >99 % (AUC), t_R = 12.3 min.

Example 98

Preparation of 1-(2,5-Dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-phenylpyridin-2(1*H*)-one hydrochloride

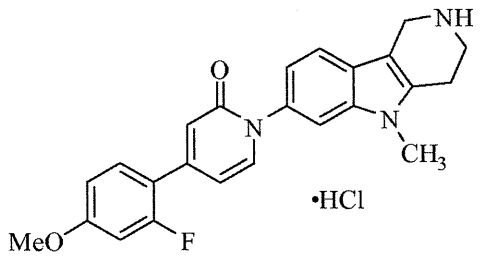


Chemical Formula: $C_{24}H_{24}ClN_3O$
Exact Mass: 405.16
Molecular Weight: 405.92

Following the procedure of Example 25 (step b), but substituting phenylboronic acid for 4-fluorophenylboronic acid, the title compound (56 mg, 83%) was obtained as an off-white solid: mp 290–295 °C (decompose); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.46 (s, 1H), 7.80–7.74 (m, 3H), 7.63 (s, 1H), 7.56–7.52 (m, 4H), 7.11 (d, J = 8.0 Hz, 1H), 6.78 (s, 1H), 6.70 (d, J = 7.0 Hz, 1H), 4.68–4.65 (m, 1H), 4.34–4.30 (m, 1H), 3.82–3.79 (m, 1H), 3.71 (s, 3H), 3.53–3.51 (m, 1H), 3.20 (m, 2H), 3.00 (d, J = 4.0 Hz, 3H); ESI MS *m/z* 370 $[M + H]^+$; HPLC (Method A) 98% (AUC), t_R = 12.5 min.

Example 99

Preparation of 4-(2-Fluoro-4-methoxyphenyl)-1-(5-methyl-2,3,4,5-tetrahydro-*1H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(*1H*)-one hydrochloride



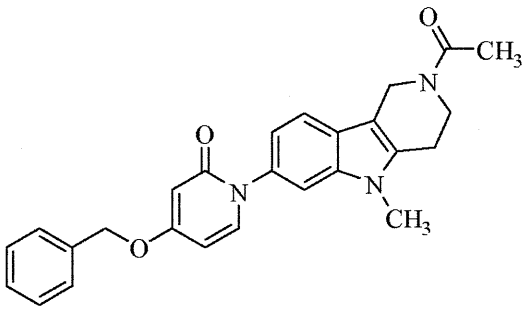
Chemical Formula: $C_{24}H_{23}ClFN_3O_2$
Exact Mass: 439.15
Molecular Weight: 439.91

Following the procedure of Example 25 (step b), but substituting 2-fluoro-4-methoxyphenylboronic acid for 4-fluorophenylboronic acid and eliminating the

methylation step, the title compound (34 mg, 19%) was obtained as a green powder: mp 270–274 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.72 (d, J = 7.0 Hz, 1H), 7.63–7.56 (m, 3H), 7.14 (dd, J = 8.5, 1.5 Hz, 1H), 6.92 (dd, J = 8.5, 2.5 Hz, 1H), 6.87 (dd, J = 13.0, 2.5 Hz, 1H), 6.84 (s, 1H), 6.77–6.75 (m, 1H), 4.50 (s, 2H), 3.88 (s, 3H), 3.76 (s, 3H), 3.68 (t, J = 6.0 Hz, 2H), 3.22 (t, J = 6.0 Hz, 2H); ESI MS m/z 404 $[M + H]^+$; HPLC (Method A) >99 % (AUC), t_R = 12.3 min

Example 100

Preparation of 1-(2-Acetyl-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(benzyloxy)pyridin-2(1*H*)-one

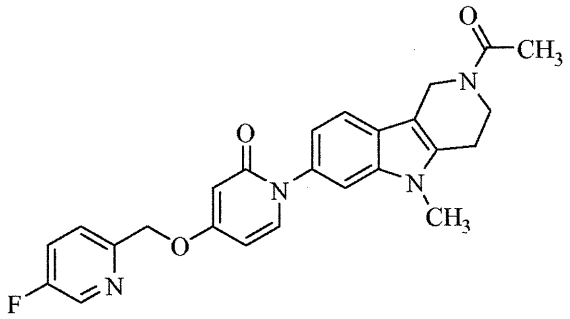


Chemical Formula: $C_{26}H_{25}N_3O_3$
Exact Mass: 427.19
Molecular Weight: 427.50

To a solution of 4-(benzyloxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (0.2 g, 0.5 mmol) in CH_2Cl_2 (6 mL) was added triethylamine (0.20 mL, 1.4 mmol) followed by acetyl chloride (50 μL, 0.71 mmol). The reaction was stirred at room temperature until complete. After the solvent was removed under reduced pressure, the residue was purified by flash column chromatography (silica gel, 5 % CH_3OH in CH_2Cl_2) to give the title compound (72.2 mg, 36%) as a yellow solid and as a mixture of rotamers: mp 225–230 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.36 (m, 6H), 7.32–7.30 (m, 2H), 7.06–7.00 (m, 1H), 6.09 (d, J = 3.0 Hz, 1H), 6.07–6.04 (m, 1H), 5.06 (s, 2H), 4.82 (s, 1H), 4.67 (s, 1H), 4.03 (t, J = 5.5 Hz, 1H), 3.84 (t, J = 5.5 Hz, 1H), 3.64 (s, 3H), 2.90 (t, J = 5.5 Hz, 1H), 2.84 (t, J = 5.5 Hz, 1H), 2.24, 2.22 (2 × s, 3H); ESI MS m/z 428 $[M + H]^+$; HPLC (Method A) 95.7 % (AUC), t_R = 16.8 min.

Example 101

Preparation of 1-(2-Acetyl-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-((5-fluoropyridin-2-yl)methoxy)pyridin-2(1*H*)-one



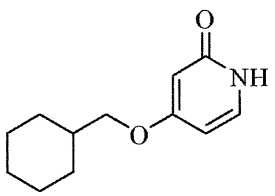
Chemical Formula: $C_{25}H_{23}FN_4O_3$
Exact Mass: 446.18
Molecular Weight: 446.47

Following the procedure of Example 100, but substituting 4-((5-fluoropyridin-2-yl)methoxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-pyridin-2(1*H*)-one for 4-(benzyloxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one, the title compound (71 mg, 61%) was obtained as a yellow solid and as a mixture of rotamers: mp 220–224 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, J = 1.5 Hz, 1H), 7.54–7.46 (m, 3H), 7.35 (d, J = 7.5 Hz, 1H), 7.32 (d, J = 2.0 Hz, 1H), 7.03 (ddd, J = 20, 8.0, 1.5 Hz, 1H), 6.15–6.08 (m, 2H), 5.18 (s, 2H), 4.83, 4.70 (2 × s, 2H), 4.04 (t, J = 5.5 Hz, 1H), 3.85 (t, J = 5.5 Hz, 1H), 3.65, 3.64 (2 × s, 3H), 2.91 (t, J = 5.5 Hz, 1H), 2.85 (t, J = 5.5 Hz, 1H), 2.23, 2.25 (2 × s, 3H); ESI MS *m/z* 447 $[M + H]^+$; HPLC (Method A) 96.4 % (AUC), t_R = 14.5 min.

Example 102

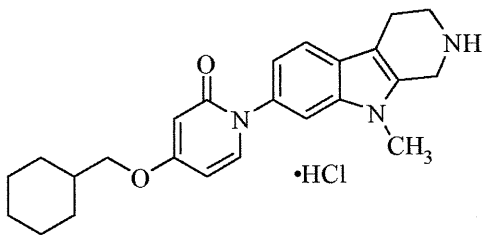
Preparation of 4-(Cyclohexylmethoxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

a) 4-(Cyclohexylmethoxy)pyridin-2(1*H*)-one



Chemical Formula: $C_{12}H_{17}NO_2$
Exact Mass: 207.1259
Molecular Weight: 207.2689

To a solution of cyclohexylmethanol (1.1 mL, 9.3 mmol) in DMF (8 mL) was added NaH (60% weight dispersion in mineral oil, 0.37 g, 9.3 mmol) in one portion. After the bubbles disappeared, 4-chloropyridine *N*-oxide (1.0 g, 7.7 mmol) was added. The reaction was stirred at room temperature under Ar until complete. The reaction was quenched with water and the aqueous mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O and 5% aqueous LiCl and dried over Na_2SO_4. After filtration and concentration, the residue was purified by flash column chromatography (silica gel, 10% CH_3OH in CH_2Cl_2) to give a yellow solid. The yellow solid was suspended in Ac_2O (5 mL) and heated at 140 °C for 4 h. The reaction mixture was cooled, diluted with CH_3OH/H_2O (10 mL, 1:1) and stirred at room temperature for 1 h. 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 (0.92 g, 58%) as a brown solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.03 (s, 1H), 7.21 (d, J = 7.2 Hz, 1H), 5.83 (dd, J = 7.2, 2.4 Hz, 1H), 5.64 (d, J = 2.4 Hz, 1H), 3.72 (d, J = 6.0 Hz, 2H), 1.84–1.68 (m, 6H), 1.30–1.01 (m, 5H).

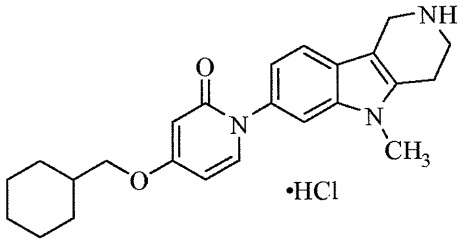


Chemical Formula: $C_{24}H_{30}ClN_3O_2$
Exact Mass: 427.20
Molecular Weight: 427.97

Following the procedure of Example 1 (steps c and d), but substituting 4-(cyclohexylmethoxy)pyridin-2(*1H*)-one for 4-benzyloxypyridone, the title compound (56 mg, 81 %) was obtained as a yellow solid: mp 256–260 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.67–7.65 (m, 2H), 7.50 (s, 1H), 7.09 (d, J = 8.5 Hz, 1H), 6.35 (d, J = 6.0 Hz, 1H), 6.10 (s, 1H), 4.58 (s, 2H), 3.92 (d, J = 5.5 Hz, 2H), 3.75 (s, 3H), 3.63 (t, J = 6.0 Hz, 2H), 3.15 (d, J = 6.0 Hz, 2H), 1.92–1.74 (m, 6H), 1.39–1.19 (m, 5H); ESI MS *m/z* 392 $[M + H]^+$; HPLC (Method A) 97.8 % (AUC), t_R = 14.4 min.

Example 103

Preparation of 4-(Cyclohexylmethoxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

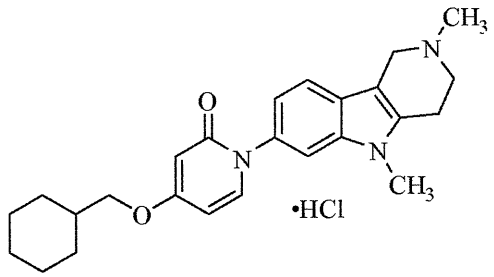


Chemical Formula: $C_{24}H_{30}ClN_3O_2$
Exact Mass: 427.20
Molecular Weight: 427.97

Following the procedure of Example 102, but substituting substituting *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(*5H*)-carboxylate for *tert*-butyl 7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(9*H*)-carboxylate, the title compound (197 mg, 100 %) was obtained as a pale green solid: mp 245–250 °C (decompose); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (s, 2H), 7.55 (d, J = 8.5 Hz, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.50 (s, 1H), 6.99 (dd, J = 8.5, 1.5 Hz, 1H), 6.04 (dd, J = 7.5, 2.5 Hz, 1H), 5.85 (d, J = 2.5 Hz, 1H), 4.35 (s, 2H), 3.82 (d, J = 6.0 Hz, 2H), 3.68 (s, 3H), 3.54–3.53 (m, 2H), 3.09 (t, J = 5.5 Hz, 2H), 1.80–1.65 (m, 6H), 1.30–1.01 (m, 5H); ESI MS *m/z* 392 $[M + H]^+$; HPLC (Method A) >99 % (AUC), t_R = 14.3 min.

Example 104

Preparation of 4-(Cyclohexylmethoxy)-1-(2,5-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{25}H_{32}ClN_3O_2$
Exact Mass: 441.22
Molecular Weight: 441.99

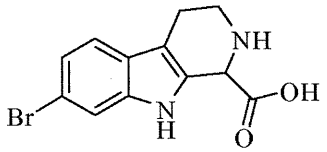
To a solution of 4-(cyclohexylmethoxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride (110 mg, 0.26 mmol) in CH_3OH (5 mL) was added triethylamine (90 μL, 2.5 mmol), formaldehyde (30 μL, 0.39 mmol) and $NaBH(OAc)_3$ (110 mg, 0.52 mmol). The reaction was stirred at room temperature until complete. The solvent was removed under reduced pressure, and the residue was

dissolved in CH_2Cl_2. The organic solution was washed with H_2O and 5% aqueous LiCl and dried over Na_2SO_4. After filtration and concentration, the residue was purified by flash column chromatography (silica gel, 10% CH_3OH in CH_2Cl_2) to give 4-(cyclohexylmethoxy)-1-(2,5-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one as a white solid (73 mg, 69 %). The free base was converted to the HCl salt to give the title compound (84 mg, 100 %) as a white powder: mp 270–272 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.53 (s, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 1.5 Hz, 1H), 7.00 (dd, J = 8.5, 1.5 Hz, 1H), 6.04 (dd, J = 7.5, 2.5 Hz, 1H), 5.85 (d, J = 3.0 Hz, 1H), 4.64 (d, J = 13 Hz, 1H), 4.30 (dd, J = 14, 7.5 Hz, 1H), 3.82 (d, J = 6.0 Hz, 2H), 3.80–3.78 (m, 1H), 3.69 (s, 3H), 3.51–3.47 (m, 1H), 3.18 (t, J = 5.5 Hz, 2H), 2.98 (d, J = 4.5 Hz, 3H), 1.80–1.65 (m, 6H), 1.30–1.01 (m, 5H); ESI MS *m/z* 406 $[M + H]^+$; HPLC (Method A) >99 % (AUC), t_R = 14.4 min.

Example 105

Preparation of 4-(Benzyloxy)-1-(1-(hydroxymethyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

a) 7-Bromo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-1-carboxylic acid



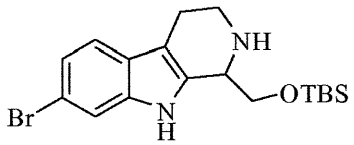
Chemical Formula: $C_{12}H_{11}BrN_2O_2$
Exact Mass: 294.00
Molecular Weight: 295.13

Glyoxylic acid monohydrate (3.69 g, 40.1 mmol) was added to a solution of a 2:1 mixture of 2-(6-bromo-1*H*-indol-3-yl)ethanamine and 2-(4-bromo-1*H*-indol-3-yl)ethanamine (7.38 g, 30.9 mmol) in 0.4 N HCl (50 mL), and the resulting solution was stirred at 25 °C for 30 min. The solution was adjusted to pH 3.5 with 6 N NaOH solution, and the resulting tan suspension was stirred at 25 °C for 22 h. The suspension was adjusted to pH 5 with 6 N NaOH solution, and the resulting suspension was filtered. The filtered solid was dried under reduced pressure to afford 3.85 g (42%) of a 2:1 mixture of the title compound and an undesired regioisomer as a tan solid: ^{1}H NMR (300 MHz,

DMSO-d_6) δ 10.90 (s, 1H), 9.00 (br s, 1H), 7.63 (s, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.12–7.04 (m, 1H), 4.66 (s, 1H), 3.50–2.70 (m, 4H).

Undesired regioisomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.09 (s, 1H), 9.00 (br s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.12–7.04 (m, 1H), 6.91 (overlapping dd, J = 8.0 Hz, 1H), 4.66 (s, 1H), 3.50–2.70 (m, 4H).

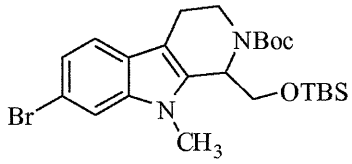
b) 7-Bromo-1-((*tert*-butyldimethylsilyloxy)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole



Chemical Formula: $C_{18}H_{27}BrN_2OSi$
Exact Mass: 394.11
Molecular Weight: 395.41

A 1.0 M solution of $LiAlH_4$ in THF (26 mL, 26.1 mmol) was added to a solution of a 2:1 mixture of 7-bromo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-1-carboxylic acid and the undesired regioisomer (3.85 g, 13.1 mmol) in THF (50 mL) under N_2, and the resulting solution was heated at reflux for 1 h. The solution was cooled to 0 °C and H_2O, 6 N NaOH in H_2O and H_2O were added carefully in succession. The resulting suspension was filtered through celite. The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) afforded 2.48 g of a tan foam. Et_3N (6.2 mL, 44.3 mmol) was added to a suspension of TBSCl (6.68 g, 44.3 mmol) and the above tan foam in CH_2Cl_2 (50 mL) under N_2, and the resulting suspension was stirred at 25 °C overnight. H_2O was added to the suspension, and the phases were separated. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 Et_2O/MeOH/NH_4OH), 100:0 to 75:25) yielded the title compound (1.186 g, 32%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.45 (d, J = 1.7 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.18 (dd, J = 8.4, 1.7 Hz, 1H), 4.19–4.10 (m, 1H), 3.92 (dd, J = 9.2, 5.0 Hz, 1H), 3.69 (dd, J = 9.2, 9.2 Hz, 1H), 3.32 (ddd, J = 12.6, 4.2, 4.2 Hz, 1H), 3.11–3.01 (m, 1H), 2.75–2.62 (m, 2H), 0.97 (s, 9H), 0.13 (s, 6H).

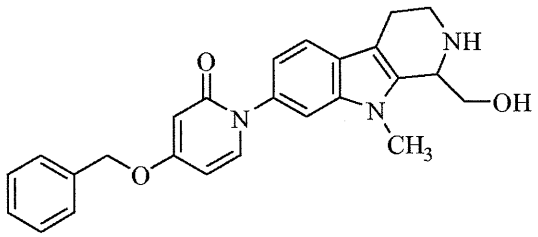
c) *tert*-Butyl 7-bromo-1-((*tert*-butyldimethylsilyloxy)methyl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{24}H_{37}BrN_2O_3Si$
Exact Mass: 508.18
Molecular Weight: 509.55

Boc_2O (752 mg, 3.45 mmol) was added to a suspension of 7-Bromo-1-((*tert*-butyldimethyl-silyloxy)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (1.239 g, 3.14 mmol) and K_2CO_3 (476 mg, 3.45 mmol) in a 1:1 mixture of H_2O/*i*-PrOH (80 mL), and the resulting suspension was stirred at 25 °C for 2 h. The suspension was filtered, and the solid was concentrated under reduced pressure. MeI (0.19 mL, 3.1 mmol) was added to a suspension of the above solid and Cs_2CO_3 (1.34 g, 4.12 mmol) in DMSO (20 mL) under N_2, and the resulting suspension was stirred at 25 °C for 4 h. H_2O was added to the suspension, and the resulting suspension was filtered. The solid was dried under reduced pressure to afford the title compound (728 mg, 46%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (br s, 1H), 7.37–7.28 (m, 1H), 7.23–7.15 (m, 1H), 5.49–5.43 (m, 0.6H), 5.37–5.32 (m, 0.4H), 4.56–4.48 (m, 0.4H), 4.35–4.24 (m, 0.6H), 3.98–3.84 (m, 2H), 3.68 (s, 3H), 3.43–3.35 (m, 0.6H), 3.30–3.21 (m, 0.4H), 2.90–2.75 (m, 1H), 2.72–2.63 (m, 1H), 1.50 (s, 9H), 0.90–0.82 (m, 9H), 0.14–0.02 (m, 6H).

d) 4-(Benzyloxy)-1-(1-(hydroxymethyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one

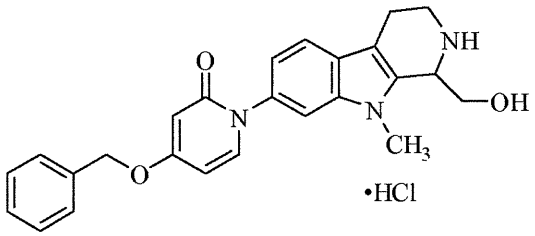


Chemical Formula: $C_{25}H_{25}N_3O_3$
Exact Mass: 415.19
Molecular Weight: 415.48

A suspension of *tert*-butyl 7-bromo-1-((*tert*-butyldimethylsilyloxy)methyl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (727 mg, 1.47 mmol), 4-(benzyl-oxy)pyridin-2(1*H*)-one (591 mg, 2.94 mmol), CuI (110 mg, 0.576 mmol), 8-hydroxyquinoline (84 mg, 0.58 mmol) and Cs_2CO_3 (720 mg, 2.21 mmol) in DMSO (10 mL) was degassed under reduced pressure for 45 min. The suspension was put under Ar

and heated at 135 °C with stirring for 14 h. The suspension was cooled, 1:1 MeOH/NH_4OH (40 mL) was added, and the resulting suspension was stirred for 30 min. CH_2Cl_2 was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 Et_2O/MeOH/NH_4OH) 100:0 to 0:100) afforded the amine as a yellow amorphous solid. A 1.0 M solution of TBAF in THF (0.57 mL, 0.57 mmol) was added to a solution of the above yellow semi-solid in THF (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 1.5 h. H_2O and CH_2Cl_2 were added to the solution and the phases were separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 Et_2O/MeOH/NH_4OH) 100:0 to 0:100) yielded a yellow amorphous solid. TFA (2 mL) was added to a solution of the above amorphous solid in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 1 h. The solution was concentrated under reduced pressure. The resulting residue was diluted with CH_2Cl_2 and neutralized with a saturated aqueous $NaHCO_3$ solution. The phases were separated. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH) 100:0 to 0:100) yielded the title compound (56 mg, 9%) as a viscous oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 1H), 7.46–7.37 (m, 5H), 7.32 (d, J = 7.5 Hz, 1H), 7.30 (d, J = 1.5 Hz, 1H), 7.03 (dd, J = 8.0, 1.5 Hz, 1H), 6.11 (d, J = 2.5 Hz, 1H), 6.06 (dd, J = 7.5, 2.5 Hz, 1H), 5.08 (s, 2H), 4.14 (dd, J = 10.0, 4.5 Hz, 1H), 3.80 (dd, J = 10.0, 4.5 Hz, 1H), 3.69–3.62 (m, 4H), 3.23 (ddd, J = 14.0, 4.5, 4.5 Hz, 1H), 3.12–3.05 (m, 1H), 2.78–2.73 (m, 2H); ESI MS *m/z* 416 $[M + H]^+$.

e) 4-(Benzyloxy)-1-(1-(hydroxymethyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



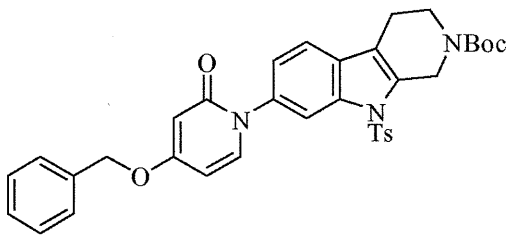
Chemical Formula: $C_{25}H_{26}ClN_3O_3$
Exact Mass: 451.17
Molecular Weight: 451.95

A 1.0 M solution of HCl in Et_2O (0.13 mL, 0.13 mmol) was added to a solution of 4-(benzyloxy)-1-(1-(hydroxymethyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one (55 mg, 0.13 mmol) in CH_2Cl_2 (10 mL) under N_2 and stirred at 25 °C for 1 h. The solution was concentrated to afford the title compound (32 mg, 54%) as an off-white powder: mp 168–170 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.48 (br s, 1H), 9.10 (br s, 1H), 7.56 (overlapping dd, J = 8.5 Hz, 2H), 7.52 (s, 1H), 7.49–7.41 (m, 4H), 7.40–7.36 (m, 1H), 7.01 (dd, J = 7.0, 1.5 Hz, 1H), 6.12 (dd, J = 7.5, 1.5 Hz, 1H), 5.98 (d, J = 1.5 Hz, 1H), 5.72 (t, J = 3.3 Hz, 1H), 5.16 (s, 2H), 4.89–4.82 (m, 1H), 4.07–4.01 (m, 1H), 3.80–3.71 (m, 1H), 3.72 (s, 3H), 3.61–3.50 (m, 1H), 3.49–3.43 (m, 1H), 3.02–2.94 (m, 2H); ESI MS *m/z* 416 $[M + H]^+$.

Example 106

Preparation of 4-(Benzyloxy)-1-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

a) *tert*-Butyl 7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate

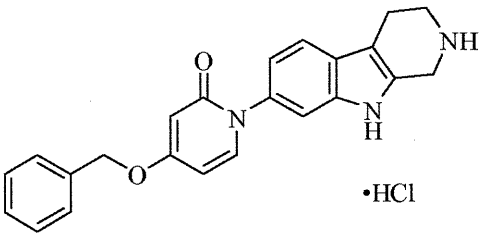


Chemical Formula: $C_{35}H_{35}N_3O_6S$
Exact Mass: 625.22
Molecular Weight: 625.73

A suspension of 4-(benzyloxy)pyridin-2(1*H*)-one (426 mg, 2.12 mmol), *tert*-butyl 7-bromo-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (1.28 g, 2.54 mmol), CuI (484 mg, 2.54 mmol), 8-hydroxyquinoline (369 mg, 2.54 mmol) and Cs_2CO_3 (760 mg, 2.33 mmol) in DMSO (10 mL) was degassed under reduced pressure for 45 min.

The suspension was put under Ar and heated at 135 °C with stirring for 1.5 h. The suspension was cooled, 4:1 CH_2Cl_2/(9:1 MeOH/NH_4OH) (50 mL) was added and the resulting suspension was stirred at 25 °C for 10 min. The suspension was passed through a plug of silica gel and the filtrate was washed with brine. The solution was dried over Na_2SO_4 and concentrated under reduced pressure to afford an amorphous solid. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH) 100:0 to 0:100) yielded the title compound (715 mg, 54%) as an off-white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (br s, 1H), 7.82–7.73 (m, 2H), 7.48–7.35 (m, 6H), 7.33–7.23 (m, 4H), 6.12–5.97 (m, 2H) 5.07 (s, 2H), 4.90 (br s, 2H), 3.72–3.64 (m, 2H), 2.73–2.63 (m, 2H), 2.34 (s, 3H), 1.51 (s, 9H).

b) 4-(Benzyloxy)-1-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{23}H_{22}ClN_3O_2$
Exact Mass: 407.14
Molecular Weight: 407.89

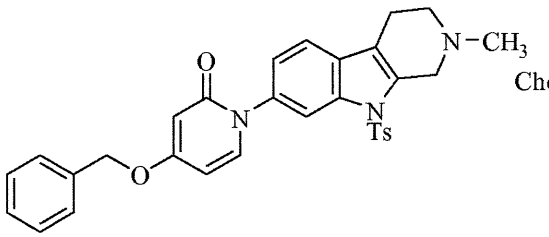
TFA (2 mL) was added to a solution of *tert*-butyl 7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (678 mg, 1.09 mmol) in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 1 h. Saturated $NaHCO_3$ solution and EtOAc were added, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4. The organic solution was concentrated under reduced pressure to afford 510 mg of an off-white solid. NaOH (469 mg, 11.7 mmol) was added to a solution of the off-white solid (123 mg) in CH_2Cl_2/MeOH (10 mL) that had been degassed with N_2. The resulting solution was heated at 40 °C with stirring for 5 h under N_2. The solution was allowed to cool, saturated NH_4Cl solution and CH_2Cl_2 were added, and the phases were separated. The organic phase was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated under reduced pressure to yield an off-white solid. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH) 100:0

to 0:100) afforded a white solid. 1 M HCl in Et_2O (0.28 ml, 0.28 mmol) was added to a solution of the white solid in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 30 min. The resulting suspension was filtered. The solid was washed with CH_2Cl_2 and dried under reduced pressure to afford the title compound (26 mg, 24%) as a white solid: mp 246–248 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.22 (s, 1H), 9.29 (br s, 2H), 7.54 (dd, J = 12.0, 8.0 Hz, 2H), 7.50–7.41 (m, 4H), 7.40–7.33 (m, 2H), 6.96 (dd, J = 8.0, 1.5 Hz, 1H), 6.09 (dd, J = 7.5, 2.5 Hz, 1H), 5.97 (d, J = 2.5 Hz, 1H), 5.15 (s, 2H), 4.38 (s, 2H), 3.50–3.42 (m, 2H) 3.00–2.92 (m, 2H); ESI MS *m/z* 372 $[M + H]^+$.

Example 107

Preparation of 4-(Benzyloxy)-1-(2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

a) 4-(Benzyloxy)-1-(2-methyl-9-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one

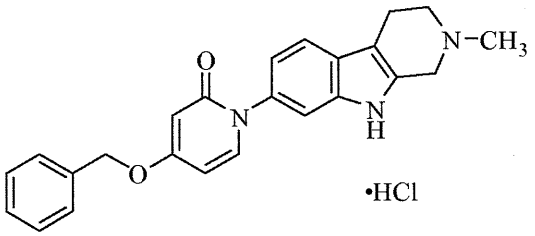


Chemical Formula: $C_{31}H_{29}N_3O_4S$
Exact Mass: 539.19
Molecular Weight: 539.64

TFA (2 mL) was added to a solution of *tert*-butyl 7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (678 mg, 1.09 mmol) in CH_2Cl_2 (10 mL) under N_2 and the resulting solution was stirred at 25 °C for 1 h. Saturated $NaHCO_3$ solution and EtOAc were added to the solution and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4. The organic solution was concentrated under reduced pressure to afford 510 mg of an off-white solid. Formaldehyde (37% in H_2O, 0.04 mL, 0.49 mmol) was added to a solution of the off-white solid (170 mg) in 1:1 MeOH/CH_2Cl_2 (10 mL) and the resulting solution was stirred at 25 °C for 45 min. $NaBH(OAc)_3$ (137 mg, 0.648 mmol) was added to the solution and the resulting suspension was stirred at 25 °C for 30 min. The suspension was concentrated under reduced pressure and the resulting

residue was diluted with CH_2Cl_2 and saturated $NaHCO_3$ solution. The phases were separated. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to yield the title compound (174 mg, 89%) as a viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J = 1.5 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.47–7.35 (m, 6H), 7.33–7.28 (m, 1H), 7.26–7.21 (m, 3H), 6.12–6.05 (m, 2H), 5.07 (s, 2H), 3.92 (br s, 2H), 2.79–2.70 (m, 4H), 2.56 (s, 3H), 2.33 (s, 3H).

b) 4-(Benzyloxy)-1-(2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



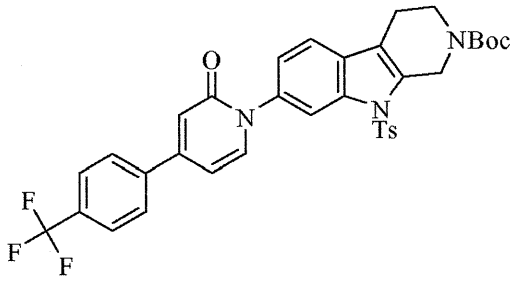
Chemical Formula: $C_{24}H_{24}ClN_3O_2$
Exact Mass: 421.16
Molecular Weight: 421.92

NaOH (644 mg, 16.1 mmol) was added to a solution of the 4-(benzyloxy)-1-(2-methyl-9-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one (174 mg, 0.322 mmol) in CH_2Cl_2/MeOH (10 mL) that had been degassed with N_2. The resulting solution was heated at reflux with stirring for 2 h under N_2. The solution was allowed to cool, saturated NH_4Cl solution and CH_2Cl_2 were added, and the phases were separated. The organic phase was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated under reduced pressure to yield a white solid. 1 M HCl in Et_2O (0.38 ml, 0.38 mmol) was added to a solution of the white solid in 9:1 CH_2Cl_2/MeOH (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 30 min. The solution was concentrated, and the residue was diluted with a small amount of CH_2Cl_2/CH_3CN. The resulting suspension was filtered, and the solid was dried under reduced pressure to yield the title compound (46 mg, 34%) as a white solid: mp 168–170 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.30 (s, 1H), 10.50–10.41 (m, 1H), 7.58–7.52 (m, 2H), 7.49–7.40 (m, 4H), 7.39–7.35 (m, 2H), 6.96 (br d, J = 8.0 Hz, 1H), 6.09 (br d, J = 7.5 Hz, 1H), 5.97 (br s, 1H), 5.15 (s, 2H), 4.60 (br d, J = 15.0 Hz, 1H), 4.41 (dd, J = 15.0, 7.5 Hz, 1H), 3.78–3.71 (m, 1H), 3.45–3.38 (m, 1H), 3.09–2.98 (m, 5H); ESI MS *m/z* 386 $[M + H]^+$.

Example 108

Preparation of 1-(2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one hydrochloride

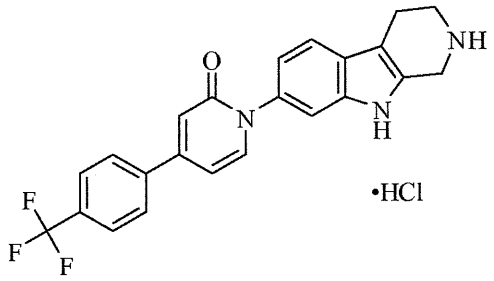
a) *tert*-Butyl 7-(2-oxo-4-(4-(trifluoromethyl)phenyl)pyridin-1(2*H*)-yl)-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{35}H_{32}F_3N_3O_5S$
Exact Mass: 663.20
Molecular Weight: 663.71

A suspension of 4-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one (121 mg, 0.504 mmol), *tert*-butyl 7-bromo-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (305 mg, 0.605 mmol), CuI (115 mg, 0.605 mmol), 8-hydroxyquinoline (88 mg, 0.605 mmol) and Cs_2CO_3 (181 mg, 0.605 mmol) in DMSO (5 mL) was degassed under reduced pressure for 45 min. The suspension was put under Ar and heated at 135 °C with stirring for 2.5 h. The suspension was cooled, 4:1 CH_2Cl_2/(9:1 MeOH/NH_4OH) (25 mL) was added and the resulting suspension was stirred at 25 °C for 10 min. The suspension was passed through a plug of silica gel and the filtrate was washed with brine. The solution was dried over Na_2SO_4 and concentrated under reduced pressure to afford an amorphous solid. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH) 100:0 to 0:100) gave the title compound (170 mg, 51%) as a pink foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (br s, 1H), 7.83–7.74 (m, 6H), 7.53 (d, J = 7.2 Hz, 1H), 7.51–7.45 (m, 1H), 7.35–7.23 (m, 3H), 6.93 (d, J = 1.8 Hz, 1H), 6.54 (dd, J = 7.2, 1.8 Hz, 1H), 4.91 (br s, 2H), 3.75–3.65 (m, 2H), 2.73–2.68 (m, 2H), 2.36 (s, 3H), 1.52 (s, 9H).

b) 1-(2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one hydrochloride



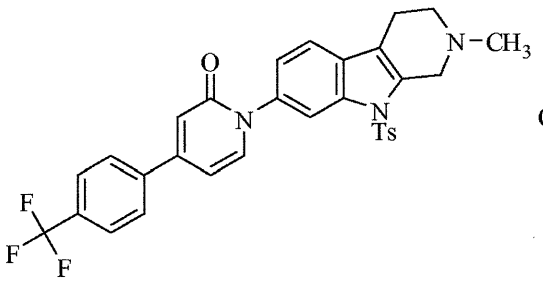
Chemical Formula: $C_{23}H_{19}ClF_3N_3O$
Exact Mass: 445.12
Molecular Weight: 445.86

TFA (1 mL) was added to a solution of *tert*-butyl 7-(2-oxo-4-(4-(trifluoro-methyl)phenyl)pyridin-1(2*H*)-yl)-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (170 mg, 0.256 mmol) in CH_2Cl_2 (5 mL) under N_2, and the resulting solution was stirred at 25 °C for 30 min. Saturated $NaHCO_3$ solution and CH_2Cl_2 were added to the solution, and the phases were separated. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford 145 mg of a pink solid. NaOH (227 mg, 5.67 mmol) was added to a solution of the pink solid (64 mg) in CH_2Cl_2/MeOH (10 mL) that had been degassed with N_2. The resulting solution was heated at reflux with stirring for 7 h under N_2. The solution was allowed to cool, saturated NH_4Cl solution and CH_2Cl_2 were added, and the phases were separated. The organic phase was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated under reduced pressure to yield a yellow powder. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH) 100:0 to 0:100) afforded a yellow solid. 1 M HCl in Et_2O (0.07ml, 0.06 mmol) was added to a solution of the yellow solid in 9:1 CH_2Cl_2/MeOH (10 mL) under N_2 and the resulting solution was stirred at 25 °C for 30 min. The solution was concentrated under reduced pressure to yield the title compound (27 mg, 54%) as a yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.28 (s, 1H), 9.21 (br s, 2H), 8.01 (d J = 8.3 Hz, 2H), 7.88 (d, J = 8.3 Hz, 2H), 7.80 (d, J = 7.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 1.5 Hz, 1H), 7.07 (dd, J = 8.0, 1.5 Hz, 1H), 6.87 (d, J = 2.0 Hz, 1H), 6.72 (dd, J = 7.0, 2.0 Hz, 1H), 4.40 (s, 2H), 3.52–3.48 (m, 2H), 2.99 (t, J = 6.0 Hz, 2H); ESI MS *m/z* 410 $[M + H]^+$.

Example 109

Preparation of 1-(2-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(4-(trifluoro-methyl)phenyl)pyridin-2(1*H*)-one hydrochloride

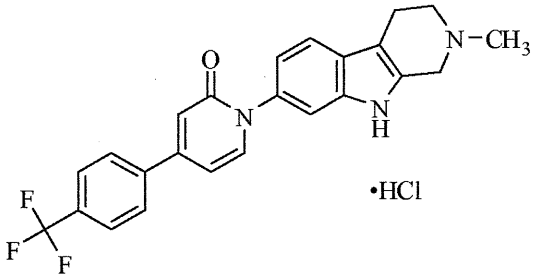
a) 1-(2-Methyl-9-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one



Chemical Formula: $C_{31}H_{26}F_3N_3O_3S$
Exact Mass: 577.16
Molecular Weight: 577.62

TFA (1 mL) was added to a solution of *tert*-butyl 7-(2-oxo-4-(4-(trifluoro-methyl)phenyl)pyridin-1(2*H*)-yl)-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (170 mg, 0.256 mmol) in CH_2Cl_2 (5 mL) under N_2, and the resulting solution was stirred at 25 °C for 30 min. Saturated $NaHCO_3$ solution and CH_2Cl_2 were added to the solution, and the phases were separated. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford 145 mg of a pink solid. Formaldehyde (37% in H_2O, 0.02 mL, 0.2 mmol) was added to a solution of the pink solid (80 mg) in 1:1 MeOH/CH_2Cl_2 (4 mL) and the resulting solution was stirred at 25 °C for 45 min. $NaBH(OAc)_3$ (60 mg, 0.28 mmol) was added to the solution and the resulting suspension was stirred at 25 °C for 30 min. The suspension was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 and saturated $NaHCO_3$ solution. The phases were separated. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to yield the title compound (61 mg, 74%) as a pink foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 1.8 Hz, 1H), 7.79–7.71 (m, 6H), 7.53 (d, J = 7.2 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.32 (dd, J = 8.4, 1.8 Hz, 1H), 7.27–7.22 (m, 2H), 6.93 (d, J = 1.8 Hz, 1H), 6.53 (dd, J = 7.2, 1.8 Hz, 1H), 3.93 (br s, 2H), 2.80–2.60 (m, 4H), 2.57 (s, 3H), 2.34 (s, 3H).

b) 1-(2-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(4-(trifluoro-methyl)phenyl)pyridin-2(1*H*)-one hydrochloride



•HCl

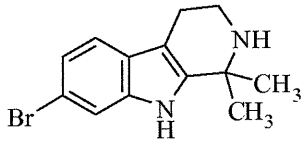
Chemical Formula: $C_{24}H_{21}ClF_3N_3O$
Exact Mass: 459.13
Molecular Weight: 459.89

NaOH (211 mg, 5.28 mmol) was added to a solution of 1-(2-methyl-9-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one (61 mg, 0.11 mmol) in CH_2Cl_2/MeOH (10 mL) that had been degassed with N_2. The resulting solution was heated at reflux with stirring for 7 h under N_2. The solution was allowed to cool, saturated NH_4Cl solution and CH_2Cl_2 were added, and the phases were separated. The organic phase was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated under reduced pressure to yield a yellow solid. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH) 100:0 to 0:100) afforded a yellow solid. 1 M HCl in Et_2O (0.06 ml, 0.06 mmol) was added to a solution of the yellow solid in 9:1 CH_2Cl_2/MeOH (10 mL) under N_2 and the resulting solution was stirred at 25 °C for 30 min. The solution was concentrated under reduced pressure to yield the title compound (28 mg, 58%) as a yellow solid: mp 200–204 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.36 (s, 1H), 10.35 (br s, 1H), 8.02 (d, J = 8.3 Hz, 2H), 7.88 (d, J = 8.3 Hz, 2H), 7.80 (d, J = 7.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.49 (br s, 1H), 7.07 (dd, J = 8.0, 1.5 Hz, 1H), 6.87 (d, J = 1.5 Hz, 1H), 6.72 (d, J = 7.0, 1.5 Hz, 1H), 4.62 (br d, J = 16.0 Hz, 1H), 4.49–4.40 (m, 1H), 3.81–3.73 (m, 1H), 3.49–3.39 (m, 1H), 3.12–3.00 (m, 5H); ESI MS *m/z* 424 $[M + H]^+$.

Example 110

Preparation of 4-(Benzyloxy)-1-(1,1,9-trimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

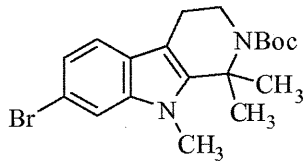
a) 7-Bromo-1,1-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole



Chemical Formula: $C_{13}H_{15}BrN_2$
Exact Mass: 278.04
Molecular Weight: 279.18

Concentrated HCl (10 mL) was added to a suspension of a 2:1 mixture of 2-(6-bromo-1*H*-indol-3-yl)ethanamine and 2-(4-bromo-1*H*-indol-3-yl)ethanamine (9.90 g, 41.4 mmol) and Na_2SO_4 (30 g) in 1:1 acetone/*n*-butanol (100 mL). The resulting suspension was heated at 60 °C with stirring for 4 d. The suspension was cooled and concentrated under reduced pressure. The residue was diluted with EtOAc, and the suspension was filtered. The filtrate was washed with saturate $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH) 100:0 to 0:100) yielded the title compound (1.68 g, 15%) as a red foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (br s, 1H), 7.45 (d, J = 1.5 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.19 (dd, J = 8.5, 1.5 Hz, 1H), 3.20 (t, J = 5.5 Hz, 2H), 2.68 (t, J = 5.5 Hz, 2H), 1.47 (s, 6H).

b) *tert*-Butyl 7-bromo-1,1,9-trimethyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate

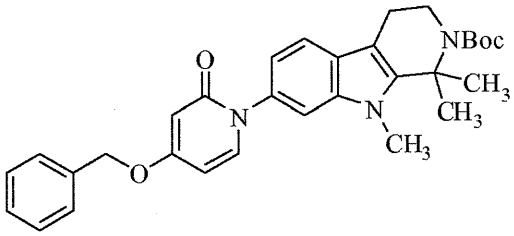


Chemical Formula: $C_{19}H_{25}BrN_2O_2$
Exact Mass: 392.11
Molecular Weight: 393.32

Boc_2O (7.88 g, 36.1 mmol) was added to a suspension of 7-bromo-1,1-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (1.68 g, 6.02 mmol) and K_2CO_3 (1.66 g, 12.0 mmol) in 1:1 H_2O/*i*-PrOH (80 mL), and the resulting suspension was stirred at 25 °C for 2 h. The suspension was filtered. The solid was washed with H_2O and dried under reduced pressure to afford 1.285 g of a white solid. NaH (60% dispersion in oil, 152 mg, 3.80 mmol) was added to a solution of the white solid (720 mg) in DMF (10 mL) under N_2 and the resulting suspension was stirred at 25 °C for 30 min. MeI (0.18 mL, 2.9 mmol) was added to the suspension, and the resulting suspension was stirred at 25 °C for 30 min. The suspension was cooled to 0 °C, and H_2O was added slowly. Hexanes was added and the phases were separated. The organic phase was dried over Na_2SO_4 and concentrated under

reduced pressure. Flash chromatography (silica gel, hexanes/(1:1 EtOAc/hexanes) 100:0 to 60:40) yielded the title compound (471 mg, 36%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 1.5 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.20 (dd, J = 8.4, 1.5 Hz, 1H), 3.79–3.72 (m, 5H), 2.73 (t, J = 5.4 Hz, 2H), 1.88 (s, 6H), 1.53 (s, 9H).

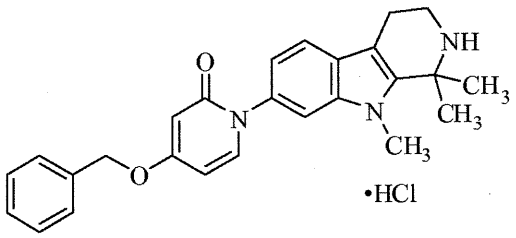
c) *tert*-Butyl 7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-1,1,9-trimethyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{31}H_{35}N_3O_4$
Exact Mass: 513.26
Molecular Weight: 513.63

A suspension of 4-(benzyloxy)pyridin-2(1*H*)-one (107 mg, 0.532 mmol), *tert*-butyl 7-bromo-1,1,9-trimethyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (251 mg, 0.639 mmol), CuI (122 mg, 0.639 mmol), 8-hydroxyquinoline (93 mg, 0.639 mmol) and Cs_2CO_3 (190 mg, 0.585 mmol) in DMSO (10 mL) was degassed under reduced pressure for 45 min. The suspension was put under Ar and heated at 135 °C with stirring overnight. The suspension was cooled, 40:9:1 CH_2Cl_2/MeOH/NH_4OH was added and the resulting suspension was stirred at 25 °C for 30 min. The suspension was passed through a plug of silica gel, and the filtrate was washed with brine. The solution was dried over Na_2SO_4 and concentrated under reduced pressure to afford an amorphous solid. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH) 100:0 to 1:1) yielded the title compound (74 mg, 27%) as a white powder: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 8.1 Hz, 1H), 7.46–7.35 (m, 4H), 7.33–7.25 (m, 3H), 7.12 (dd, J = 8.1, 2.1 Hz, 1H), 6.09 (d, J = 2.6 Hz, 1H), 6.04 (dd, J = 7.5, 2.6 Hz, 1H), 5.06 (s, 2H), 3.80 (s, 3H), 3.77 (t, J = 4.8 Hz, 2H), 2.77 (t, J = 4.8 Hz, 2H), 1.89 (s, 6H), 1.54 (s, 9H).

d) 4-(Benzyloxy)-1-(1,1,9-trimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{26}H_{28}ClN_3O_2$
Exact Mass: 449.19
Molecular Weight: 449.97

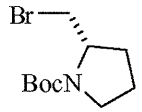
TFA (1 mL) was added to a solution of *tert*-butyl 7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-1,1,9-trimethyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (72 mg, 0.14 mmol) in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 30 min. Saturated $NaHCO_3$ solution and CH_2Cl_2 were added to the solution and the phases were separated. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by semi-preparative HPLC (Phenomenex Luna C18 (2), 250.0 × 21.20 mm, 10 micron, H_2O with 0.05% TFA and CH_3CN with 0.05% TFA) afforded 14 mg of clear crystals. 1 M HCl in Et_2O (0.04 ml, 0.04 mmol) was added to a solution of the clear crystals in CH_2Cl_2 (10 mL) under N_2 and the resulting solution was stirred at 25 °C for 30 min. The solution was concentrated under reduced pressure to yield the title compound (15 mg, 24%) as an off-white powder: mp 296–298; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.59 (s, 2H), 7.58–7.51 (m, 3H), 7.49–7.41 (m, 4H), 7.40–7.35 (m, 1H), 7.01 (dd, J = 8.5, 1.5 Hz, 1H), 6.10 (dd, J = 7.5, 2.8 Hz, 1H), 5.97 (d, J = 2.8 Hz, 1H), 5.16 (s, 2H), 3.80 (s, 3H), 3.52–3.48 (m, 2H), 2.99 (t, J = 6.0 Hz, 2H), 1.81 (s, 6H); ESI MS *m/z* 414 $[M + H]^+$.

Example 111

Preparation of (*S*)-4-(Benzyloxy)-1-(9-methyl-2-(pyrrolidin-2-ylmethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

a) (*S*)-*tert*-Butyl 2-(bromomethyl)pyrrolidine-1-carboxylate

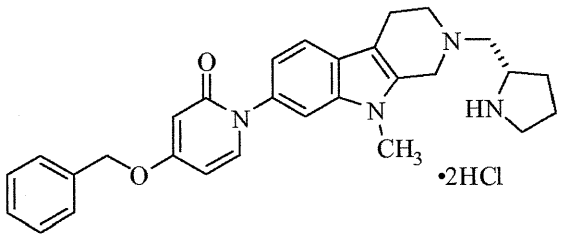
Beilstein Registry Number 6325435



Chemical Formula: $C_{10}H_{18}BrNO_2$
Exact Mass: 263.05
Molecular Weight: 264.16

This compound was prepared in accordance with the procedure of Kawara et al., *Tetrahedron Lett.*, **1994**, *35*, 8805–8808.

b) (*S*)-4-(Benzyloxy)-1-(9-methyl-2-(pyrrolidin-2-ylmethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride



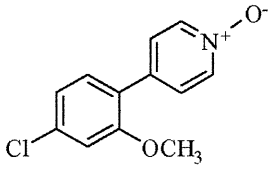
Chemical Formula: $C_{29}H_{34}Cl_2N_4O_2$
Exact Mass: 540.21
Molecular Weight: 541.51

A suspension of 4-(benzyloxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one (250 mg, 0.646 mmol), (*S*)-*tert*-butyl 2-(bromomethyl)pyrrolidine-1-carboxylate (342 mg, 1.29 mmol) and Cs_2CO_3 (841 mg, 2.58 mmol) in DMSO (10 mL) under N_2 was stirred at 25 °C for 16 h. The suspension was heated at 60 °C for 1 d. The suspension was cooled, and H_2O was added. The suspension was filtered. The solid was washed with H_2O and dried under reduced pressure. Flash chromatograph (silica gel, hexanes/(9:0.9:0.1 Et_2O/MeOH/NH_4OH), 100:0 to 0:100) afforded 18 mg of a yellow solid. TFA (1 mL) was added to a solution of the yellow solid in CH_2Cl_2 (5 mL) under N_2 and the resulting solution was stirred at 25 °C for 3.5 h. Saturated $NaHCO_3$ solution and CH_2Cl_2 were added and the phases were separated. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatograph (silica gel,(1:1 EtOAc/hexanes)/(9:0.9:0.1 Et_2O/MeOH/NH_4OH), 100:0 to 0:100) yielded 10 mg of a yellow solid. 1 M HCl in Et_2O (0.04 ml, 0.04 mmol) was added to a solution of the yellow solid in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 30 min. The solution was concentrated under reduced pressure to yield the title compound (10 mg, 3%) as an off-white powder: mp 160–162 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.25 (br s, 1H), 7.56 (d, J = 7.5 Hz, 1H), 7.54–7.40 (m, 6H), 7.39–7.34 (m, 1H), 7.04–6.93 (m, 1H), 6.11 (dd, J = 7.5, 2.5 Hz, 1H), 5.97 (d, J = 2.5 Hz, 1H), 5.16 (s, 2H), 3.98–3.45 (m, 11H), 3.39 (s, 1H), 3.30–3.21 (m, 2H), 2.25–2.10 (m, 1H), 2.05–1.74 (m, 2H), 1.73–1.60 (m, 1H); ESI MS *m/z* 469 $[M + H]^+$.

Example 112

Preparation of 4-(4-Chloro-2-methoxyphenyl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

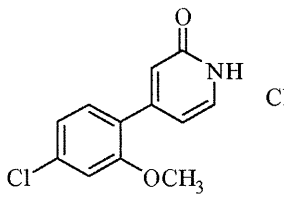
a) 4-(4-Chloro-2-methoxyphenyl)pyridine 1-oxide



Chemical Formula: $C_{12}H_{10}ClNO_2$
Exact Mass: 235.04
Molecular Weight: 235.67

4-Chloropyridine-*N*-oxide (500 mg, 3.85 mmol), 2-methoxy-4-chlorophenylboronic acid (862 mg, 4.63 mmol) and K_2CO_3 (1.59 g, 11.55 mmol) were suspended in DMSO (5 mL) and $PdCl_2$(dppf) (314 mg, 0.385 mmol) was added. The reaction mixture was placed under vacuum for 20 min and flushed with N_2. This process was repeated, and the reaction mixture was heated at 120 °C for 3 h. The reaction mixture was cooled to 25 °C and partitioned between methylene chloride and 5% lithium chloride. The aqueous phase was removed, and the organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. Flash chromatography (ISCO 40 g column, methylene chloride/MeOH 100:0 to 90:10) provided the title compound (673 mg, 74%) as a tan solid: ^{1}H NMR (300 MHz, CD_3OD) δ 8.21 (dd, J = 5.4, 1.8 Hz, 2H), 7.47 (dd, J = 5.6, 1.6 Hz, 2H), 7.26 (d, J = 8.2 Hz, 1H), 7.06 (dd, J = 8.3, 2.4 Hz, 1H), 7.00 (d, J = 1.7 Hz, 1H), 3.87 (s, 3H); ESI MS *m/z* 235 $[M + H]^+$.

b) 4-(4-Chloro-2-methoxyphenyl)pyridin-2(1*H*)-one

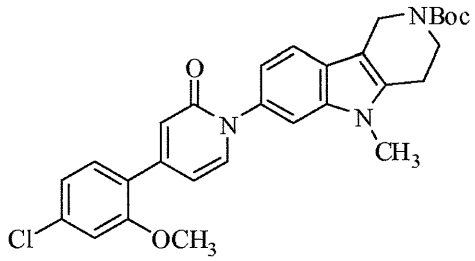


Chemical Formula: $C_{12}H_{10}ClNO_2$
Exact Mass: 235.04
Molecular Weight: 235.67

4-(4-Chloro-2-methoxyphenyl)pyridine 1-oxide (673 mg, 2.86 mmol) and acetic anhydride (10 mL) were heated at reflux for 3 h. The mixture was concentrated under reduced pressure, and a 1:1 solution of H_2O/MeOH (20 mL) was added. The reaction mixture was heated to reflux for 1 h, cooled to 25 °C and concentrated under reduced pressure. The

resulting residue was dissolved in hot 2-propanol (3 mL), triturated with Et_2O, sonicated for 30 min then placed in the freezer. The solid was filtered off providing the title compound (550 mg, 91%) as a tan solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.54 (s, 1H), 7.35–7.33 (m, 2H), 7.01 (s, 1H), 7.08 (d, J = 6.6 Hz, 1H), 6.36 (s, 1H), 6.28 (s, 1H), 3.82 (s, 3H); ESI MS m/z 235 $[M + H]^+$.

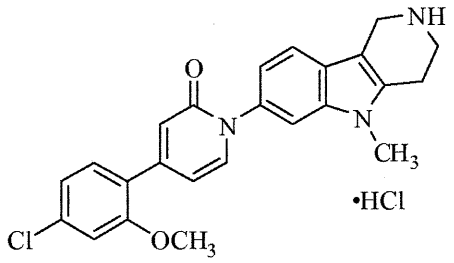
c) *tert*-Butyl 7-(4-(4-chloro-2-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{29}H_{30}ClN_3O_4$
Exact Mass: 519.19
Molecular Weight: 520.02

A suspension of 4-(4-chloro-2-methoxyphenyl)pyridin-2(1*H*)-one (126 mg, 0.534 mmol), *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (234 mg, 0.641 mmol), CuI (122 mg, 0.641 mmol), 8-hydroxyquinoline (93 mg, 0.64 mmol) and Cs_2CO_3 (191 mg, 0.587 mmol) in DMSO (5 mL) was degassed under reduced pressure for 45 min. The suspension was put under Ar and heated at 135 °C with stirring overnight. The suspension was cooled, 40:9:1 CH_2Cl_2/MeOH/NH_4OH was added, and the resulting suspension was stirred at 25 °C for 10 min. The suspension was passed through a plug of silica gel, and the filtrate was washed with brine. The solution was dried over Na_2SO_4 and concentrate under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH) 100:0 to 0:100) gave the title compound (123 mg, 44%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 8.1 Hz, 1H), 7.42–7.35 (m, 2H), 7.31 (d, J = 8.1 Hz, 1H), 7.12–7.02 (m, 2H), 6.99 (d, J = 1.8 Hz, 1H), 6.81 (d, J = 1.8 Hz, 1H), 6.44 (dd, J = 7.2, 1.8 Hz, 1H), 4.65 (br s, 2H), 3.88 (s, 3H), 3.90–3.81 (m, 2H), 3.65 (s, 3H), 2.87–2.79 (m, 2H), 1.51 (s, 9H).

d) 4-(4-Chloro-2-methoxyphenyl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



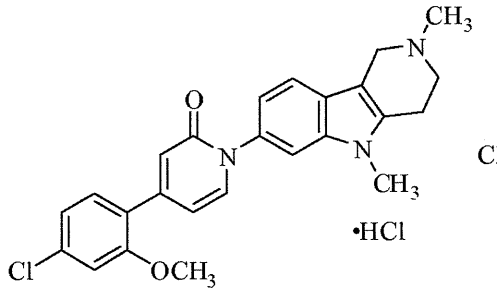
Chemical Formula: $C_{24}H_{23}Cl_2N_3O_2$
Exact Mass: 455.12
Molecular Weight: 456.36

TFA (2 mL) was added to a solution of *tert*-butyl 7-(4-(4-chloro-2-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (124 mg, 0.238 mmol) in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 1 h. Saturated $NaHCO_3$ solution and CH_2Cl_2 were added to the solution, and the phases were separated. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH) 100:0 to 0:100) yielded 70 mg of an off-white solid. 1 M HCl in Et_2O (0.03 ml, 0.03 mmol) was added to a solution of the off-white solid (10 mg) in CH_2Cl_2 (10 mL) under N_2 and the resulting solution was stirred at 25 °C for 30 min. The solution was concentrated under reduced pressure to yield the title compound (9 mg, 26%) as an off-white powder: mp 290–292 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.17 (br s, 2H), 7.65 (d, J = 7.0 Hz, 1H), 7.62 (d, J = 1.8 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 1.8 Hz, 1H), 7.14 (dd, J = 8.0, 1.8 Hz, 1H), 7.09 (dd, J = 8.5, 1.8 Hz, 1H), 6.57 (d, J = 2.0 Hz, 1H), 6.47 (dd, J = 7.0, 2.0 Hz, 1H), 4.37 (br s, 2H), 3.87 (s, 3H), 3.70 (s, 3H), 3.57–3.52 (m, 2H), 3.10 (t, J = 6.0 Hz, 2H); ESI MS *m/z* 420 $[M + H]^+$.

Example 113

Preparation of 4-(4-Chloro-2-methoxyphenyl)-1-(2,5-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

a) 4-(4-Chloro-2-methoxyphenyl)-1-(2,5-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



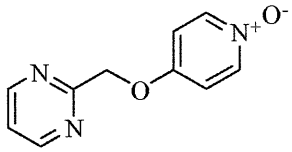
Chemical Formula: $C_{25}H_{25}Cl_2N_3O_2$
Exact Mass: 469.13
Molecular Weight: 470.39

TFA (2 mL) was added to a solution of *tert*-butyl 7-(4-(4-chloro-2-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (124 mg, 0.238 mmol) in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 1 h. Saturated $NaHCO_3$ solution and CH_2Cl_2 were added to the solution, and the phases were separated. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) yielded 70 mg of an off-white solid. Formaldehyde (37% in H_2O, 0.02 mL, 0.2 mmol) was added to a solution of the off-white solid (43 mg) in 1:1 MeOH/CH_2Cl_2 (5 mL) and the resulting solution was stirred at 25 °C for 45 min. $NaBH(OAc)_3$ (43 mg, 0.20 mmol) was added to the solution, and the resulting suspension was stirred at 25 °C for 30 min. The suspension was concentrated under reduced pressure, and the resulting residue was diluted with CH_2Cl_2 and saturated $NaHCO_3$ solution. The phases were separated. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by semi-preparative HPLC (Phenomenex Luna C18 (2), 250.0 × 21.20 mm, 10 micron, H_2O with 0.05% TFA and CH_3CN with 0.05% TFA) afforded 13 mg of an off-white solid. 1 M HCl in Et_2O (0.03 ml, 0.03 mmol) was added to a solution of the off-white solid in CH_2Cl_2 (10 mL) under N_2 and the resulting solution was stirred at 25 °C for 30 min. The solution was concentrated under reduced pressure to yield the title compound (14 mg, 17%) as an off-white powder: mp 270–272 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.15 (br s, 1H), 7.66 (d, J = 7.0 Hz, 1H), 7.63 (d, J = 1.5 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 1.8 Hz, 1H), 7.14 (dd, J = 8.5, 1.5 Hz, 1H), 7.11 (dd, J = 8.0, 1.8 Hz, 1H), 6.57 (d, J = 2.0 Hz, 1H), 6.47 (dd, J = 7.0, 2.0 Hz, 1H), 4.67 (d, J = 13.5 Hz, 1H), 4.33 (dd, J = 14.3, 6.0 Hz, 1H), 3.87 (s, 3H), 3.86–3.79 (m, 1H), 3.71 (s, 3H), 3.55–3.47 (m, 1H), 3.24–3.15 (m, 2H), 3.01 (s, 3H); ESI MS *m/z* 434 $[M + H]^+$.

Example 114

Preparation of 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(pyrimidin-2-ylmethoxy)pyridin-2(1*H*)-one dihydrochloride

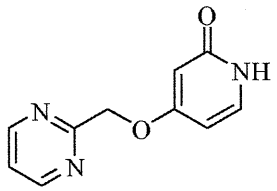
a) 4-(Pyrimidin-2-ylmethoxy)pyridine 1-oxide



Chemical Formula: $C_{10}H_9N_3O_2$
Exact Mass: 203.07
Molecular Weight: 203.20

Following the procedure of Example 137 (step a), but substituting pyrimidin-2ylmethanol (3.0 g, 27 mmol) for imidazo[1,2-*a*]pyridine-2-ylmethanol, the title compound (0.95 g, 17%) was prepared as an orange solid: ^{1}H NMR (300 MHz, CD_3OD) δ 8.81 (d, J = 5.1 Hz, 2H), 8.23–8.21 (m, 2H), 7.45 (t, J = 4.8 Hz, 1H), 7.24–7.21 (m, 2H), 5.46 (s, 2H).

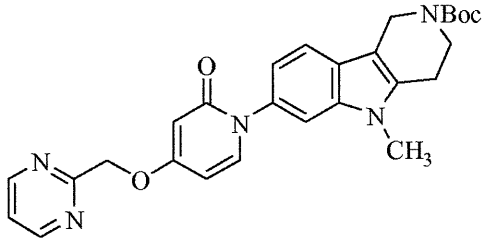
b) 4-(Pyrimidin-2-ylmethoxy)pyridin 2(1*H*)-one



Chemical Formula: $C_{10}H_9N_3O_2$
Exact Mass: 203.07
Molecular Weight: 203.20

Following the procedure of Example 137 (step b), but substituting 4-(pyrimidin-2-ylmethoxy)pyridine 1-oxide (0.95 g, 4.6 mmol) for 4-(imidazo[1,2-*a*]pyridin-2-ylmethoxy)pyridine 1-oxide, the title compound (0.55 g, 58%) was prepared as a dark brown solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 (br s, 1H), 8.84 (d, J = 4.5 Hz, 2H), 7.48 (t, J = 5.0 Hz, 1H), 7.25–7.23 (m, 1H), 5.92 (dd, J = 7.0, 2.5 Hz, 1H), 5.66 (d, J = 8.0, 2.5 Hz, 1H), 5.23 (s, 2H).

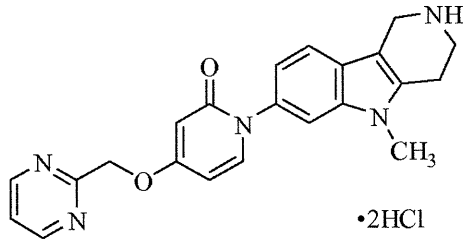
c) *tert*-Butyl 5-methyl-7-(2-oxo-4-(pyrimidin-2-ylmethoxy)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{27}H_{29}N_5O_4$
Exact Mass: 487.22
Molecular Weight: 487.55

A suspension of 4-(pyrimidin-2-ylmethoxy)pyridin-2(1*H*)-one (242 mg, 1.19 mmol), *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (522 mg, 1.43 mmol), CuI (272 mg, 1.43 mmol), 8-hydroxyquinoline (35 mg, 0.24 mmol) and Cs_2CO_3 (426 mg, 1.31 mmol) in DMSO (10 mL) was degassed under reduced pressure for 45 min. The suspension was put under Ar and heated at 135 °C with stirring overnight. The suspension was cooled, 40:9:1 CH_2Cl_2/MeOH/NH_4OH (50 mL) was added, and the resulting suspension was stirred at 25 °C for 1 h. The suspension was passed through a plug of silica gel, and the filtrate was washed with brine. The solution was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(4:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) yielded the title compound (256 mg, 44%) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (d, J = 4.5 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.31–7.27 (m, 3H), 7.01 (br d, J = 8.0 Hz, 1H), 6.17 (dd, J = 7.5, 2.8 Hz, 1H), 6.00 (d, J = 2.8 Hz, 1H), 5.32 (s, 2H), 4.64 (br s, 2H), 3.88–3.79 (m, 2H), 3.62 (s, 3H), 2.84–2.78 (m, 2H), 1.50 (s, 9H).

d) 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(pyrimidin-2-ylmethoxy)pyridin-2(1*H*)-one dihydrochloride



Chemical Formula: $C_{22}H_{23}Cl_2N_5O_2$
Exact Mass: 459.12
Molecular Weight: 460.36

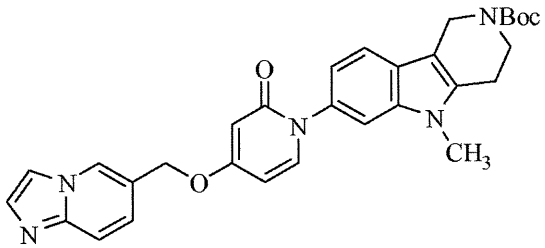
TFA (2 mL) was added to a solution of *tert*-butyl 5-methyl-7-(2-oxo-4-(pyrimidin-2-ylmethoxy)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (256 mg, 0.525 mmol) in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred

at 25 °C for 1 h. Saturated $NaHCO_3$ solution and CH_2Cl_2 were added to the solution, and the phases were separated. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(4:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) yielded 35 mg of a yellow foam. 1 M HCl in Et_2O (0.08 ml, 0.08 mmol) was added to a solution of the yellow foam (16 mg) in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 30 min. The solution was concentrated under reduced pressure to yield the title compound (16 mg, 14%) as an off-white powder: mp 234–236 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.10 (br s, 2H), 8.88 (d, J = 5.0 Hz, 2H), 7.58–7.52 (m, 4H), 6.99 (dd, J = 8.0, 1.8 Hz, 1H), 6.14 (dd, J = 7.5, 2.5 Hz, 1H), 5.86 (d, J = 2.5 Hz, 1H), 5.33 (s, 2H), 4.36 (br s, 2H), 3.68 (s, 3H), 3.57–3.52 (m, 2H), 3.11–3.05 (m, 2H); ESI MS *m/z* 388 $[M + H]^+$.

Example 115

Preparation of 4-(Imidazo[1,2-*a*]pyridin-6-ylmethoxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

a) *tert*-Butyl 7-(4-(imidazo[1,2-*a*]pyridin-6-ylmethoxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate

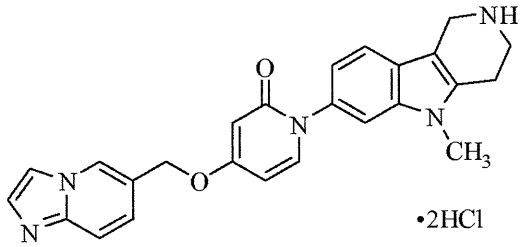


Chemical Formula: $C_{30}H_{31}N_5O_4$
Exact Mass: 525.24
Molecular Weight: 525.60

A suspension of 4-(imidazo[1,2-*a*]pyridin-6-ylmethoxy)pyridin-2(1*H*)-one (270 mg, 1.12 mmol), *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (493 mg, 1.35 mmol), CuI (257 mg, 1.35 mmol), 8-hydroxyquinoline (98 mg, 0.67 mmol) and Cs_2CO_3 (401 mg, 1.23 mmol) in DMSO (10 mL) was degassed under reduced pressure for 45 min. The suspension was put under Ar and heated at 135 °C with stirring for 4.5 h. The suspension was cooled, 40:9:1 CH_2Cl_2/MeOH/NH_4OH (50 mL) was added, and the resulting suspension was stirred at 25 °C for 30 min. The suspension was passed through a plug of silica gel, and the filtrate was washed with brine. The solution

was dried over Na_2SO_4 and concentrate under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(4:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) yielded the title compound (167 mg, 28%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34–8.25 (m, 1H), 7.79–7.61 (m, 3H), 7.58–7.50 (m, 1H), 7.40–7.25 (m, 3H), 7.07–6.69 (m, 1H), 6.17–6.10 (m, 1H), 6.09–6.02 (m, 1H), 5.11 (s, 2H), 4.65 (br s, 2H), 3.92–3.80 (m, 2H), 3.65 (s, 3H), 2.89–2.80 (m, 2H), 1.52 (s, 9H); ESI MS *m/z* 526 $[M + H]^+$.

b) 4-(Imidazo[1,2-*a*]pyridin-6-ylmethoxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride



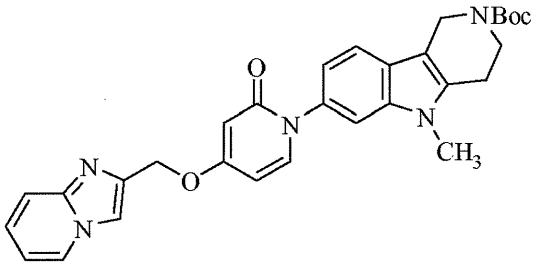
Chemical Formula: $C_{25}H_{25}Cl_2N_5O_2$
Exact Mass: 497.14
Molecular Weight: 498.40

TFA (2 mL) was added to a solution of *tert*-butyl 7-(4-(imidazo[1,2-*a*]pyridin-6-ylmethoxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (167 mg, 0.317 mmol) in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 1 h. Saturated $NaHCO_3$ solution and CH_2Cl_2 were added to the solution, and the phases were separated. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(4:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) yielded 51 mg of a yellow solid. Purification by semi-preparative HPLC (Phenomenex Luna C18 (2), 250.0 × 21.20 mm, 10 micron, H_2O with 0.05% TFA and CH_3CN with 0.05% TFA) afforded 7 mg of a white solid. 1 M HCl in Et_2O (0.03 ml, 0.03 mmol) was added to a solution of the white solid (7 mg) in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 30 min. The solution was concentrated under reduced pressure to yield the title compound (8 mg, 5%) as a white powder: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.28 (br s, 2H), 9.06 (s, 1H), 8.38 (s, 1H), 8.19 (s, 1H), 8.05–7.94 (m, 2H), 7.62 (d, J = 7.5 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 1.5 Hz, 1H), 6.99 (dd, J = 8.0, 1.5 Hz, 1H), 6.13 (dd, J = 7.5, 2.5 Hz, 1H), 6.09 (d, J = 2.5 Hz, 1H), 5.33 (s, 2H), 4.35 (br s, 2H), 3.69 (s, 3H), 3.56–3.50 (m, 2H), 3.12–3.05 (m, 2H); ESI MS *m/z* 426 $[M + H]^+$.

Example 116

Preparation of 4-(Imidazo[1,2-*a*]pyridin-2-ylmethoxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

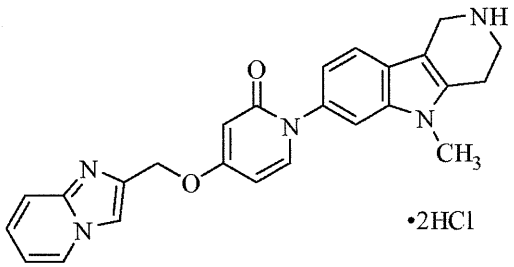
a) *tert*-Butyl 7-(4-(imidazo[1,2-*a*]pyridin-2-ylmethoxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{30}H_{31}N_5O_4$
Exact Mass: 525.24
Molecular Weight: 525.60

A suspension of 4-(imidazo[1,2-*a*]pyridin-2-ylmethoxy)pyridin-2(1*H*)-one (231 mg, 0.960 mmol), *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (421 mg, 1.15 mmol), CuI (219 mg, 1.15 mmol), 8-hydroxyquinoline (84 mg, 0.576 mmol) and Cs_2CO_3 (345 mg, 1.06 mmol) in DMSO (10 mL) was degassed under reduced pressure for 45 min. The suspension was put under Ar and heated at 135 °C with stirring overnight. The suspension was cooled, 40:9:1 CH_2Cl_2/MeOH/NH_4OH (50 mL) was added, and the resulting suspension was stirred at 25 °C for 30 min. The suspension was passed through a plug of silica gel, and the filtrate was washed with brine and 10% $CuSO_4$ solution. The solution was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(4:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) gave the title compound (132 mg, 26%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 6.9 Hz, 1H), 7.70 (br s, 1H), 7.62 (d, J = 8.7 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.33–7.18 (m, 3H), 7.02 (d, J = 7.5 Hz, 1H), 6.82 (dd, J = 6.9, 6.9 Hz, 1H), 6.17 (d, J = 2.1 Hz, 1H), 6.08 (dd, J = 7.5, 2.1 Hz, 1H), 5.25 (s, 2H), 3.84 (br s, 2H), 3.63 (s, 3H), 2.84–2.79 (m, 2H), 1.72–1.60 (m, 2H), 1.50 (s, 9H).

b) 4-(Imidazo[1,2-*a*]pyridin-2-ylmethoxy)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride



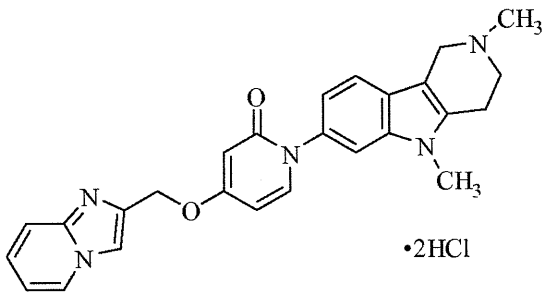
Chemical Formula: $C_{25}H_{25}Cl_2N_5O_2$
Exact Mass: 497.14
Molecular Weight: 498.40

TFA (1 mL) was added to a solution of *tert*-butyl 7-(4-(imidazo[1,2-*a*]pyridin-2-ylmethoxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (132 mg, 0.251 mmol) in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 1 h. Saturated $NaHCO_3$ solution and CH_2Cl_2 were added to the solution, and the phases were separated. The aqueous phase was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(4:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) yielded 42 mg of an off-white solid. 1 M HCl in Et_2O (0.07 ml, 0.07 mmol) was added to a solution of the off-white solid (15 mg) in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 30 min. The solution was concentrated under reduced pressure to yield the title compound (15 mg, 34%) as a white powder: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.30 (br s, 2H), 8.84 (s, 1H), 8.37 (s, 1H), 7.89–7.70 (m, 2H), 7.64–7.53 (m, 2H), 7.50 (s, 1H), 7.37–7.29 (m, 1H), 7.03–6.97 (m, 1H), 6.20–6.09 (m, 2H), 5.41 (s, 2H), 4.35 (br s, 2H), 3.69 (s, 3H), 3.58–3.50 (m, 2H), 3.13–3.07 (m, 2H); ESI MS *m/z* 426 $[M + H]^+$.

Example 117

Preparation of 1-(2,5-Dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(imidazo[1,2-*a*]pyridin-2-ylmethoxy)pyridin-2(1*H*)-one dihydrochloride

a) 1-(2,5-Dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(imidazo[1,2-*a*]pyridin-2-ylmethoxy)pyridin-2(1*H*)-one dihydrochloride



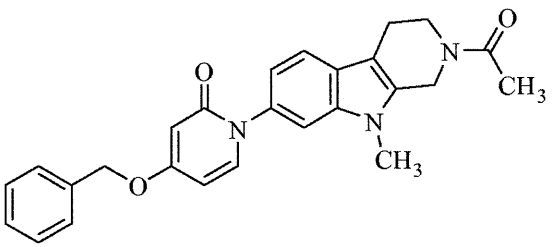
•2HCl

Chemical Formula: $C_{26}H_{27}Cl_2N_5O_2$
Exact Mass: 511.15
Molecular Weight: 512.43

TFA (1 mL) was added to a solution of *tert*-butyl 7-(4-(imidazo[1,2-*a*]pyridin-2-ylmethoxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (132 mg, 0.251 mmol) in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 1 h. Saturated $NaHCO_3$ solution and CH_2Cl_2 were added to the solution, and the phases were separated. The aqueous phase was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(4:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) yielded 42 mg of an off-white solid. Formaldehyde (37% in H_2O, 0.01 mL, 0.12 mmol) was added to a solution of the off-white solid (27 mg) in 1:1 MeOH/CH_2Cl_2 (5 mL), and the resulting solution was stirred at 25 °C for 45 min. $NaBH(OAc)_3$ (27 mg, 0.13 mmol) was added to the solution, and the resulting suspension was stirred at 25 °C for 30 min. The suspension was concentrated under reduced pressure, and the residue was diluted with CH_2Cl_2 and saturated $NaHCO_3$ solution. The phases were separated. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford 25 mg of a viscous oil. 1 M HCl in Et_2O (0.11 ml, 0.11 mmol) was added to a solution of the off-white solid in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 30 min. The solution was concentrated under reduced pressure to yield the title compound (25 mg, 30%) as an off-white powder: ^{1}H NMR (500 MHz, DMSO-d_6) 10.79 (br s, 1H), 8.87 (d, J = 6.5 Hz, 1H), 8.41 (s, 1H), 7.90–7.78 (m, 2H), 7.61 (d, J = 7.5 Hz, 1H), 7.53–7.49 (m, 2H), 7.42–7.35 (m, 1H), 7.00 (dd, J = 8.5, 1.5 Hz, 1H), 6.15 (d, J = 2.5Hz, 1H), 6.12 (dd, J = 7.5, 2.5 Hz, 1H), 5.43 (s, 2H), 4.62 (d, J = 14.0 Hz, 1H), 4.29 (dd, J = 14.0, 7.5 Hz, 1H), 3.80–3.75 (m, 1H), 3.69 (s, 3H), 3.55–3.46 (m, 1H), 3.23–3.16 (m, 2H), 2.97 (s, 3H); ESI MS *m/z* 440 $[M + H]^+$.

Example 118

Preparation of 1-(2-Acetyl-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(benzyloxy)pyridin-2(1*H*)-one

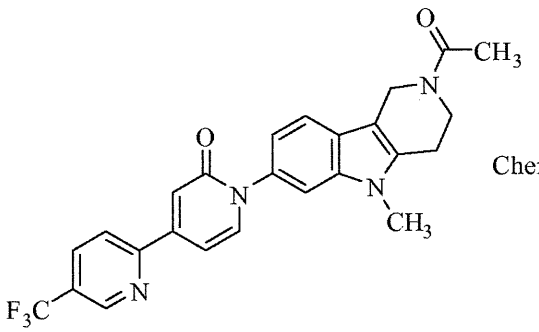


Chemical Formula: $C_{26}H_{25}N_3O_3$
Exact Mass: 427.19
Molecular Weight: 427.50

AcCl (0.023 mL, 0.32 mmol) was added to a solution of 4-(benzyloxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride (100 mg, 0.216 mmol), DMAP (5 mg, 0.04 mmol) and Et_3N (0.09 mL, 0.6 mmol) in CH_2Cl_2 (20 mL) under N_2, and the resulting solution was stirred at 25 °C for 4 h. H_2O was added to the solution, and the phases were separated. The organic phase was washed with saturated NH_4Cl solution, dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) afforded the title compound (61 mg, 66%) as a mixture of rotomers as a white powder: mp 80–82 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.56 (d, J = 7.5 Hz, 1H), 7.52–7.35 (m, 7H), 6.94 (dd, J = 8.0, 1.5 Hz, 1H), 6.12–6.08 (m, 1H), 5.97 (d, J = 3.0 Hz, 1H), 5.15 (s, 2H), 4.77–4.72 (m, 2H), 3.82–3.72 (m, 2H), 3.69–3.65 (m, 3H), 3.82–2.78 (m, 1.3H), 2.71–2.68 (m, 0.7H), 2.16 (s, 3H); ESI MS *m/z* 428 $[M + H]^+$.

Example 119

Preparation of 1-(2-Acetyl-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one

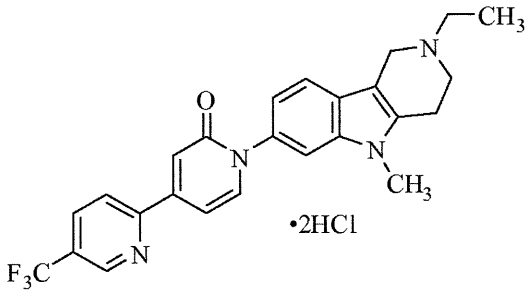


Chemical Formula: $C_{25}H_{21}F_3N_4O_2$
Exact Mass: 466.16
Molecular Weight: 466.46

AcCl (0.03 mL, 0.4 mmol) was added to a solution of 1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one (125 mg, 0.294 mmol), DMAP (7 mg, 0.06 mmol) and Et_3N (0.08 mL, 0.6 mmol) in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 17 h. H_2O was added to the solution, and the phases were separated. The organic phase was washed with saturated NH_4Cl solution, dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) afforded the title compound (116 mg, 84%) as a mixture of rotomers as a white powder: mp 232–236 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.38 (d, J = 8.3 Hz, 1H), 8.35 (d, J = 8.3 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.59–7.54 (m, 2H), 7.28 (d, J = 1.5 Hz, 1H), 7.08–7.03 (m, 2H), 4.70 (s, 0.8H), 4.68 (s, 1.2H), 3.88 (t, J = 5.5 Hz, 0.8H), 3.83 (t, J = 5.5 Hz, 1.2 H), 3.67 (s, 3H), 2.97–2.91 (m, 1.2H), 2.86–2.81 (m, 0.8H), 2.15 (s, 1.8H), 2.13 (s, 1.2H); ESI MS *m/z* 467 $[M + H]^+$.

Example 120

Preparation of 1-(2-Ethyl-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one dihydrochloride



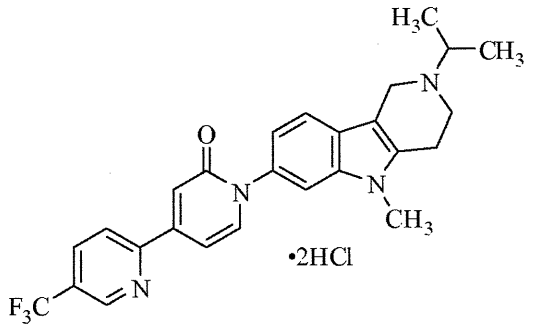
Chemical Formula: $C_{25}H_{25}Cl_2F_3N_4O$
Exact Mass: 524.14
Molecular Weight: 525.39

2-Picoline borane (63 mg, 0.59 mmol) was added to a suspension of 1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one dihydrochloride (98 mg, 0.20 mmol) and acetylaldhyde (0.03 mL, 1 mmol) in 9:1 CH_2Cl_2/AcOH (10 mL) under N_2, and the resulting solution was stirred under N_2 for 4 h. Acetylaldhyde (0.03 mL, 1 mmol) was added to the solution under N_2 and the resulting solution was stirred at 25 °C for 15 min. The solution was neutralized with saturated $NaHCO_3$ solution, and the phases were separated. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1

EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) afforded 67 mg of a yellow powder. 2 N HCl in Et_2O (0.15 mL, 0.330 mmol) was added to a solution of the yellow powder in 1:1 MeOH/CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 15 min. Et_2O was added to the solution, and the resulting suspension was filtered under N_2 to afford the title compound (78 mg, 75%) as a yellow powder: mp 300–302 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.16 (br s, 1H), 9.15 (s, 1H), 8.42–8.35 (m, 2H), 7.85 (d, J = 7.0 Hz, 1H), 7.65 (d, J = 1.5 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H), 7.13 (dd, J = 8.5, 1.5 Hz, 1H), 7.08 (dd, J = 7.5, 2.0 Hz, 1H), 4.70 (d, J = 12.5 Hz, 1H), 4.32 (dd, J = 14.5, 8.0 Hz, 1H), 3.91–3.83 (m, 1H), 3.72 (s, 3H), 3.52–3.43 (m, 1H), 3.41–3.30 (m, 2H), 3.24–3.16 (m, 2H), 1.38 (t, J = 7.3 Hz, 3H); ESI MS *m/z* 453 $[M + H]^+$.

Example 121

Preparation of 1-(2-Isopropyl-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one dihydrochloride



Chemical Formula: $C_{26}H_{27}Cl_2F_3N_4O$
Exact Mass: 538.15
Molecular Weight: 539.42

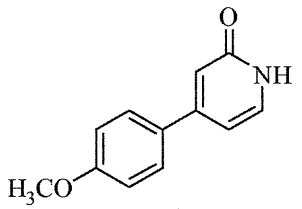
2-Picoline borane (87 mg, 0.81 mmol) was added to a suspension of 1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one dihydrochloride (134 mg, 0.27 mmol) and acetone (0.10 mL, 1.4 mmol) in 9:1 CH_2Cl_2/AcOH (10 mL) under N_2, and the resulting solution was stirred for 24 h. Acetone (1 mL) was added to the solution and the resulting solution was stirred at 25 °C for 24 h. Acetone (1 mL) and 2-picoline borane (87 mg, 0.81 mmol) were added to the solution, and the resulting solution was stirred at reflux for 24 h. The solution was cooled, H_2O was added, and the reaction mixture was neutralized with saturated $NaHCO_3$ solution. The phases were separated, and the organic phase was dried over Na_2SO_4 and concentrated

under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) afforded 88 mg of a yellow powder. 2 N HCl in Et_2O (0.15 mL, 0.330 mmol) was added to a solution of the yellow powder in 1:1 MeOH/CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 30 min. Et_2O was added to the solution, and the resulting solid was collected by filtration under N_2. The solid was washed with Et_2O to afford the title compound (25 mg, 17%) as a yellow powder: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.80 (br s, 1H), 9.15 (d, J = 2.0 Hz, 1H), 8.42–8.35 (m, 2H), 7.85 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 1.5 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H), 7.14 (dd, J = 8.5, 1.5 Hz, 1H), 7.08 (dd, J = 7.5, 2.0 Hz, 1H), 4.58 (d, J = 13.0 Hz, 1H), 4.48–4.40 (m, 1H), 3.90–3.82 (m, 1H), 3.78–3.70 (m, 4H), 3.51–3.42 (m, 1H), 3.38–3.15 (m, 2H), 1.45–1.36 (m, 6H); ESI MS *m/z* 467 $[M + H]^+$.

Example 122

Preparation of 4-(4-Methoxyphenyl)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

a) 4-(4-Methoxyphenyl)pyridin-2(1*H*)-one

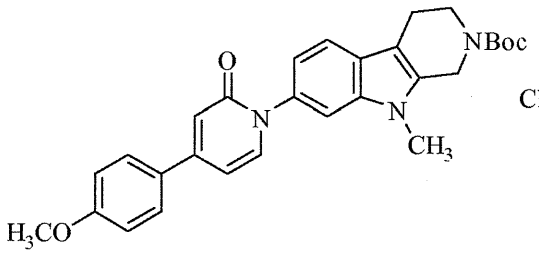


Chemical Formula: $C_{12}H_{11}NO_2$
Exact Mass: 201.08
Molecular Weight: 201.22

A suspension of 4-bromo-2-methoxypyridine (1.22 g, 6.49 mmol), 4-methoxyphenyl boronic acid (1.97 g, 13.0 mmol), $PdCl_2$(dppf) (530 mg, 0.649 mmol) and K_2CO_3 (1.79 g, 13.0 mmol) in DMSO (10 mL) was degassed under reduced pressure for 45 min. The suspension was put under Ar and stirred at 95 °C for 2 h. The suspension was cooled, H_2O was added, and the suspension was filtered to afford a light colored solid. Flash chromatography (silica gel, hexanes/(1:1 EtOAc/hexanes), 100:0 to 0:100) afforded 1.10 g of a white powder. The white powder was diluted with concentrated HCl solution (50 mL) and stirred at reflux for 12 h. The reaction was cooled and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1

CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) afforded the title compound (313 mg, 24%) as a white powder: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.47 (s, 1H), 7.65 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 6.8 Hz, 1H), 7.01 (d, J = 8.7 Hz, 2H), 6.51 (br s, 1H), 6.47 (d, J = 6.8 Hz, 1H), 3.79 (s, 3H).

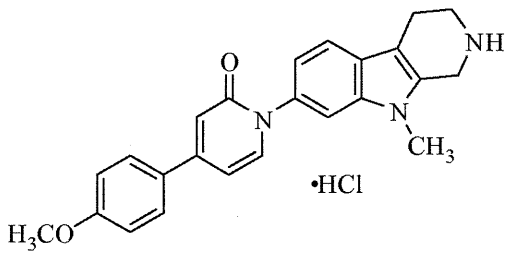
b) *tert*-Butyl 7-(4-(4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{29}H_{31}N_3O_4$
Exact Mass: 485.23
Molecular Weight: 485.57

A suspension of 4-(4-methoxyphenyl)pyridin-2(1*H*)-one (103 mg, 0.510 mmol), *tert*-butyl 7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (223 mg, 0.612 mmol), CuI (116 mg, 0.612 mmol), 8-hydroxyquinoline (15 mg, 0.10 mmol) and Cs_2CO_3 (183 mg, 0.561 mmol) in DMSO (10 mL) was degassed under reduced pressure for 45 min. The suspension was put under Ar and stirred at 135 °C overnight. The suspension was cooled, 9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH was added, and the resulting suspension was stirred at 25 °C for 30 min. The suspension was passed through a plug of silica gel, and the filtrate was washed with brine. The resulting solution was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) afforded the title compound (98 mg, 40%) as a yellow powder: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.53 (m, 3H), 7.46 (d, J = 7.2 Hz, 1H), 7.36 (br s, 1H), 7.08 (dd, J = 8.1, 1.5 Hz, 1H), 7.01 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 1.8 Hz, 1H), 6.51 (dd, J = 7.2, 1.8 Hz, 1H), 4.68–4.60 (m, 2H), 3.88 (s, 3H), 3.82–3.73 (m, 2H), 3.65 (s, 3H), 2.85–2.78 (m, 2H), 1.52 (s, 9H).

c) 4-(4-Methoxyphenyl)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



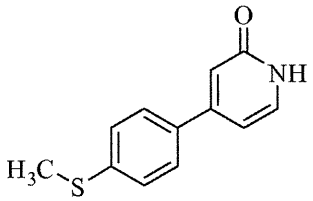
Chemical Formula: $C_{24}H_{24}ClN_3O_2$
Exact Mass: 421.16
Molecular Weight: 421.92

TFA (1 ml) was added to a solution of *tert*-butyl 7-(4-(4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (98 mg, 0.20 mmol) in CH_2Cl_2 (10 mL) under N_2 and the resulting solution was stirred for 2.5 h at 25 °C. Saturated $NaHCO_3$ solution was added, and the phases were separated. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) afforded 49 mg of a white powder. 1 N HCl in Et_2O (0.07 mL, 0.07 mmol) was added to a solution of the white powder in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 1 h. The solution was concentrated under reduced pressure to yield the title compound (47 mg, 55%) as a yellow powder: mp 306–308 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.43 (br s, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 7.0 Hz, 1H), 7.61–7.58 (m, 2H), 7.11–7.05 (m, 3H), 6.73 (d, J = 2.0 Hz, 1H), 6.68 (dd, J = 7.0, 2.0 Hz, 1H), 4.51–4.45 (m, 2H), 3.83 (s, 3H), 3.70 (s, 3H), 3.48–3.42 (m, 2H), 2.99 (t, J = 6.0 Hz, 2H); ESI MS *m/z* 386 $[M + H]^+$.

Example 123

Preparation of 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(4-(methylthio)phenyl)pyridin-2(1*H*)-one hydrochloride

a) 4-(4-(Methylthio)phenyl)pyridin-2(1*H*)-one

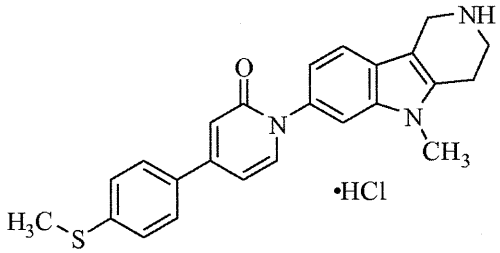


Chemical Formula: $C_{12}H_{11}NOS$
Exact Mass: 217.06
Molecular Weight: 217.29

A suspension of 4-bromo-2-methoxypyridine (1.225 g, 6.511 mmol), 4-methylthiophenyl boronic acid (2.188 g, 13.02 mmol), $PdCl_2$(dppf) (531 mg, 0.651 mmol)

and K_2CO_3 (1.797 g, 13.02 mmol) in DMSO (10 mL) was degassed under reduced pressure for 25 min. The suspension was put under N_2 and stirred at 95 °C for 16 h. The suspension was cooled, H_2O was added, and the suspension was filtered to afford a light colored solid. Flash chromatography (silica gel, hexanes/(1:1 EtOAc/hexanes), 100:0 to 0:100) afforded 1.10 g of a white powder. The white powder was diluted with concentrated HCl solution (50 mL) and stirred at reflux for 24 h. The reaction was cooled and concentrated under reduced pressure. The residue was neutralized with saturated $NaHCO_3$ solution, and the solid was collected by filtration. The solid was washed with H_2O to afford the title compound (1.103 g, 71%) as a tan solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.65 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 6.9 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 6.57 (d, J = 1.7 Hz, 1H), 6.50 (dd, J = 6.9, 1.7 Hz, 1H), 3.34 (s, 3H).

b) 1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(4-(methylthio)phenyl)pyridine-2(1*H*)-one hydrochloride



Chemical Formula: $C_{24}H_{24}ClN_3OS$
Exact Mass: 437.13
Molecular Weight: 437.98

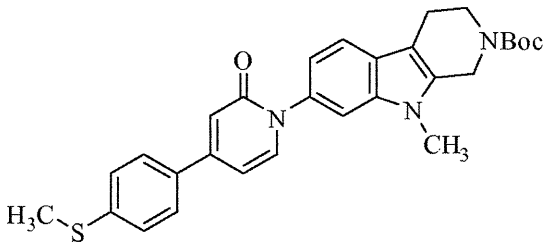
A suspension of 4-(4-(methylthio)phenyl)pyridine-2(1*H*)-one (134 mg, 0.615 mmol), *tert*-butyl 7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (247 mg, 0.676 mmol), CuI (140 mg, 0.738 mmol), 8-hydroxyquinoline (18 mg, 0.12 mmol) and Cs_2CO_3 (220 mg, 0.676 mmol) in DMSO (10 mL) was degassed under reduced pressure for 45 min. The suspension was put under N_2 and stirred at 135 °C overnight. The suspension was cooled, 9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH was added, and the resulting suspension was stirred at 25 °C for 30 min. The suspension was passed through a plug of silica gel, and the filtrate was washed with brine. The resulting solution was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) afforded 179 mg of a yellow powder. 2 N HCl in Et_2O (300 mL) was added to a solution

of the yellow powder in 1:1 CH_2Cl_2/MeOH (8 mL) under N_2, and the resulting suspension was stirred at 25 °C for 17 h. The suspension was filtered and the solid was washed with CH_2Cl_2 and 99:1 CH_2Cl_2/MeOH to afford the title compound (41 mg, 15%) as an off-white solid: mp 306–310 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.27 (br s, 2H), 7.77–7.71 (m, 3H), 7.61–7.58 (m, 2H), 7.39 (d, J = 8.5 Hz, 2H), 7.09 (dd, J = 8.5, 2.0 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 6.69 (dd, J = 7.5, 2.0 Hz, 1H), 4.36 (br s, 2H), 3.70 (s, 3H), 3.56–3.51 (m, 2H), 3.10 (t, J = 5.5 Hz, 2H), 2.54 (s, 3H); ESI MS m/z 402 $[M + H]^+$.

Example 124

Preparation of 1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(4-(methylthio)phenyl)pyridine-2(1*H*)-one hydrochloride

a) *tert*-Butyl 9-methyl-7-(4-(4-(methylthio)phenyl)-2-oxopyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate

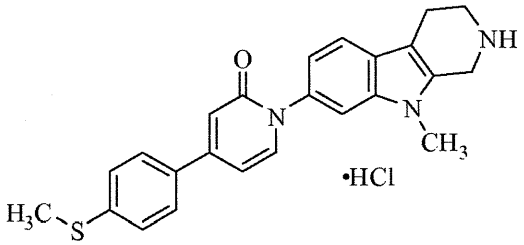


Chemical Formula: $C_{29}H_{31}N_3O_3S$
Exact Mass: 501.21
Molecular Weight: 501.64

A suspension of 4-(4-(methylthio)phenyl)pyridine-2(1*H*)-one (110 mg, 0.505 mmol), *tert*-butyl 7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (203 mg, 0.555 mmol), CuI (115 mg, 0.606 mmol), 8-hydroxyquinoline (15 mg, 0.10 mmol) and Cs_2CO_3 (181 mg, 0.555 mmol) in DMSO (10 mL) was degassed under reduced pressure for 45 min. The suspension was put under N_2 and stirred at 135 °C overnight. The suspension was cooled, 9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH was added, and the resulting suspension was stirred at 25 °C for 30 min. The suspension was passed through a plug of silica gel, and the filtrate was washed with brine. The resulting solution was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) afforded the title compound (97 mg, 38%) as an off-white powder: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.54 (m, 3H), 7.48 (d, J= 7.5 Hz, 1H), 7.38–7.32 (m, 3H), 7.08 (dd, J = 8.5,

2.0 Hz, 1H), 6.89 (d, J = 2.0 Hz, 1H), 6.50 (dd, J = 7.5, 2.0 Hz, 1H), 4.70–4.61 (m, 2H), 3.81–3.73 (m, 2H), 3.65 (s, 3H), 2.84–2.78 (m, 2H), 2.54 (s, 3H), 1.52 (s, 9H).

b) 1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(4-(methylthio)phenyl)pyridine-2(1*H*)-one hydrochloride



Chemical Formula: $C_{24}H_{24}ClN_3OS$
Exact Mass: 437.13
Molecular Weight: 437.98

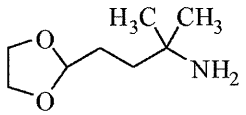
TFA (1 ml) was added to a solution of *tert*-butyl 9-methyl-7-(4-(4-(methylthio)phenyl)-2-oxopyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (97 mg, 0.19 mmol) in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred for 1.5 h at 25 °C. Saturated $NaHCO_3$ solution was added to the reaction mixture, and the resulting suspension was filtered. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) afforded 35 mg of a yellow powder. 2 N HCl in Et_2O (0.09 mL, 0.09 mmol) was added to a solution of the yellow solid in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 15 min. Et_2O was added to the solution, and the resulting suspension was filtered under N_2. The solid was washed with Et_2O to afford the title compound (37 mg, 17%) as a yellow powder: mp 300–304 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.32 (br s, 2H), 7.75 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 7.3 Hz, 1H), 7.62–7.58 (m, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.10 (dd, J = 8.5, 2.0 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 6.69 (dd, J = 7.3, 2.0 Hz, 1H), 4.49 (br s, 2H), 3.70 (s, 3H), 3.60–3.32 (m, 2H), 2.99 (t, J = 5.5 Hz, 2H), 2.54 (s, 3H); ESI MS m/z 402 $[M + H]^+$.

Example 125

Preparation of 4-(Benzyloxy)-1-(3,3,9-trimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridine-2(1*H*)-one hydrochloride

a) 4-(1,3-Dioxolan-2-yl)-2-methylbutan-2-amine

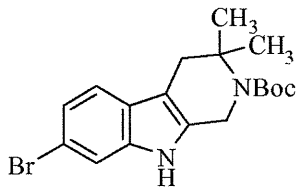
Beilstein Registry Number 9387059



Chemical Formula: $C_8H_{17}NO_2$
Exact Mass: 159.13
Molecular Weight: 159.23

This compound was prepared in accordance with the procedure of Hinderaker, et al., *Protien Sci.* **2003**, *12*, 1188–1194.

b) *tert*-Butyl 7-bromo-3,3-dimethyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate

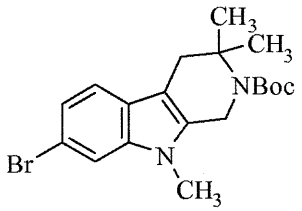


Chemical Formula: $C_{18}H_{23}BrN_2O_2$
Exact Mass: 378.09
Molecular Weight: 379.29

A mixture of 4-(1,3-dioxolan-2-yl)-2-methylbutan-2-amine (3.28 g, 20.4 mmol), 3-bromophenylhydrazine hydrochloride (4.34 g, 19.4 mmol) and $ZnCl_2$ (2.90 g, 21.3 mmol) was stirred at 180 °C for 2.5 h. The mixture was cooled to 120 °C, MeOH was added, and the resulting suspension was concentrated on silica gel. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) afforded 4.20 g of a red amorphous solid. Glyoxylic acid (1.87 g, 20.4 mmol) was added to a suspension of the red amorphous solid in 4:2:1 H_2O/MeOH/(concentrated HCl solution) (70 mL), and the resulting solution was stirred at 25 °C for 30 min. The solution was adjusted to pH 3.5 with 6 N NaOH in H_2O, and the resulting solution was stirred at 25 °C overnight. The solution was adjusted to pH 5 with saturated $NaHCO_3$ solution and the suspension was filtered. The solid was diluted with 2 N HCl in H_2O, and the resulting suspension was stirred at reflux for 2.5 h. The solution was concentrated under reduced pressure and neutralized with saturated $NaHCO_3$ solution. The resulting suspension was filtered, and the solid was dissolved in CH_2Cl_2. The resulting solution was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) afforded 577 mg of a white solid. Boc_2O (2.71 g, 12.4 mmol) was added to a suspension of the white solid and K_2CO_3 (571 mg, 4.14 mmol) in 1:1 H_2O/*i*-PrOH (40 mL), and the resulting suspension was

stirred at 25 C for 5.5 h. The suspension was concentrated under reduced pressure, and the residue was diluted with water. The solid was collected by filtration, and flash chromatography (silica gel, hexanes/(1:1 EtOAc/hexanes), 100:0 to 0:100) afforded the title compound (200 mg, 3%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.47 (br s, 1H), 7.31 (br d, J = 8.7 Hz, 1H), 7.20 (br d, J = 8.7 Hz, 1H), 4.62 (br s, 2H), 2.77 (br s, 2H), 1.53 (s, 6H), 1.48 (s, 9H).

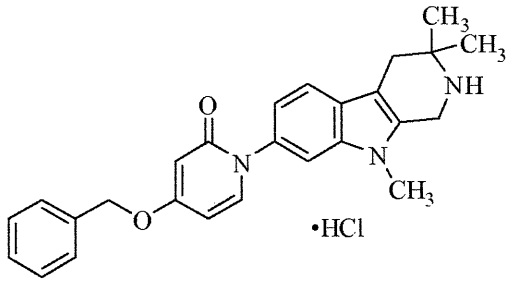
c) *tert*-Butyl 7-bromo-3,3,9-trimethyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{19}H_{25}BrN_2O_2$
Exact Mass: 392.11
Molecular Weight: 393.32

NaH (60% dispersion in oil, 42 mg, 1.1 mmol) was added to a solution of *tert*-butyl 7-bromo-3,3-dimethyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (200 mg, 0.528 mmol) in DMF (10 mL) under N_2, and the resulting suspension was stirred at 25 °C for 30 min. MeI (0.05 mL, 0.8 mmol) was added to the suspension, and the resulting suspension was stirred at 25 °C for 1 h. H_2O was added, and the resulting solid was collected by filteration. Flash chromatography (silica gel, hexanes/(1:1 EtOAc/hexanes), 100:0 to 0:100) afforded the title compound (145 mg, 70%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 1.5 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.18 (dd, J = 8.3, 1.5 Hz, 1H), 4.62 (s, 2H), 3.61 (s, 3H), 2.77 (s, 2H), 1.52 (s, 6H), 1.49 (s, 9H).

d) 4-(Benzyloxy)-1-(3,3,9-trimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridine-2(1*H*)-one hydrochloride



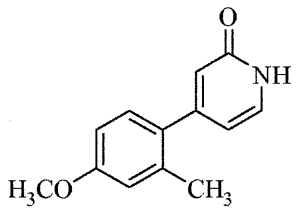
Chemical Formula: $C_{26}H_{28}ClN_3O_2$
Exact Mass: 449.19
Molecular Weight: 449.97

A suspension of 4-(benzyloxy)pyridine-2(1*H*)-one (67 mg, 0.34 mmol), *tert*-butyl 7-bromo-3,3,9-trimethyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (145 mg, 0.369 mmol), CuI (76 mg, 0.40 mmol), 8-hydroxyquinoline (10 mg, 0.07 mmol) and Cs_2CO_3 (120 mg, 0.369 mmol) in DMSO (10 mL) was degassed under reduced pressure for 45 min. The suspension was put under Ar and stirred at 135 °C overnight. The suspension was cooled, 9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH (10 mL) was added, and the resulting suspension was stirred at 25 °C for 30 min. The suspension was passed through a plug of silica gel, and the filtrate was washed with brine. The resulting solution was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) afforded 28 mg of a white solid. TFA (1 ml) was added to a solution of the white solid in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred for 1 h at 25 °C. Saturated $NaHCO_3$ solution was added to the solution, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were dried over Na_2SO_4. The resulting solution was concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) afforded 14 mg of a white powder. 2 N HCl in Et_2O (0.01 mL, 0.02 mmol) was added to a solution of the white solid in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 30 min. The solution was concentrated under reduced pressure to afford the title compound (5.2 mg, 3%) as a white powder: mp 184–186 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.34 (br s, 2H), 7.57 (d, J = 7.5 Hz, 1H), 7.53–7.50 (m, 2H), 7.49–7.41 (m, 4H), 7.40–7.35 (m, 1H), 6.99 (dd, J = 8.0, 2.0 Hz, 1H), 6.11 (dd, J = 8.0, 2.5 Hz, 1H), 5.98 (d, J = 2.5 Hz, 1H), 5.16 (s, 2H), 4.50 (br s, 2H), 3.70 (s, 3H), 2.89 (s, 2H), 1.42 (s, 6H); ESI MS *m/z* 414 $[M + H]^+$.

Example 126

Preparation of 4-(4-Methoxy-2-methylphenyl)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

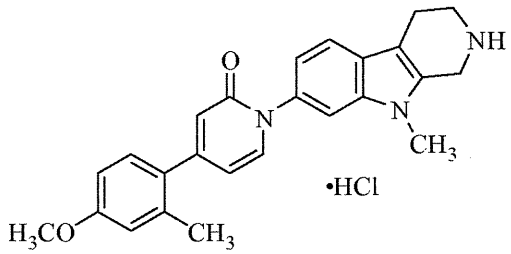
a) 4-(4-Methoxy-2-methylphenyl)pyridin-2(1*H*)-one



Chemical Formula: $C_{13}H_{13}NO_2$
Exact Mass: 215.09
Molecular Weight: 215.25

A suspension of 4-bromo-2-methoxypyridine (341 mg, 1.82 mmol), 4-methyloxy-2-methylphenyl boronic acid (452 mg, 2.72 mmol), $Pd(PPh_3)_2Cl_2$ (133 mg, 0.182 mmol) and K_2CO_3 (503 mg, 3.64 mmol) in DMSO (10 mL) was degassed under reduced pressure for 1 h. The suspension was put under Ar and stirred at 90 °C for 2 h. The suspension was cooled, H_2O was added, and the suspension was filtered to afford a light colored solid. Flash chromatography (silica gel, hexanes/(1:1 EtOAc/hexanes), 100:0 to 0:100) afforded 235 mg of a white powder. The white powder was diluted with concentrated HCl solution (20 mL) and stirred at reflux for 24 h. The reaction was cooled and concentrated under reduced pressure. The residue was neutralized with saturated $NaHCO_3$ solution, and the solid was collected by filtration. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) afforded the title compound (62 mg, 16%) as a white powder: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.54 (br s, 1H), 7.35 (d, J = 6.9 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.87–6.76 (m, 2H), 6.15–6.09 (m, 2H), 3.75 (s, 3H), 1.97 (s, 3H).

b) 4-(4-Methoxy-2-methylphenyl)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{25}H_{26}ClN_3O_2$
Exact Mass: 435.17
Molecular Weight: 435.95

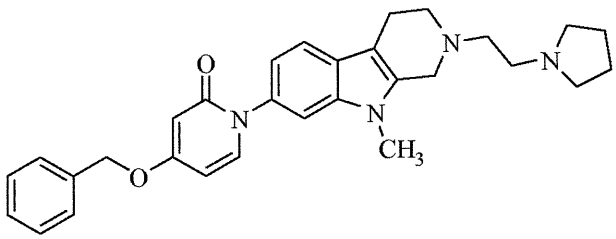
A suspension of 4-(4-methoxy-2-methylphenyl)pyridin-2(1*H*)-one (62 mg, 0.29 mmol), *tert*-butyl 7-bromo-3,3,9-trimethyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (126 mg, 0.344 mmol), CuI (66 mg, 0.34 mmol), 8-hydroxyquinoline (8 mg, 0.06 mmol) and Cs_2CO_3 (103 mg, 0.316 mmol) in DMSO (10 mL) was degassed under

reduced pressure for 45 min. The suspension was put under Ar and stirred at 135 °C overnight. The suspension was cooled, 9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH (10 mL) was added, and the resulting suspension was stirred at 25 °C for 1 h. The suspension was passed through a plug of silica gel, and the filtrate was washed with brine. The resulting solution was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) afforded 52 mg of a yellow amorphous solid. TFA (1 ml) was added to a solution of the yellow amorphous solid in CH_2Cl_2 (10 mL) under N_2 and the resulting solution was stirred for 1 h at 25 °C. Saturated $NaHCO_3$ solution was added to the solution, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were dried over Na_2SO_4. The resulting solution was concentrated under reduced pressure. Flash chromatography (silica gel, (1:1 EtOAc/hexanes)/(9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) afforded 19 mg of a viscous oil. 1 N HCl in Et_2O (0.05 mL, 0.05 mmol) was added to a solution of the viscous oil in CH_2Cl_2 (10 mL) under N_2, and the resulting solution was stirred at 25 °C for 30 min. The solution was concentrated under reduced pressure to afford the title compound (16 mg, 13%) as a white powder: mp 308–310 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.44 (br s, 2H), 7.67 (d, J = 7.0 Hz, 1H), 7.63 (d, J = 1.5 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.11 (dd, J = 8.5, 1.5 Hz, 1H), 6.92 (d, J = 2.5 Hz, 1H), 6.88 (dd, J = 8.5, 2.5 Hz, 1H), 6.37 (s, 1H), 6.34 (dd, J = 7.5, 1.5 Hz, 1H), 4.89 (br s, 2H), 3.79 (s, 3H), 3.70 (s, 3H), 3.49–3.43 (m, 2H), 2.99 (t, J = 6.0 Hz, 2H), 2.36 (s, 3H); ESI MS *m/z* 400 $[M + H]^+$.

Example 127

Preparation of 4-(Benzyloxy)-1-(9-methyl-2-(2-(pyrrolidin-1-yl)ethyl)-2,3,4,9,-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridine-2(1*H*)-one hydrochloride

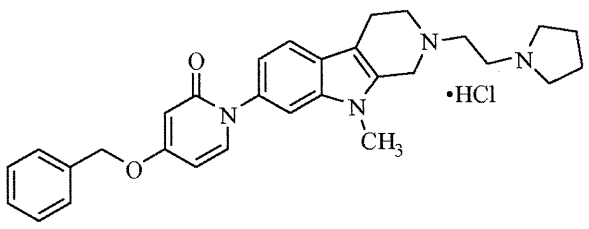
a) 4-(Benzyloxy)-1-(9-methyl-2-(2-(pyrrolidin-1-yl)ethyl)-2,3,4,9,-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridine-2(1*H*)-one



Chemical Formula: $C_{30}H_{34}N_4O_2$
Exact Mass: 482.27
Molecular Weight: 482.62

1-(2-Chloroethyl)pyrrolidine hydrochloride (50 mg, 0.29 mmol) was added to a solution of 4-(benzyloxy)-1-(9-methyl-2,3,4,9,-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridine-2(1*H*)-one (0.10 g, 0.27 mmol) and diisoproylethyl amine (0.14 mL) in EtOH (4 mL), and the resulting solution was heated at 65 °C for 2 h. The reaction mixture was concentrated to dryness under reduced pressure. Purification by flash column chromatography (40 g ISCO column, CH_2Cl_2/(80:18:2 CH_2Cl_2/MeOH/NH_4OH), 100:0 hold 5 column volumes increased to to 0:100 over 20 column volumes) followed by preparative TLC (Analtech, 20 × 20 cm, 1000 microns, uV 254, 80:18:2 CH_2Cl_2/MeOH/NH_4OH) followed by preparative HPLC (Phenomenex Luna C18 (2), 250.0 × 21.2 mm, 10 micron, H_2O with 0.05% TFA and CH_3CN with 0.05% TFA) and filtration through SCX-2 column gave the title compound (10 mg, 7%) as a yellow solid: ^{1}H NMR (500 MHz, CD_3OD) δ 7.54 (d, J = 7.5 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.46–7.33 (m, 6H), 6.96 (dd, J = 8.0, 1.5 Hz, 1H), 6.26 (dd, J = 7.5, 2.5, Hz, 1H), 6.11 (d, J = 3.0 Hz, 1H), 5.16 (s, 2H), 3.82 (s, 2H), 3.64 (s, 3H), 3.01–2.99 (m, 2H), 2.94–2.85 (m, 10H), 1.91–1.90 (m, 4H); HPLC (Method A) 95.1% (AUC), t_R = 13.8 min.

b) 4-(Benzyloxy)-1-(9-methyl-2-(2-(pyrrolidin-1-yl)ethyl)-2,3,4,9,-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridine-2(1*H*)-one hydrochloride



Chemical Formula: $C_{30}H_{35}ClN_4O_2$
Exact Mass: 518.24
Molecular Weight: 519.08

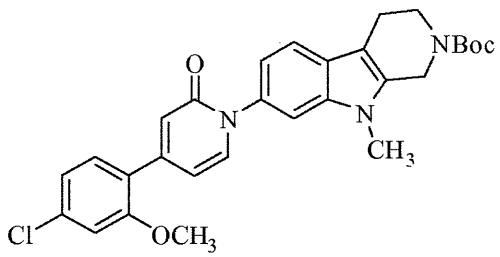
2 N HCl in Et_2O (20 μL, 0.04 mmol) was added to a solution of 4-(benzyloxy)-1-(9-methyl-2-(2-(pyrrolidin-1-yl)ethyl)-2,3,4,9,-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-

yl)pyridine-2(1*H*)-one (10 mg, 0.020 mmol) in CH_2Cl_2 (3 mL) and the reaction was stirred at ambient temperature for 1 h under N_2. The reaction was concentrated to dryness under reduced pressure to provide the title compound (10 mg, quantitative) as a yellow solid: ^{1}H NMR (500 MHz, CD_3OD) δ 7.62–7.57 (m, 2H), 7.47–7.34 (m, 6H), 7.03 (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), 4.55–4.43 (m, 2H), 3.72 (s, 3H), 3.38–3.14 (m, 12H), 2.14 (m, 4H); ESI MS *m/z* 483 $[M + H]^+$; HPLC (Method A) 92.8% (AUC), t_R = 13.6 min.

Example 128

Preparation of 4-(4-Chloro-2-methoxyphenyl)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

a) *tert*-Butyl-7-(4-(4-chloro-2-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate

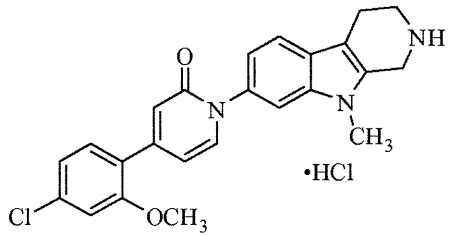


Chemical Formula: $C_{29}H_{30}ClN_3O_4$
Exact Mass: 519.19
Molecular Weight: 520.02

tert-Butyl-7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (0.19 g, 0.81 mmol), 4-(4-chloro-2-methoxyphenyl)pyridin-2(1*H*)-one (0.30 g, 0.81 mmol), Cs_2CO_3 (0.29 g, 0.89 mmol) were diluted with DMSO (3.3 mL), and argon was bubbled through the suspension for 10 min. 8-Hydroxyquinoline (59 mg, 0.41 mmol) and copper iodide (0.18 g, 0.97 mmol) were added, and the resulting suspension was placed under vacuum for 15 min. The system was flushed with argon, and the degassing/argon flushing process was repeated a total of three times. The reaction mixture was heated at 130 °C for 18 h and stirred under argon. The suspension was cooled. A solution of 20% NH_4OH in MeOH (40 mL) was added, and the resulting mixture was stirred for 1 h. The mixture was diluted with CH_2Cl_2 and filtered through celite. The filtrate was washed with brine (2 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (40g ISCO (1:1 hexanes/EtOAc)/(80:18:2

CH_2Cl_2/MeOH/NH_4OH), 100:0 for 3 column volumnes then increase to 50:50 over 10 column volumnes and hold for 10 column volumes) gave the title compound (0.23 g, 54%) as an olive-green film: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.65 (d, J = 7.0 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 1.5 Hz, 1H), 7.13 (dd, J = 8.0, 1.5 Hz, 1H), 7.02 (dd, J = 8.0, 1.5 Hz, 1H), 6.55 (d, J = 2.0 Hz, 1H), 6.54 (dd, J = 7.0, 1.5 Hz, 1H), 4.64 (s, 2H), 3.87 (s, 3H), 3.68–3.66 (m, 5H), 2.74–2.72 (m, 2H), 1.46 (s, 9H).

b) 4-(4-Chloro-2-methoxyphenyl)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{24}H_{23}Cl_2N_3O_2$
Exact Mass: 455.12
Molecular Weight: 456.36

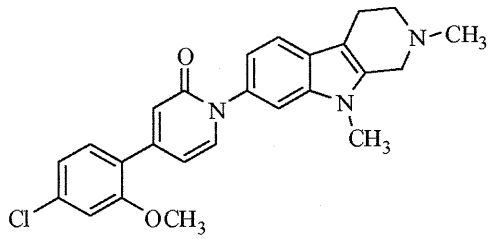
Trifluoroacetic acid (1.0 mL) was added to a solution of *tert*-butyl-7-(4-(4-chloro-2-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (0.23 g, 0.44 mmol) in CH_2Cl_2 (2 mL) under argon and stirred for 1 h. The mixture was concentrated under reduced pressure, and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$ solution. The organic phase was removed, and the aqueous phase was extracted with CH_2Cl_2 (10 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash column chromatography (12 g ISCO CH_2Cl_2/(80:18:2 CH_2Cl_2/MeOH/NH_4OH), 100:0 for 2 column volumes to 0:100 over 20 column volumes and hold for 10 column volumes) provided the free base of the title compound. The free base was converted to the HCl salt using 2 N HCl in Et_2O as of Example 129 (step b), providing the title compound (0.13 g, 33%) as a yellow solid: mp 294–300 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.43 (br s, 2H), 7.65 (d, J = 7.0 Hz, 1H), 7.61 (d, J =1.5 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 2.0 Hz, 1H), 7.13 (dd, J = 8.5, 2.0 Hz, 1H), 7.09 (dd, J = 8.0, 2.0 Hz, 1H), 6.56 (d, J = 2.0 Hz, 1H), 6.47 (dd, J = 7.0,

1.5 Hz, 1H), 4.49–4.47 (m, 2H), 3.87 (m, 3H), 3.69 (s, 3H), 3.47–3.43 (m, 2H), 3.00–2.97 (m, 2H); ESI MS *m/z* 420 $[M + H]^+$; HPLC (Method A) 96.7% (AUC), t_R = 15.5 min.

Example 129

Preparation of 4-(4-Chloro-2-methoxyphenyl)-1-(2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

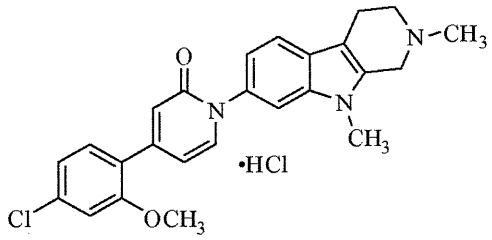
a) 4-(4-Chloro-2-methoxyphenyl)-1-(2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one



Chemical Formula: $C_{25}H_{24}ClN_3O_2$
Exact Mass: 433.16
Molecular Weight: 433.93

4-(4-Chloro-2-methoxyphenyl)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one (83 mg, 0.20 mmol) and 37% aqueous formaldehyde (24 μL, 0.30 mmol) were dissolved in 1:1 MeOH/CH_2Cl_2 (1.4 mL) and stirred at room temperature for 45 min. Sodium triacetoxyborohydride (84 mg, 0.40 mmol) was added, and the reaction was stirred at ambient temperature for 30 min. The reaction mixture was neutralized with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 25 mL). The combined organics were washed with brine (25mL), dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. Purification by flash column chromatography (12 g ISCO (1:1 hexanes/EtOAc)/(80:18:2 CH_2Cl_2/MeOH/NH_4OH), 95:5 to 10:90 over 20 column volumes, hold for 10 column volumes) provided the title compound (77 mg, 89%) as a yellow film: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 7.0 Hz, 1H), 7.35–7.34 (m, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.07–7.03 (m, 2H), 7.00–6.99 (m, 1H), 6.81–6.80 (m, 1H), 6.43–6.42 (m, 1H), 3.87 (s, 3H), 3.66–3.65 (m, 2H), 3.48 (s, 3H), 2.87–2.86 (m, 2H), 2.81–2.80 (m, 2H), 2.58 (s, 3H).

b) 4-(4-Chloro-2-methoxyphenyl)-1-(2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



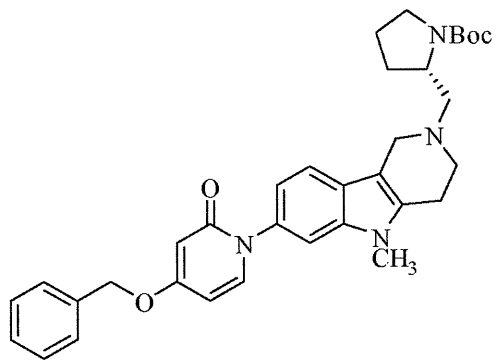
Chemical Formula: $C_{25}H_{25}Cl_2N_3O_2$
Exact Mass: 469.13
Molecular Weight: 470.39

2 N HCl in Et_2O (0.17 mL, 0.34 mmol) was added to a solution of 4-(4-chloro-2-methoxyphenyl)-1-(2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one (74 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) and the reaction was stirred at ambient temperature for 1.5 h under N_2. The solids were collected by filtration, washed with Et_2O and dried under reduced pressure to yield the title compound (54 mg, 68%) as a yellow powder: mp 272–280 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.82 (br s, 1H), 7.65 (d, J = 7.0 Hz, 1H), 7.62 (d, J = 1.5 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 1.5 Hz, 1H), 7.14–7.09 (m, 2H), 6.56 (d, J = 1.5 Hz, 1H), 6.47 (dd, J = 7.0, 1.5 Hz, 1H), 4.79–4.76 (m, 1H), 4.53–4.42 (m, 1H), 3.87 (s, 3H), 3.72–3.68 (m, 4H), 3.42–3.40 (m, 1H), 3.08–3.06 (m, 2H), 3.00 (s, 3H); ESI MS *m/z* 434 $[M + H]^+$; HPLC (Method A) 96.5% (AUC), t_R = 15.3 min.

Example 130

Preparation of (*S*)-4-(Benzyloxy)-1-(5-methyl-2-pyrrolidin-2-ylmethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7yl)pyridine-2(1*H*)-one hydrochloride

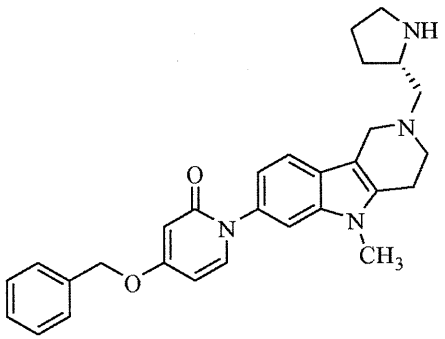
a) (*S*)-*tert*-Butyl 2-((7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indol-2(5*H*)-yl)methyl)pyrrolidine-1-carboxylate



Chemical Formula: $C_{34}H_{40}N_4O_4$
Exact Mass: 568.30
Molecular Weight: 568.71

A solution of (*S*)-*tert*-butyl-2-(bromomethyl)pyrrolidine-1-carboxylate (0.45 g, 1.7 mmol) in DMSO (1.5 mL) was added to a solution of 4-(benzyloxy)-1-(9-methyl-2,3,4,9,-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridine-2(1*H*)-one (0.33 g, 0.85 mmol), and Cs_2CO_3 (1.10 g, 3.4 mmol) in DMSO (2.8 mL), and the resulting solution was heated at 60 °C for 18 h. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine (2 × 25 mL), dried over Na_2SO_4 and concentrated to dryness under reduced pressure. Purification by flash column chromatography (40 g ISCO column, CH_2Cl_2/(80:18:2 CH_2Cl_2/MeOH/NH_4OH), 100:0 hold 5 column volumes, increased to 0:100:0 over 20 column volumes) provided a clear film. The film was diluted with EtOAc and washed with brine (4 × 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide the title compound (19 mg, 3%) as a clear film: ESI MS *m/z* 569 $[M + H]^+$.

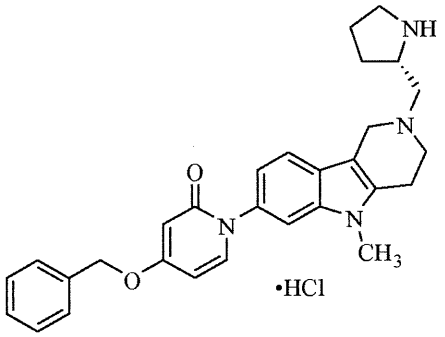
b) (*S*)-4-(Benzyloxy)-1-(5-methyl-2-pyrrolidin-2-ylmethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7yl)pyridine-2(1*H*)-one



Chemical Formula: $C_{29}H_{32}N_4O_2$
Exact Mass: 468.25
Molecular Weight: 468.59

Trifluoroacetic acid (1.0 mL) was added to a solution of (*S*)-*tert*-butyl 2-((7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indol-2(5*H*)-yl)methyl)pyrrolidine-1-carboxylate (19 mg, 0.033 mmol) in 2:1 $CDCl_3$/MeOH (1.5 mL) under argon and stirred for 30 min. The mixture was concentrated to dryness under reduced pressure. Flash column chromatography (4 g ISCO CH_2Cl_2/(80:18:2 CH_2Cl_2/MeOH/NH_4OH), 95:5 for 20 column volumes to 0:100 over 40 column volumes and hold for 100 column volumnes) yielded the title compound (10 mg, 65%) as a clear film: ESI MS *m/z* 469 $[M + H]^+$

c) (*S*)-4-(Benzyloxy)-1-(5-methyl-2-pyrrolidin-2-ylmethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7yl)pyridine-2(1*H*)-one hydrochloride



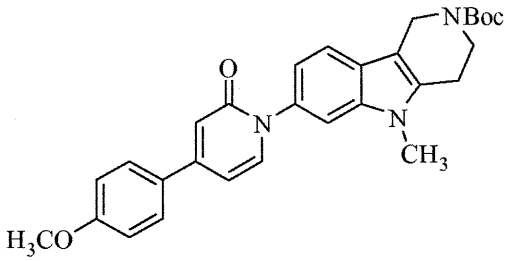
Chemical Formula: $C_{29}H_{33}ClN_4O_2$
Exact Mass: 504.23
Molecular Weight: 505.05

2 N HCl in Et_2O (0.12 μL, 0.024 mmol) was added to a solution of (*S*)-4-(benzyloxy)-1-(5-methyl-2-pyrrolidin-2-ylmethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7yl)pyridine-2(1*H*)-one) (10 mg, 0.021 mmol) in CH_2Cl_2 (0.6 mL), and the solution was stirred at ambient temperature for 1.5 h under N_2. The reaction mixture was concentrated under reduced pressure to provide the title compound (6.0 mg, 56%) as a white solid: ^{1}H NMR (500 MHz, CD_3OD) δ 7.59–7.56 (m, 2H), 7.47–7.45 (m, 3H), 7.42–7.39 (m, 2H), 7.37–7.34 (m, 1H), 7.06 (dd, J = 8.5, 2.0 Hz, 1H), 6.29 (dd, J = 7.5, 2.5 Hz, 1H), 6.12 (d, J = 3.0 Hz, 1H), 5.18 (s, 2H), 4.70–4.49 (br m, 2H), 4.28–4.26 (m, 1H), 3.75–3.73 (m, 7H), 3.46–3.43 (m, 2H), 3.34–3.33 (m, 2H), 2.46–2.43 (m, 1H), 2.21–2.08 (m, 2H), 1.91–1.86 (m, 1H); ESI MS *m/z* 469 $[M + H]^+$; HPLC (Method A) 93.8% (AUC), t_R = 13.5 min.

Example 131

Preparation of 4-(4-Methoxyphenyl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

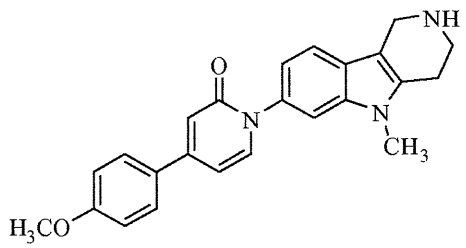
c) *tert*-Butyl 7-(4-(4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{29}H_{31}N_3O_4$
Exact Mass: 485.23
Molecular Weight: 485.57

tert-Butyl-7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (0.19 g, 0.54 mmol), 4-(4-methoxyphenyl)pyridin-2(1*H*)-one (90 mg, 0.45 mmol) and Cs_2CO_3 (0.16 g, 0.49 mmol) were suspensed in DMSO (2.0 mL) and degassed under vacuum for 15 min. The system was then flushed with Ar and 8-hydroxyquinoline (19 mg, 0.13 mmol) and copper iodide (0.10 g, 0.54 mmol) were added. The degassing/Ar flushing process was repeated twice more, and the reaction mixture was heated at 133 °C for 18 h under N_2. The suspension was cooled, diluted with 20% NH_4OH/MeOH (25mL) and stirred at ambient temperature for 30 min. The suspension was further diluted with CH_2Cl_2 (100 mL). The solution was filtered through silica gel and concentrated under reduced pressure. The concentrate was diluted with CH_2Cl_2 and washed with brine (3 × 25 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness. Flash column chromatography (12 g ISCO column, (1:1 hexanes/ EtOAc)/(80:18:2 CH_2Cl_2/MeOH/NH_4OH), 100:0 for 10 column volumes, increased to 50:50 over 20 column volumes and then hold for 5 column volumes) gave the title compound (75 mg, 34%) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.37 (d, J = 1.5 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 2.0 Hz, 1H), 6.50 (dd, J = 7.0, 2.0 Hz, 1H), 4.66–4.64 (m, 2H), 3.87 (s, 3H), 3.85–3.84 (m, 2H), 3.64 (s, 3H), 2.84–2.83 (m, 2H), 1.50 (s, 9H).

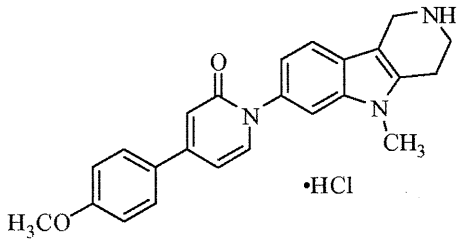
b) 4-(4-Methoxyphenyl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one



Chemical Formula: $C_{24}H_{23}N_3O_2$
Exact Mass: 385.18
Molecular Weight: 385.46

Trifluoroacetic acid (1.0 mL) was added to a solution of *tert*-butyl 7-(4-(4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (74 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) under N_2 and stirred for 2 h at ambient temperature. The mixture was concentrated, and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$ solution. The organic phase was removed, and the aqueous phase was extracted with CH_2Cl_2 (4 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (12 g ISCO CH_2Cl_2/(80:18:2 CH_2Cl_2/MeOH/NH_4OH), 100:0 for 5 column volumes to 0:100 over 20 column volumes and hold for 5 column volumnes) yielded the title compound (46 mg, 78%) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 9.0 Hz, 2H), 7.50–7.46 (m, 2H), 7.36 (d, J = 2.0 Hz, 1H), 7.05 (dd, J = 8.5, 2.0 Hz, 1H), 7.00 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 1.5 Hz, 1H), 6.49 (dd, J = 7.0, 2.0 Hz, 1H), 4.08 (s, 2H), 3.87 (s, 3H), 3.63 (s, 3H), 3.27 (t, J = 6.0 Hz, 2H), 2.77 (t, J = 5.5 Hz, 2H).

c) 4-(4-Methoxyphenyl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



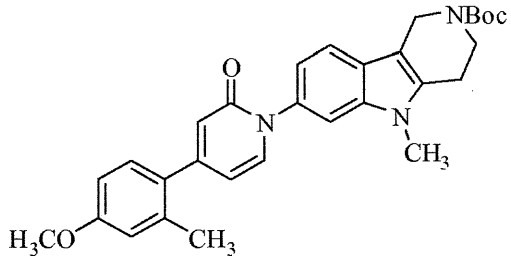
Chemical Formula: $C_{24}H_{24}ClN_3O_2$
Exact Mass: 421.16
Molecular Weight: 421.92

2 N HCl in Et_2O (0.12 mL, 0.24 mmol) was added to a solution of 4-(4-methoxyphenyl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (45 mg, 0.12 mmol) in CH_2Cl_2 (2.0 mL), and the solution was stirred at ambient temperature for 2.5 h under N_2. The reaction mixture was concentrated, partially diluted with H_2O and lyophilized to provide the title compound (46 mg, 95%) as a yellow powder: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.26 (br s, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 7.0 Hz, 1H), 7.60–7.57 (m, 2H), 7.09–7.06 (m, 3H), 6.73 (d, J = 2.0 Hz, 1H), 6.68 (dd, J = 7.5, 2.0 Hz, 1H), 4.37–4.35 (m, 2H), 3.83 (s, 3H), 3.70 (s, 3H), 3.54–3.53 (m, 2H), 3.10 (t, J = 6.0 Hz, 2H); ESI MS *m/z* 386 $[M + H]^+$.

Example 132

Preparation of 4-(4-Methoxy-2-methylphenyl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

a) *tert*-Butyl 7-(4-(4-methoxy-2-methylphenyl)-2-oxopyridin-1(*2H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(*5H*)-carboxylate

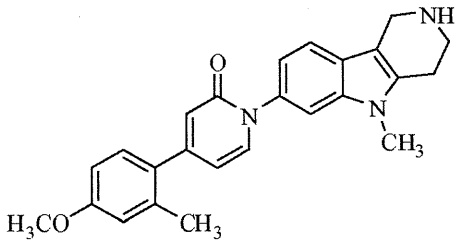


Chemical Formula: $C_{30}H_{33}N_3O_4$
Exact Mass: 499.25
Molecular Weight: 499.60

tert-Butyl-7-bromo-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (0.35 g, 0.96 mmol), 4-(4-methoxy-2-methylphenyl)pyridin-2(1*H*)-one (0.21 g, 0.96 mmol) and Cs_2CO_3 (0.35 g, 1.1 mmol) were suspensed in DMSO (5.6 mL), and the resulting suspension was degassed under vacuum for 15 min. The system was then flushed with Ar, and 8-hydroxyquinoline (42 mg, 0.29 mmol) and copper iodide (0.22 g, 1.2 mmol) were added. The evacuation/Ar flushing process was repeated twice more, and the reaction mixture was heated at 130 °C for 18 h under N_2. The suspension was cooled, diluted with 20% NH_4OH/MeOH (10mL) and stirred at ambient temperature for 30 min. The reaction was further diluted with CH_2Cl_2 (100 mL). The solution was filtered through silica gel and concentrated. The concentrate was diluted with CH_2Cl_2 and washed with brine (4 × 20 mL). The organic phase was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. Flash column chromatography (12 g ISCO column, (1:1 hexanes/EtOAc)/(80:18:2 CH_2Cl_2/MeOH/NH_4OH), 100:0 for 5 column volumes, increased to 50:50 over 20 column volumes and then hold for 5 column volumes, increase to 0:100 over 10 column volumes and hold for 5 column volumes) gave the title compound (0.25 g, 52%) as a yellow film: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 6.5 Hz, 1H), 7.39 (d, J = 1.5 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 7.0 Hz, 1H), 6.82–6.80

(m, 2H), 6.60 (d, J = 1.5 Hz, 1H), 6.24 (dd, J = 6.5, 1.5 Hz, 1H), 4.67–4.65 (m, 2H), 3.86–3.83 (m, 5H), 3.65 (s, 3H), 2.93 (m, 3H), 2.82–2.84 (m, 2H), 1.50 (s, 9H).

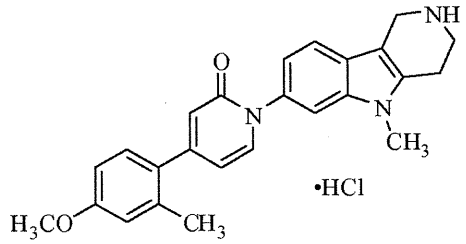
b) 4-(4-Methoxy-2-methylphenyl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one



Chemical Formula: $C_{25}H_{25}N_3O_2$
Exact Mass: 399.19
Molecular Weight: 399.48

Trifluoroacetic acid (1.0 mL) was added to a solution of *tert*-butyl 7-(4-(4-methoxy-2-methylphenyl)-2-oxopyridin-1(2*H*)-yl)-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (0.25 g, 0.50 mmol) in CH_2Cl_2 (2.0 mL) under N_2 and stirred for 1 h. The reaction mixture was made basic with saturated $NaHCO_3$ solution and the resultion solution was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (12 g ISCO CH_2Cl_2/(80:18:2 CH_2Cl_2/MeOH/NH_4OH), 100:0 for 5 column volumes to 0:100 over 20 column volumes and hold for 40 column volumes) yielded the title compound (0.16 g, 80%) as an off-white film: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 7.0 Hz, 1H), 7.38 (m, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.07 (dd, J = 8.5, 2.0 Hz, 1H), 6.82–6.80 (m, 2H), 6.60 (d, J = 1.5 Hz, 1H), 6.23 (dd, J = 7.0, 1.5 Hz, 1H), 4.09 (s, 2H), 3.84 (s, 3H), 3.64 (s, 3H), 2.77 (t, J = 5.5 Hz, 2H), 2.27 (t, J = 6.0 Hz, 2H), 2.39 (s, 3H).

c) 4-(4-Methoxy-2-methylphenyl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



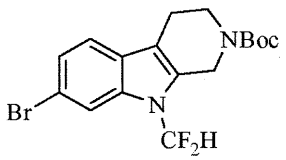
Chemical Formula: $C_{25}H_{26}ClN_3O_2$
Exact Mass: 435.17
Molecular Weight: 435.95

2 N HCl in Et_2O (0.40 mL, 0.80 mmol) was added to a solution of 4-(4-methoxy-2-methylphenyl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (0.16 g, 0.40 mmol) in CH_2Cl_2 (1.5 mL), and the solution was stirred at ambient temperature for 1 h under N_2. The solids were collected by filtration, washed with Et_2O and dried to yield the title compound (0.15 g, 85%) as an off-white powder: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.39 (br s, 2H), 7.67 (d, J = 7.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 2.0 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.10 (dd, J = 8.5, 2.0 Hz, 1H), 6.92 (d, J = 2.5 Hz, 1H), 6.88 (dd, J = 8.0, 2.5 Hz, 1H), 6.37 (d, J = 2.0 Hz, 1H), 6.34 (dd, J = 7.0, 2.0 Hz, 1H), 4.36–4.34 (m, 2H), 3.79 (s, 3H), 3.71 (s, 3H), 3.53–3.52 (m, 2H), 3.10 (t, J = 6.0 Hz, 2H), 2.35 (s, 3H); ESI MS *m/z* 400 $[M + H]^+$; HPLC (Method A) 95.8 % (AUC), t_R = 14.5 min.

Example 133

Preparation of (4-Benzyloxy)-1-(9-(difluoromethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

a) *tert*-Butyl 7-bromo-9-(difluoromethyl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(9*H*)-carboxylate

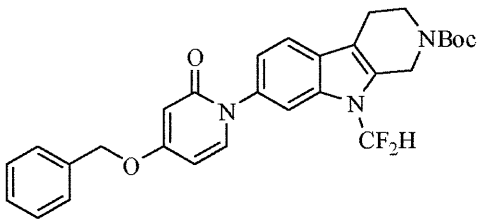


Chemical Formula: $C_{17}H_{19}BrF_2N_2O_2$
Exact Mass: 400.06
Molecular Weight: 401.25

Sodium hydride (60% in mineral oil, 0.347 g, 8.71 mmol) was added to a solution of *tert*-butyl 7-bromo-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (2.04 g, 5.81 mmol) in DMF (20 mL) at room temperature under N_2 and stirred for 30 minutes. Difluoroiodomethane (~1.5 mL), which had been condensed with a cold finger into a separate flask, was added via syringe. The reaction was sealed with a rubber septum and stirred overnight at ambient temperature. The mixture was quenched with H_2O. EtOAc was added and the mixture was stirred for 40 minutes. The mixture was extracted with EtOAc (3 × 40 mL), and the combined organic extracts were washed with brine (2 × 20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography

(40+M Biotage column, hexanes/(4:1 hexanes /EtOAc), 100:0 to 0:100) provided the title compound (0.93 g, 40%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.17 (t, J = 56.0 Hz, 1H), 7.33 (m, 2H), 4.71 (s, 2H), 3.75 (m, 2H), 2.74 (s, 2H), 1.50 (s, 9H).

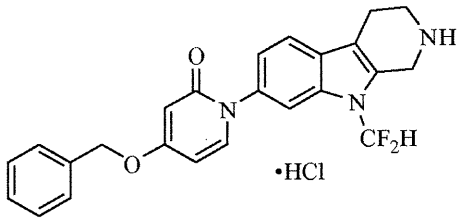
b) *tert*-Butyl 7-(4-benzyloxy)-2-oxopyridin-1(2*H*)-yl)-9-(difluoromethyl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{29}H_{29}F_2N_3O_4$
Exact Mass: 521.21
Molecular Weight: 521.56

tert-Butyl 7-bromo-9-(difluoromethyl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(9*H*)-carboxylate (0.936 g, 2.33 mmol), 4-benzyloxypyridone (0.469 g, 2.33 mmol), Cs_2CO_3 (0.834 g, 2.57 mmol) and H_2O (1 drop) were diluted with DMSO (10.4 mL) and argon was bubbled through the suspension for 10 minutes. 8-Hydroxyquinoline (0.101 g, 0.699 mmol) and copper iodide (133 mg, 0.699 mmol) were added, and the resulting suspension was placed under vacuum for 15 min. The system was flushed with argon. The degassing/argon flushing process was repeated a total of three times. The reaction mixture was heated to 130 °C for 18 h and stirred under argon. The suspension was cooled. A solution of 20% NH_4OH in MeOH (40 mL) was added, and the resulting mixture was stirred for 1 h. The mixture was diluted with CH_2Cl_2 and filtered through celite. The filtrate was washed with brine (3 × 25mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (40+M Biotage column, (20% EtOAc in hexanes)/(50% EtOAc in hexanes)/(80:18:2 CH_2Cl_2/MeOH/NH_4OH), 100:0:0 to 0:100:0 over 1.2 L then 0:100:0 to 0:0:100 over 1.2 L) gave the title compound (0.41 g, 33%) as a yellow foam: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.10 (t, J = 58.0 Hz, 1H), 7.74 (d, J = 1.4 Hz, 1H), 7.60 (d, J = 3.2 Hz, 1H), 7.58 (d, J = 3.9 Hz, 1H), 7.47–7.35 (m, 5H), 7.16 (dd, J = 8.3, 1.7 Hz, 1H), 6.12 (dd, J = 7.6, 2.6 Hz, 1H), 5.99 (d, J = 2.7 Hz, 1H), 5.15 (s, 2H), 4.72 (m, 2H), 4.03 (s, 2H), 3.70 (m, 2H), 1.44 (s, 9H).

c) (4-Benzyloxy)-1-(9-(difluoromethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



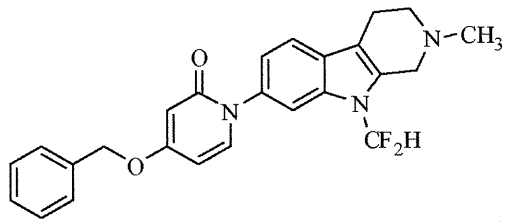
Chemical Formula: $C_{24}H_{22}ClF_2N_3O_2$
Exact Mass: 457.14
Molecular Weight: 457.90

2 N HCl in Et_2O (15.0 mL) was added to a solution of *tert*-butyl 7-(4-benzyloxy)-2-oxopyridin-1(2*H*)-yl)-9-(difluoromethyl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(9*H*)-carboxylate (0.39 g, 0.75 mmol) in 1:1 MeOH/CH_2Cl_2 (5 mL). The reaction was stirred at ambient temperature for 2 h under N_2. The reaction was diluted with Et_2O, and the resulting solids were collected by filtration to yield the title compound (0.31 g, 92%) as a yellow solid: mp 220–230 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.60 (br s, 2H), 8.11 (t, J = 58.0 Hz, 1H), 7.78 (d, J = 1.5 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.48–7.36 (m, 5H), 7.22 (dd, J = 8.5, 1.5 Hz, 1H), 6.14 (dd, J = 7.5, 2.5 Hz, 1H), 5.99 (d, J = 2.5 Hz, 1H), 5.16 (s, 2H), 4.52 (m, 2H), 3.49–3.48 (m, 2H), 2.99 (m, 2H); ESI MS *m/z* 422 $[M + H]^+$; HPLC (Method A) 96.5% (AUC), t_R = 14.4 min.

Example 134

Preparation of (4-Benzyloxy)-1-(9-(difluoromethyl)-2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

a) (4-Benzyloxy)-1-(9-(difluoromethyl)-2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one

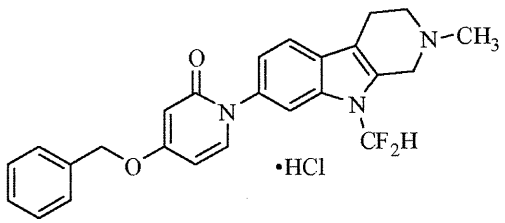


Chemical Formula: $C_{25}H_{23}F_2N_3O_2$
Exact Mass: 435.18
Molecular Weight: 435.47

(4-Benzyloxy)-1-(9-(difluoromethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (83 mg, 20 mmol) and 37% aqueous formaldehyde (22 μL, 0.30 mmol) were dissolved in 1:1 CH_2Cl_2/MeOH (1.0 mL) and stirred at ambient temperature

for 45 min. Sodium triacetoxyborohydride (83 mg, 0.39 mmol) was added, and the resulting suspension was stirred at ambient temperature for 15 min. The suspension was concentrated, and the residue was diluted with saturated $NaHCO_3$ solution. The aqueous solution was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (10 g Biotage SNAP column, CH_2Cl_2 /(80:18:2 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100) gave the title compound (57 mg, 67%) as a clear oil. ESI MS *m/z* 436 $[M + H]^+$; HPLC (Method A) 98.9% (AUC), t_R = 14.3 min.

b) (4-Benzyloxy)-1-(9-(difluoromethyl)-2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



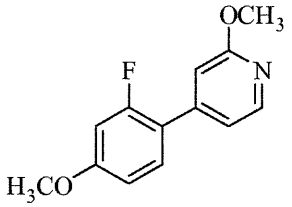
Chemical Formula: $C_{25}H_{24}ClF_2N_3O_2$
Exact Mass: 471.15
Molecular Weight: 471.93

A solution of (4-benzyloxy)-1-(9-(difluoromethyl)-2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one (58 mg, 0.13 mmol) in CH_2Cl_2 (1.0 mL) was treated with anhydrous 1.0 M HCl in diethyl ether (0.13 mL, 0.13 mmol). The reaction was stirred at ambient temperature for 1 h, and the solids were collected and dried to yield the title compound (53 mg, 86%) as a yellow solid: mp 250–256°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.89 (br s, 1H), 8.15 (t, *J* = 58.0 Hz, 1H), 7.82 (d, *J* = 1.5 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.47–7.36 (m, 5H), 7.23 (dd, *J* = 8.4, 1.5 Hz, 1H), 6.14 (dd, *J* = 7.6, 2.7 Hz, 1H), 6.00 (d, *J* = 2.7 Hz, 1H), 5.16 (s, 2H), 4.77 (m, 1H), 4.55 (m, 1H), 3.76–3.75 (m, 1H), 3.45–3.40 (m, 1H), 3.07–3.02 (m, 5H); ESI MS *m/z* 436 $[M + H]^+$; HPLC (Method A) 98.9% (AUC), t_R = 14.4 min.

Example 135

Preparation of 4-(2-Fluoro-4-methoxyphenyl)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

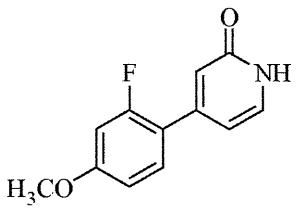
a) 4-(2-Fluoro-4-methoxyphenyl)-2-methoxypyridine



Chemical Formula: $C_{13}H_{12}FNO_2$
Exact Mass: 233.09
Molecular Weight: 233.24

4-Bromo-2-methoxypyridine (1.39 g, 7.42 mmol), 2-fluoro-4methoxyphenylboronic acid (2.40 g, 14.1 mmol), K_2CO_3 (2.05 g, 14.8 mmol) and bis(triphenylphosphine) palladium(II)chloride ($Pd(PPh_3)_2Cl_2$) (52 mg, 0.74 mmol) were stirred in DMSO (8.5 mL) under vacuum for 20 min. The flask was flushed with argon and the mixture was heated to 90°C for 3 h. Upon cooling, the mixture was diluted with brine, and the aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with water (3 × 20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (40+M Biotage column, CH_2Cl_2/(80:18:2 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 80:20) provided the title compound (0.98 g, 57%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 5.4 Hz, 1H), 7.42–7.38 (m, 1H), 7.07 (d, J = 5.4 Hz, 1H), 6.93 (s, 1H), 6.80 (dd, J = 8.6, 2.5 Hz, 1H), 6.74 (dd, J = 12.6, 2.5 Hz, 1H), 3.99 (s, 3H), 3.85 (s, 3H).

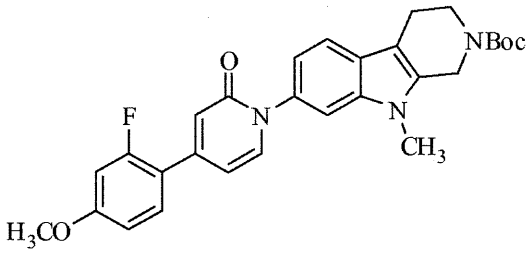
b) 4-(2-Fluoro-4-methoxyphenyl)pyridin-2(1*H*)-one



Chemical Formula: $C_{12}H_{10}FNO_2$
Exact Mass: 219.07
Molecular Weight: 219.21

4-(2-Fluoro-4-methoxyphenyl)-2-methoxypyridine (1.34 g, 5.72 mmol) was stirred in concentrated hydrochloric acid (25.5 mL) at reflux for 18 h. The reaction was cooled to 0 °C and neutralized with solid NaOH. The resulting solids were collected by filtration and dried under vacuum to yield the title compound (1.09 g, 87%) as a light brown solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.52–7.38 (m, 2H), 6.97–6.85 (m, 2H), 6.42–6.33 (m, 2H), 3.80 (s, 3H); ESI MS *m/z* 220 $[M + H]^+$.

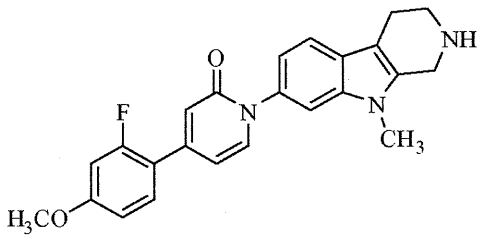
c) *tert*-Butyl-7(4(2-fluoro-4-methoxyphenyl)-2-oxopyridin-2(1*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{29}H_{30}FN_3O_4$
Exact Mass: 503.22
Molecular Weight: 503.56

Following the procedure of Example 133 (step b), but substituting 4-(2-fluoro-4-methoxyphenyl)pyridin-2(1*H*)-one (359 mg, 1.64 mmol) for 4-benzyloxypyridone, the title compound (288 mg, 41%) was prepared as a yellow foam: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.71 (d, J = 7.1 Hz, 1H), 7.61 (m, 1H), 7.55 (d, J = 1.6 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.04–6.99 (m, 2H), 6.94 (dd, J = 6.9, 2.5 Hz, 1H), 6.61 (s, 1H), 6.51–6.50 (m, 1H), 4.64 (s, 2H), 3.84 (s, 3H), 3.69–3.67 (m, 5H), 2.74–2.72 (m, 2H), 1.45 (s, 9H).

d) 4-(2-Fluoro-4-methoxyphenyl)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one

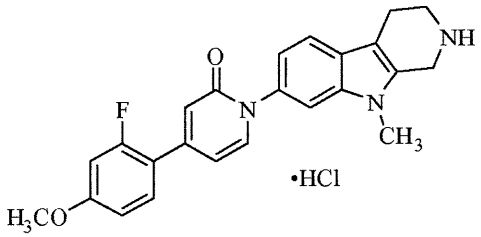


Chemical Formula: $C_{24}H_{22}FN_3O_2$
Exact Mass: 403.17
Molecular Weight: 403.45

Trifluoroacetic acid (1.0 mL) was added to a solution of *tert*-butyl-7(4(2-fluoro-4-methoxyphenyl)-2-oxopyridin-2(1*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (0.28 g, 0.56 mmol) in CH_2Cl_2 (5 mL) under argon and stirred for 1 h. The mixture was concentrated, and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$ solution. The organic phase was removed, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Preparative HPLC (Phenomenex Luna C18 (2), 250.0 × 50.0 mm, 10 micron, H_2O with 0.05% TFA and CH_3CN with 0.05% TFA) provided the title compound (87 mg, 39%) as a yellow solid: ^{1}H NMR (500 MHz, DMSO-

d_6) δ 7.71 (d, J = 7.1 Hz, 1H), 7.61 (m, 1H), 7.49–7.46 (m, 2H), 7.02–6.99 (m, 2H), 6.93 (dd, J = 8.7, 2.1 Hz, 1H), 6.60 (s, 1H), 6.50 (d, J = 7.1 Hz, 1H), 3.96 (m, 2H), 3.84 (s, 3H), 3.61 (s, 3H), 3.01–2.99 (m, 2H), 2.66 (m, 2H); ESI MS m/z 404 $[M + H]^+$.

e) 4-(2-Fluoro-4-methoxyphenyl)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



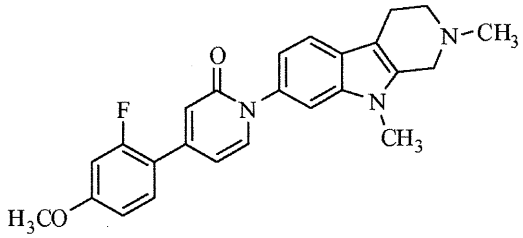
Chemical Formula: $C_{24}H_{23}ClFN_3O_2$
Exact Mass: 439.15
Molecular Weight: 439.91

A solution of 4-(2-fluoro-4-methoxyphenyl)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one (80 mg, 0.20 mmol) in CH_2Cl_2 (2.6 mL) was treated with anhydrous 1.0 M HCl in diethyl ether (0.22 mL, 0.22 mmol). The reaction was stirred at ambient temperature for 1 h, and then the solids were collected by filtration and dried to yield the title compound (68 mg, 77%) as a yellow solid: mp 290–292 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (s, 2H), 7.71 (d, J = 7.2 Hz, 1H), 7.62–7.58 (m, 3H), 7.10 (dd, J = 8.3, 1.8 Hz, 1H), 7.01 (dd, J = 13.2, 2.4 Hz, 1H), 6.94 (dd, J = 8.6, 2.3 Hz, 1H), 6.62 (s, 1H), 6.53–6.52 (m, 1H), 4.48 (s, 2H), 3.95 (s, 3H), 3.69 (s, 3H), 3.45–3.44 (m, 2H), 3.00–2.97 (m, 2H); ESI MS m/z 404 $[M + H]^+$; HPLC (Method A) >99% (AUC), t_R = 14.6 min.

Example 136

Preparation of 1-(2,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(2-fluoro-4-methoxyphenyl)pyridin-2(1*H*)-one hydrochloride

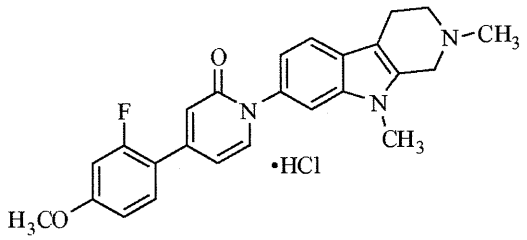
a) 1-(2,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(2-fluoro-4-methoxyphenyl)pyridin-2(1*H*)-one



Chemical Formula: $C_{25}H_{24}FN_3O_2$
Exact Mass: 417.19
Molecular Weight: 417.48

Following the procedure of Example 134 (step a), but substituting 4-(2-fluoro-4-methoxyphenyl)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one (57 mg, 0.14 mmol) for (4-benzyloxy)-1-(9-(difluoromethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one, the title compound (35 mg, 59%) was provided as an off-white solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.71 (d, J = 7.0 Hz, 1H), 7.61 (m, 1H), 7.51 (d, J = 1.8 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.02–6.99 (m, 2H), 6.94 (dd, J = 8.6, 2.4 Hz, 1H), 6.60 (s, 1H), 6.53–6.52 (m, 1H), 3.84 (s, 3H), 3.62 (m, 5H), 2.74–2.70 (m, 4H), 2.46 (s, 3H).

b) 1-(2,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(2-fluoro-4-ethoxyphenyl)pyridin-2(1*H*)-one hydrochloride



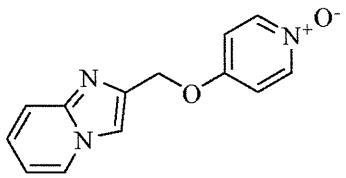
Chemical Formula: $C_{25}H_{25}ClFN_3O_2$
Exact Mass: 453.16
Molecular Weight: 453.94

Following the procedure of Example 134 (step b), but substituting 1-(2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(2-fluoro-4-methoxyphenyl)pyridin-2(1*H*)-one (35 mg, 0.84 mmol) for (4-benzyloxy)-1-(9-(difluoromethyl)-2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one, the title compound (33 mg, 87%) was provided as a yellow solid: mp 290–294 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.71 (s, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.63–7.59 (m, 3H), 7.11 (dd, J = 8.3, 1.6 Hz, 1H), 7.01 (dd, J = 13.2, 2.4 Hz, 1H), 6.94 (dd, J = 8.7, 2.4 Hz, 1H), 6.62 (s, 1H), 6.53–6.52 (m, 1H), 4.80–4.77 (m, 1H), 4.45–4.43 (m, 1H), 3.84 (s, 3H), 3.73 (br s, 1H), 3.68 (s, 3H), 3.42–3.34 (m, 1H), 3.07–3.06 (m, 2H), 3.00 (s, 3H); ESI MS *m/z* 418 $[M + H]^+$; HPLC (Method A) 97.0% (AUC), t_R = 14.0 min.

Example 137

Preparation of 4-(Imidazo[1,2-*a*]pyridin-2-ylmethoxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

a) 4-(Imidazo[1,2-*a*]pyridin-2-ylmethoxy)pyridine 1-oxide

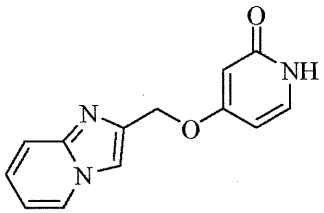


Chemical Formula: $C_{13}H_{11}N_3O_2$
Exact Mass: 241.09
Molecular Weight: 241.25

Imidazo[1,2-*a*]pyridine-2-ylmethanol (3.01 g, 20.3 mmol) was partially dissolved in 5:1 dioxane/DMF (30 mL) and the resulting slurry was added slowly to a stirring suspension of NaH (60% in mineral oil, 0.812 g, 16.9 mmol) in dioxane (29 mL). The resulting mixture was heated to 60 °C for 15 min. 4-Chloropyridine-*N*-oxide (1.5 g, 11.5

mmol) was added and the reaction mixture was heated for 1 h at 110 °C. Upon cooling, the mixture was diluted with methylene chloride and a 20% NH_4OH in MeOH solution. The resulting suspension was filtered through a silica gel plug using CH_2Cl_2 (200 mL) and 20% 4:1 MeOH/ NH_4OH in CH_2Cl_2 (500 mL). The filtrate was collected and concentrated under reduced pressure. Flash chromatography (120 g ISCO column, CH_2Cl_2/(80:18:2 CH_2Cl_2/MeOH/NH_4OH), 100:0 to 0:100 over 60 min) provided the title compound (1.5 g, 30%) as an orange-brown solid: ^{1}H NMR (300 MHz, CD_3OD) δ 8.42 (m, 1H), 8.24–8.22 (m, 2H), 7.97 (d, J = 0.5 Hz, 1H), 7.54 (dd, J = 9.1, 0.7 Hz, 1H) 7.37–7.32 (m, 1H), 7.27–7.25 (m, 2H), 6.94 (m, 1H), 5.37 (s, 2H).

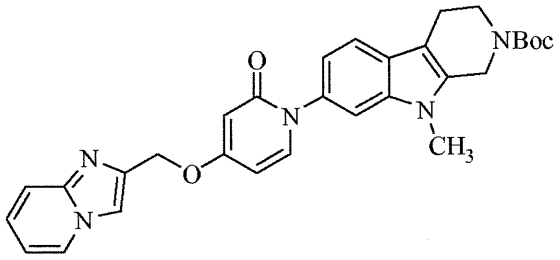
b) 4-(Imidazo[1,2-*a*]pyridin-2-ylmethoxy)pyridine-2(1*H*)-one



Chemical Formula: $C_{13}H_{11}N_3O_2$
Exact Mass: 241.09
Molecular Weight: 241.25

4-(Imidazo[1,2-*a*]pyridin-2-ylmethoxy)pyridine 1-oxide (1.50 g, 6.25 mmol) was heated at 140 °C in acetic anhydride (18 mL) for 2 h. The mixture was concentrated and heated at 80 °C for 2 h in 1:1 MeOH/ H_2O (50 mL). The resulting black solution was concentrated. The material was then partially dissolved in *i*PrOH (20 mL). Et_2O (70 mL) was added, and the mixture was allowed to sit at ambient temperature for 1 h. The resulting solids were collected by filtration and washed with Et_2O to yield the title compound (951 mg, 63%) as a dark brown solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.08 (br s, 1H), 8.54 (m, 1H), 8.01 (s, 1H), 7.53 (d, J = 9.0 Hz, 1H), 7.26–7.23 (m, 2H), 6.90 (m, 1H), 5.89–5.87 (m, 2H), 5.14 (s, 2H).

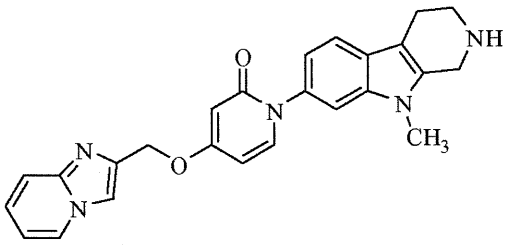
c) *tert*-Butyl-7-(4-(imidazo[1,2-*a*]pyridin-2-ylmethoxy)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{30}H_{31}N_5O_4$
Exact Mass: 525.24
Molecular Weight: 525.60

tert-Butyl-7-bromo-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (0.328 g, 0.898 mmol), 4-(imidazo[1,2-*a*]pyridin-2-ylmethoxy)pyridine-2(1*H*)-one (0.240 g, 0.998 mmol) and Cs_2CO_3 (0.358 g, 1.09 mmol) were suspended in DMSO (4.0 mL), and argon was bubbled through the system for 10 minutes. 8-Hydroxyquinoline (43.4 mg, 0.299 mmol) and copper iodide (228 mg, 1.20 mmol) were added, and resulting suspension was placed under vacuum for 15 min. The system was flushed with argon. The evacuation/argon flushing process was repeated a total of three times. The reaction mixture was heated at 130 °C for 18 h under argon. The mixture was cooled, and a solution of 20% NH_4OH in MeOH (40 mL) was added. The resulting mixture was stirred for 1 h. The mixture was diluted with CH_2Cl_2 and filtered through a silica gel plug. The filtrate was collected and concentrated. The residue was diluted with CH_2Cl_2, washed with brine (3 × 25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (80 g ISCO column, (1:1 hexanes/ EtOAc)/(80:18:2 CH_2Cl_2/MeOH/NH_4OH), 80:20 to 0:100:0 over 10 column volumes and then hold for 8 column volumes) gave the title compound (0.190 g, 40%) as a yellow foam: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.12 (d, J = 6.8 Hz, 1H), 7.69 (s, 1H), 7.61 (d, J = 9.1 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.31–7.29 (m, 2H), 7.22–7.19 (m, 1H), 7.02 (dd, J = 8.3, 1.7 Hz, 1H), 6.83–6.80 (m, 1H), 6.17 (d, J = 2.7 Hz, 1H), 6.07 (dd, J = 7.6, 2.7 Hz, 1H), 5.25 (s, 2H), 4.64 (m, 2H), 3.75 (m, 2H), 3.63 (s, 3H), 2.80 (m, 2H), 1.52 (s, 9H); ESI MS *m/z* 526 $[M + H]^+$.

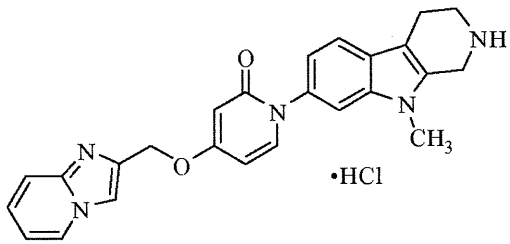
d) 4-(Imidazo[1,2-*a*]pyridin-2-ylmethoxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one



Chemical Formula: $C_{25}H_{23}N_5O_2$
Exact Mass: 425.19
Molecular Weight: 425.48

Following the procedure of Example 135 (step d), but subsituting *tert*-butyl-7-(4-(imidazo[1,2-*a*]pyridin-2-ylmethoxy)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (190 mg, 362 mmol) for *tert*-butyl-7(4(2-fluoro-4-methoxyphenyl)-2-oxopyridin-2(1*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate, the title compound (0.105 g, 68%) was prepared as a yellow film: ^{1}H NMR (500 MHz, CD_3OD) δ 8.45–8.43 (m, 1H), 7.98 (s, 1H), 7.59–7.54 (m, 3H), 7.41 (d, *J* = 1.8 Hz, 1H), 7.37–7.33 (m, 1H), 7.02 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.96–6.94 (m, 1H), 6.29 (dd, *J* = 7.6, 2.7 Hz, 1H), 6.21 (d, *J* = 2.7 Hz, 1H), 5.31 (s, 2H), 3.96 (s, 2H), 3.68 (s, 3H), 3.42 (t, *J* = 6.0 Hz, 2H), 3.00 (t, *J* = 6.0 Hz, 2H); ESI MS *m/z* 426 $[M + H]^+$.

e) 4-(Imidazo[1,2-*a*]pyridin-2-ylmethoxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one -hydrochloride



Chemical Formula: $C_{25}H_{24}ClN_5O_2$
Exact Mass: 461.16
Molecular Weight: 461.94

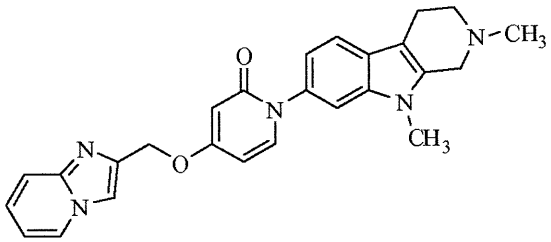
Following the procedure of Example 134 (step b), but substituting 4-(imidazo[1,2-*a*]pyridin-2-ylmethoxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one (102 mg, 0.240 mmol) for (4-benzyloxy)-1-(9-(difluoromethyl)-2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one, the title compound (95 mg, 86%) was prepared as a yellow solid: ^{1}H NMR (500 MHz, CD_3OD) δ 8.81 (d, *J* = 7.0, 1.0 Hz, 1H), 8.38 (s, 1H), 8.02–7.99 (m, 1H), 7.92 (d, *J* = 9.5 Hz, 1H), 7.66–7.62 (m, 2H), 7.52–7.49 (m, 1H), 7.46 (s, 1H), 7.05 (d, *J* = 7.0 Hz, 1H), 6.33 (dd, *J* = 7.5, 3.0 Hz, 1H), 6.23 (d, *J* = 3.0 Hz, 1H), 5.50 (s, 2H), 4.55 (s, 2H), 3.72 (s, 3H), 3.60 (t, *J*

= 6.0 Hz, 2H), 3.14–3.12 (m, 2H); ESI MS *m/z* 426 $[M + H]^+$; HPLC (Method A) 98.5% (AUC), t_R = 9.2 min.

Example 138

Preparation of 1-(2,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(imidazo[1,2-*a*]pyridin-2-ylmethoxy)pyridin-2(1*H*)-one hydrochloride

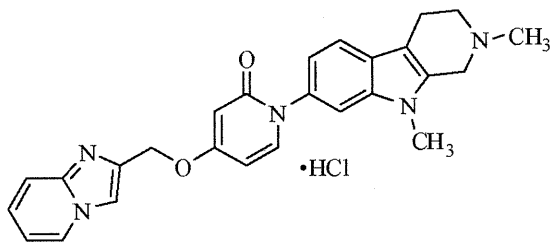
a) 1-(2,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(imidazo[1,2-*a*]pyridin-2-ylmethoxy)pyridin-2(1*H*)-one



Chemical Formula: $C_{26}H_{25}N_5O_2$
Exact Mass: 439.20
Molecular Weight: 439.51

Following the procedure of Example 134 (step a), but substituting 4-(imidazo[1,2-*a*]pyridin-2-ylmethoxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one (57 mg, 0.14 mmol) for (4-benzyloxy)-1-(9-(difluoromethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one, the title compound (25 mg, 62%) was prepared as a yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.54 (d, *J* = 7.5 Hz, 1H), 7.47–7.36 (m, 7H), 6.95 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.10 (dd, *J* = 7.5, 2.5 Hz, 1H), 5.96 (d, J = 3.0 Hz, 1H), 5.15 (s, 2H), 3.64 (m, 4H), 3.18–3.16 (m, 1H), 3.05–3.02 (m, 1H), 2.90–2.84 (m, 4H), 2.42–2.39 (m, 1H), 2.00–1.92 (m, 1H).

b) 1-(2,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(imidazo[1,2-*a*]pyridin-2-ylmethoxy)pyridin-2(1*H*)-one hydrochloride



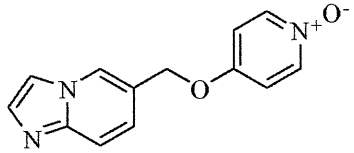
Chemical Formula: $C_{26}H_{26}ClN_5O_2$
Exact Mass: 475.18
Molecular Weight: 475.97

Following the procedure of Example 134 (step b), but substituting 1-(2,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(imidazo[1,2-*a*]pyridin-2-ylmethoxy)pyridin-2(1*H*)-one (25 mg, 0.056 mmol) for (4-benzyloxy)-1-(9-(difluoromethyl)-2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one, the title compound (27 mg, 98%) was prepared as a yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.91 (br s, 1H), 8.86 (d, J = 6.0 Hz, 1H), 8.39 (s, 1H), 7.87–7.79 (m, 2H), 7.61 (d, J = 7.5 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.51 (s, 1H), 7.37–7.35 (m, 1H), 7.01 (dd, J = 8.5, 1.0 Hz, 1H), 6.15–6.11 (m, 2H), 5.42 (s, 2H), 4.77 (d, J = 15.0 Hz, 1H), 4.43 (dd, J = 14.0, 6.0 Hz, 1H), 3.80–3.77 (m, 1H), 3.66 (s, 3H), 3.41–3.39 (m, 1H), 3.08–3.04 (m, 2H), 2.99 (s, 3H); ESI MS *m/z* 440 $[M + H]^+$; HPLC (Method A) 97.1% (AUC), t_R = 9.8 min.

Example 139

Preparation of 1-(2,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(4-(trifluoromethyl)benzyloxy)pyridin-2(1*H*)-one hydrochloride

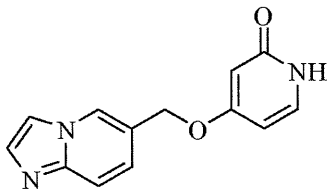
a) 4-(Imidazo[1,2-*a*]pyridin-6-ylmethoxy)pyridine 1-oxide



Chemical Formula: $C_{13}H_{11}N_3O_2$
Exact Mass: 241.09
Molecular Weight: 241.25

Following the procedure of Example 137 (step a), but substituting imidazo[1,2-*a*]pyridine-6-ylmethanol (2.91 g, 19.6 mmol) for imidazo[1,2-*a*]pyridine-2-ylmethanol, the title compound (1.69 g, 42%) was prepared as an orange solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.13–8.10 (m, 2H), 7.97 (s, 1H), 7.60–7.59 (m, 2H), 7.30 (dd, J = 9.3, 1.7 Hz, 1H), 7.14–7.11 (m, 2H), 5.18 (s, 2H).

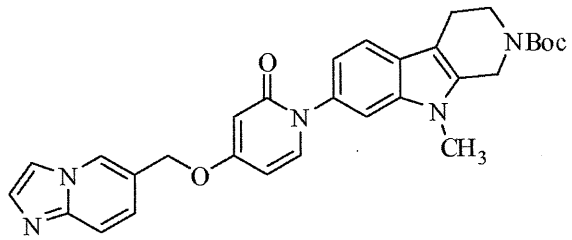
b) 4-(Imidazo[1,2-*a*]pyridin-6-ylmethoxy)pyridine-2(1*H*)-one



Chemical Formula: $C_{13}H_{11}N_3O_2$
Exact Mass: 241.09
Molecular Weight: 241.25

4-(Imidazo[1,2-*a*]pyridin-6-ylmethoxy)pyridine 1-oxide (1.69 g, 7.04 mmol) was heated at 140 °C in acetic anhydride (20 mL) for 4 h. The mixture was concentrated and heated at 80 °C for 3 h in a mixture of 1:1 MeOH/H_2O (50 mL). The resulting solution was concentrated. The residue was partially dissolved in *i*PrOH (75 mL). Et_2O (200 mL) was added, and the mixture was allowed to sit at ambient temperature for 1 h. The resulting solids were collected by filtration, washed with Et_2O and dried under reduced pressure. The solids were again subjected to *i*PrOH and Et_2O, and the solids were removed by filtration. The filtrate was concentrated to afford the title compound (0.47 g, 28%) as a dark brown solid: ^{1}H NMR (300 MHz, CD_3OD) δ 8.60 (d, J = 0.7 Hz, 1H), 7.87 (d, J = 0.6 Hz, 1H), 7.59 (d, J = 1.4 Hz, 1H), 7.57 (s, 1H), 7.40–7.27 (m, 2H), 6.18 (dd, J = 7.3, 2.5 Hz, 1H), 6.05 (d, J = 2.5 Hz, 1H), 5.13 (s, 2H).

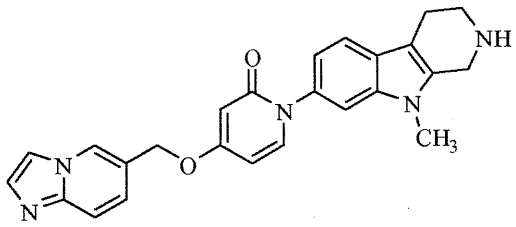
c) *tert*-Butyl-7-(4-(imidazo[1,2-*a*]pyridin-6-ylmethoxy)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{30}H_{31}N_5O_4$
Exact Mass: 525.24
Molecular Weight: 525.60

Following the procedure of Example 133 (step b), but substituting 4-(imidazo[1,2-*a*]pyridin-6-ylmethoxy)pyridine-2(1*H*)-one (218 mg, 0.901 mmol) for 4-benzyloxypyridone, the title compound (112 mg, 26%) was prepared as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.68–7.65 (m, 2H), 7.64–7.61 (m, 1H), 7.53–7.52 (m, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.28–7.26 (m, 1H), 7.22 (dd, J = 9.3, 1.5 Hz, 1H), 7.01 (dd, J = 8.2, 1.8 Hz, 1H), 6.11 (d, J = 2.7 Hz, 1H), 6.03 (dd, J = 7.5, 2.7 Hz, 1H), 5.06–5.04 (m, 2H), 4.70–4.57 (m, 2H), 3.75 (m, 2H), 3.62 (s, 3H), 2.79 (m, 2H), 1.51 (s, 9H).

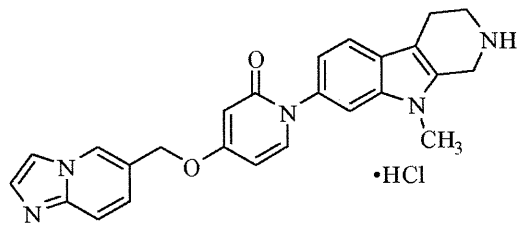
d) 4-(Imidazo[1,2-*a*]pyridin-6-ylmethoxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{25}H_{23}N_5O_2$
Exact Mass: 425.19
Molecular Weight: 425.48

Following the procedure of Example 135 (step d), but substituting *tert*-butyl-7-(4-(imidazo[1,2-*a*]pyridin-6-ylmethoxy)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (112 mg, 0.213 mmol) for *tert*-butyl-7(4(2-fluoro-4-methoxyphenyl)-2-oxopyridin-2(1*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate, the crude title compound was prepared. Preparative HPLC (Phenomenex Luna C18 (2), 250.0 × 21.2 mm, 10 micron, H_2O with 0.05% TFA and CH_3CN with 0.05% TFA) yielded the title compound (12 mg, 13%) as an off-white film: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.67–7.65 (m, 2H), 7.59 (s, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.34 (d, *J* = 7.6Hz, 1H), 7.26 (m, 1H overlapping with solvent), 7.22 (dd, *J* = 9.3, 1.6 Hz, 1H), 7.00 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.11 (d, *J* = 2.7 Hz, 1H), 6.03 (dd, *J* = 7.6, 2.7 Hz, 1H), 5.04 (s, 2H), 4.04 (s, 2H), 3.57 (s, 3H), 3.17 (t, *J* = 5.6 Hz, 2H), 2.76 (t, *J* = 5.6 Hz, 2H).

e) 4-(Imidazo[1,2-*a*]pyridin-6-ylmethoxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{25}H_{24}ClN_5O_2$
Exact Mass: 461.16
Molecular Weight: 461.94

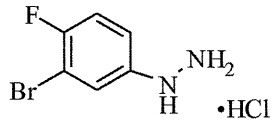
Following the procedure of Example 134 (step b), but substituting 4-(imidazo[1,2-*a*]pyridin-6-ylmethoxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one (12 mg, 0.028 mmol) for (4-benzyloxy)-1-(9-(difluoromethyl)-2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one, the title compound (14 mg, 100%) was prepared as a light yellow solid: ^{1}H NMR (500 MHz,

DMSO-d_6) δ 9.55 (br s, 2H), 9.01 (s, 1H), 8.33 (s, 1H), 8.11 (s, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.89 (d, J = 9.2 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 1.6 Hz, 1H), 7.00 (dd, J = 8.4, 1.7 Hz, 1H), 6.13 (dd, J = 7.6, 2.7 Hz, 1H), 6.08 (d, J = 2.7 Hz, 1H), 5.31 (s, 2H), 4.46 (m, 2H), 3.67 (s, 3H), 3.44 (m, 2H), 2.97 (t, J = 5.7 Hz, 2H); ESI MS *m/z* 426 $[M + H]^+$; HPLC (Method A) >99% (AUC), t_R = 9.7 min.

Example 140

Preparation of 4-(Benzyloxy)-1-(8-fluoro-2,5-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

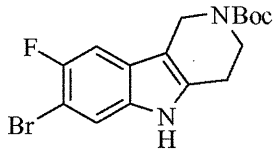
a) (3-Bromo-4-fluorophenyl)hydrazine hydrochloride



Chemical Formula: $C_6H_7BrClFN_2$
Exact Mass: 239.95
Molecular Weight: 241.49

A solution of sodium nitrite (4.2 g , 60 mmol) was added drop-wise to a mixture of 3-bromo-4-fluoroaniline (11.2 g, 58.9 mmol) and concentrated HCl (30 mL, 0.36 M) at 0 °C over 30 min. The resulting clear solution was stirred for 45 min, and a solution of $SnCl_2$•$2H_2O$ (27 g, 120 mmol) in concentrated HCl (30 mL) was added drop-wise at 0 °C over 1.5 h. The mixture was stirred for 18 h at room temperature. The resulting precipitate was collected by filtration and crystallized from ethanol to provide the title compound (6.2 g, 42 %) as a yellow powder: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.24 (s, 3H), 8.42 (s, 1H), 7.36–7.30 (m, 2H), 7.03–6.98 (m, 1H).

b) 7-Bromo-8-fluoro-3,4-dihydro-1*H*-pyrido[4,3-b]indole-2(5*H*)-carboxylate

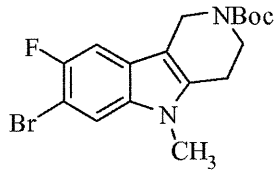


Chemical Formula: $C_{16}H_{18}BrFN_2O_2$
Exact Mass: 368.05
Molecular Weight: 369.23

A mixture of (3-bromo-4-fluorophenyl)hydrazine hydrochloride (3.0 g, 12 mmol), *tert*-butyl 4-oxopiperidine-1-carboxylate (2.48 g, 12.5 mmol) and concentrated HCl (6.0 mL, 72 mmol) in ethanol (40 mL) was stirred for 18 h at reflux. The solvent was removed under reduced pressure, the residue was suspended in dichloromethane (50 mL), and di-

tert-butyl dicarbonate (3.3 g, 15 mmol) and triethylamine (2.1 mL, 30 mmol) were added. The mixture was stirred for 18 h at ambient temperature. The resulting clear solution was concentrated, and the residue was purified by flash chromatography (silica gel, hexanes/ethyl acetate, 1:0 to 1:1) to afford the title compound (0.9 g, 20%) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.45 (d, J = 5.5 Hz, 1H), 7.14 (br s, 1H), 4.56 (br s 2H), 3.81 (br m 2H), 2.81 (br m 2H), 1.57 (s, 9H); ESI MS *m/z* 369 [M + H]$^+$.

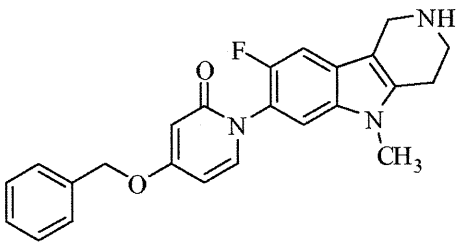
c) *tert*-Butyl 7-bromo-8-fluoro-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-b]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{17}H_{20}BrFN_2O_2$
Exact Mass: 382.07
Molecular Weight: 383.26

Sodium hydride (60% weight dispersion in mineral oil, 150 mg, 3.66 mmol) was added to a solution of *tert*-butyl 7-bromo-8-fluoro-3,4-dihydro-1*H*-pyrido[4,3-b]indole-2(5*H*)-carboxylate (0.9 g, 2.44 mmol) in 20 ml of DMF, and the mixture was stirred for 40 min at ambient temperature. Iodomethane (0.25 mL, 3.66 mmol) was added, and the resulting suspension was stirred for 2 h. The resulting mixture was concentrated under reduced pressure to ~ 1/3 of initial volume and treated with water (20 mL). The resulting precipitate was collected by filtration, sequentially washed with water and diethyl ether and dried under vacuum to afford the title compound (0.75 g, 83%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 5.4 Hz, 1H), 7.17 (d, J = 9.3 Hz, 1H), 4.45 (br s, 2H), 3.81 (br m, 2H), 3.60 (s, 3H), 2.78 (br m, 2H), 1.52 (s, 9H); ESI MS *m/z* 383 [M + H]$^+$.

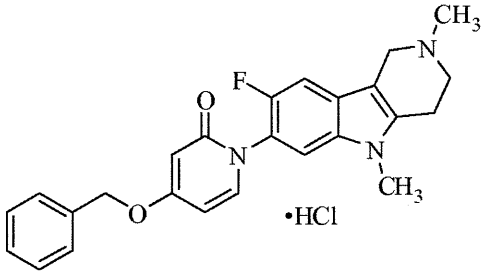
d) 4-(Benzyloxy)-1-(8-fluoro-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one



Chemical Formula: $C_{24}H_{22}FN_3O_2$
Exact Mass: 403.17
Molecular Weight: 403.45

tert-Butyl 7-bromo-8-fluoro-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (720 mg, 1.88 mmol), 4-benzyloxypyridone (380 mg, 1.9 mmol) and Cs_2CO_3 (680 mg, 2.1 mmol) were suspended in DMSO (8.0 mL) and the resulting suspension was degassed for 15 min. The system was flushed with Ar. Then 8-hydroxyquinoline (87 mg, 0.60 mmol) and copper iodide (114 mg, 0.599 mmol) were added. The degassing/Ar flushing process was repeated twice more, and the reaction mixture was heated at 133 °C for 18 h under argon. The reaction mixture was cooled, diluted with 15% solution of concentrated ammonium hydroxide in methanol (25 mL) and stirred at ambient temperature for 30 min. The reaction was further diluted with dichloromethane (75 mL). The solution was filtered through silica gel and concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 and washed with H_2O (25 mL) and brine (3 × 50 mL). The combined organics were dried over Na_2SO_4 and concentrated to dryness. The crude material was purified by flash chromatography (silica gel, (1:1 hexanes/EtOAc)/(10:1:0.1 dichloromethane/methanol/concentrated ammonium hydroxide), 1:0 to 0:1) to afford crude *tert*-butyl 7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-8-fluoro-5-methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (280 mg) as a yellow oil. This oil was dissolved in dichloromethane (3 mL) and TFA (1 mL) was added. The reaction mixture was stirred at ambient temperature for 1 h, concentrated and dried under vacuum overnight to provide the title compound (200 mg), which was used in the next step without further purification: ESI MS *m/z* 404 $[M + H]^+$.

e) 4-(Benzyloxy)-1-(8-fluoro-2,5-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



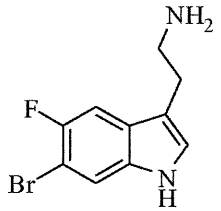
Chemical Formula: $C_{25}H_{25}ClFN_3O_2$
Exact Mass: 453.16
Molecular Weight: 453.94

To a solution of 4-(benzyloxy)-1-(8-fluoro-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (100 mg, 0.26 mmol) in dichloromethane/acetic acid (1% acetic acid, 10 mL) were sequentially added formaldehyde (37% aqueous solution, 22 μL, 0.74 mmol) and $NaBH(OAc)_3$ (316 mg, 1.49 mmol). The reaction mixture was stirred at room temperature for 2.5 h. The mixture was concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2. The organic layer was washed with H_2O and 5% aqueous LiCl, dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (silica gel, CH_2Cl_2/(10:1:0.1 CH_2Cl_2/MeOH/NH_4OH), 0:1 to 1:1) gave 4-(benzyloxy)-1-(8-fluoro-2,5-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one (78 mg, 38%) as a yellow solid. The free base was converted to the HCl salt using 1.25M HCl in methanol providing the title compound (75 mg, 95%) as a off-white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.53–7.33 (m, 7H), 7.27 (d, J = 10.5 Hz, 1H), 7.28 (dd, J = 7.8, 2.4 Hz, 1H), 6.10 (d, J = 2.7 Hz, 1H), 5.17 (s, 2H), 3.79 (br s, 2H), 3.67 (s, 3H), 3.03–3.00 (m, 4H), 2.64 (s, 3H); ESI MS *m/z* 418 $[M + H]^+$; HPLC (Method A) 95.7% (AUC), t_R = 14.5 min.

Example 141

Preparation of 4-(Benzyloxy)-1-(6-fluoro-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride.

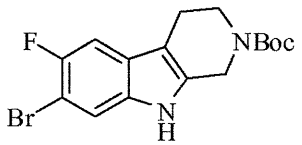
a) 2-(6-Bromo-5-fluoro-1*H*-indol-3- yl)ethanamine



Chemical Formula: $C_{10}H_{10}BrFN_2$
Exact Mass: 256.00
Molecular Weight: 257.10

4,4-Diethoxybutan-1-amine (4.72 g, 29.3 mmol) was added to (3-bromo-4-fluorophenyl)hydrazine hydrochloride (6.4 g, 27 mmol) . The resulting mixture in an open round bottom flask was placed into a preheated oil bath at 180 °C. The mixture was stirred at 180 °C for 2.5 h and then cooled to 120 °C. Methanol (300mL) was added, and the mixture was stirred at ambient temperature for 18h. The resulting suspension was filtered through a silica gel plug, and the silica gel was then washed with methanol (5 × 300 mL). The combined methanol fractions were concentrated under vacuum to provide the crude title compound (8.1 g) as a yellow solid, which was used in the next step without further purification: ESI MS *m/z* 257 $[M + H]^+$.

b) *tert*-Butyl 7-bromo-6-fluoro-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate

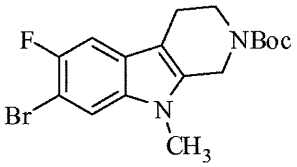


Chemical Formula: $C_{16}H_{18}BrFN_2O_2$
Exact Mass: 368.05
Molecular Weight: 369.23

Glyoxylic acid (8.6 g, 95 mmol) was added to a solution of 2-(6-bromo-5-fluoro-1*H*-indol-3-yl)ethanamine (8.1 g 31 mmol) in 2 N HCl (150 ml), and the pH of the resulting solution was adjusted to pH 3.5 with 6 N NaOH solution. The reaction mixture was stirred at ambient temperature for 18 h. The solution was adjusted to pH 5.5 with 6 N NaOH solution. The resulting precipitate was collected by filtration and dried under vacuum to afford a yellow solid. The yellow solid was suspended in 2 N HCl (100 mL), and the resulting mixture was stirred at reflux for 4.5 h. The reaction mixture was cooled to ambient temperature and was adjusted to pH 10 by addition of 2 N sodium hydroxide solution. The resulting precipitate was collected by filtration and dried under vacuum to afford a crude mixture of 7-bromo-6-fluoro-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole and

6-bromo-7-fluoro-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (2.0 g, 23%) as a yellow solid. The mixture (1.9 g, 7.1 mmol) was suspended in dichloromethane (100 mL) and di-*tert*-butyl carbonate (1.85 g, 8.7 mmol) was added, followed by addition of DMAP (100 mg, 0.82 mmol). The reaction mixture was stirred at ambient temperature for 18 h and concentrated under vacuum. The residue was purified twice by column chromatography (silica gel, hexanes/ethyl acetate, 0:1 to 1:1) to afford the title compound (300 mg, 12%) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 5.7 Hz, 1H), 7.18 (d, J = 9.0 Hz, 1H), 4.61 (s, 2H), 3.75 (br m, 2H), 2.73 (br m, 2H), 1.56 (s, 9H); ESI MS *m/z* 369 $[M + H]^+$.

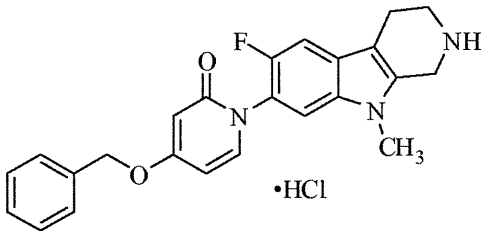
c) *tert*-Butyl 7-bromo-6-fluoro-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



Chemical Formula: $C_{17}H_{20}BrFN_2O_2$
Exact Mass: 382.07
Molecular Weight: 383.26

Sodium hydride (60% weight dispersion in mineral oil, 25 mg, 0.60 mmol) was added to a solution of *tert*-butyl 7-bromo-6-fluoro-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (150 mg, 0.40 mmol) in DMF (10 mL) at room temperature under N_2 and stirred for 1 h at ambient temperature. Methyl iodide (230 mg, 0.16 mL, 0.60 mmol) was added, and the reaction mixture was stirred for 1 h. The resulting mixture was concentrated under reduced pressure to approximately 1/3 of initial volume and treated with water (20 mL). The resulting precipitate was collected by filtration, washed with water and diethyl ether and dried under vacuum to afford the title compound (140 mg, 91%) as a yellow powder: ESI MS *m/z* 383 $[M + H]^+$.

d) 4-(Benzyloxy)-1-(6-fluoro-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride



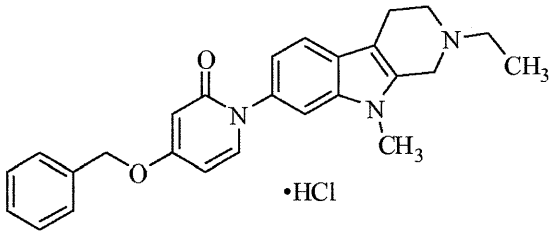
Chemical Formula: $C_{24}H_{23}ClFN_3O_2$
Exact Mass: 439.15
Molecular Weight: 439.91

tert-Butyl 7-bromo-6-fluoro-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (160 mg, 0.40 mmol), 4-benzyloxypyridone (80 mg, 0.33 mmol) and Cs_2CO_3 (390 mg, 0.38 mmol) were suspended in DMSO (8.0 mL) and degassed under vacuum for 15 min. The system was then flushed with Ar, and 8-hydroxyquinoline (30 mg, 0.18 mmol) and copper iodide (80 mg, 0.40 mmol) were added. The degassing/Ar flushing process was repeated twice, and the reaction mixture was heated at 133 °C for 18 h under argon. The mixture was cooled, diluted with 15% solution of concentrated ammonium hydroxide in methanol (25mL) and stirred at ambient temperature for 30 min. The reaction was further diluted with CH_2Cl_2 (75mL) and filtered through silica gel and concentrated. The concentrate was diluted with CH_2Cl_2 and washed with H_2O (25 mL) and brine (3 × 50mL). The combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure to dryness. The crude material was purified by flash chromatography (silica gel, (1:1 hexanes/EtOAc)/(10:1:0.1 dichloromethane/methanol/concentrated ammonium hydroxide), 1:0 to 0:1) to afford 75 mg of crude material containing the desired product. The crude mixture was dissolved in a mixture of dichloromethane and methanol (1:1, 5 mL), treated with TFA (2 mL) and stirred at ambient temperature for 30 min. The solvent was removed under reduced pressure, and the residue was neutralized by ion-exchange chromatography (SCX-2 column, 5g). Purification by preparatory TLC (silica gel, 10:1:0.1 dichloromethane/methanol/concentrated ammonium hydroxide) provided the free base of the title compound (12 mg, 10%) as a white foam: ESI MS *m/z* 404 $[M + H]^+$. The free base was dissolved in methanol (25 mL) and treated with a solution of HCl (1.25 M in methanol, 0.1 mL, 0.13 mmol). The reaction mixture was sonicated for 5 min at ambient temperature. The mixture was concentrated, and the resulting residue was lyophilized from water (5 mL) to afford the title compound (14 mg, 8%) as a white powder: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.56 (br s, 2H), 7.61 (d, J = 6.0 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.50–7.37 (m, 6H), 6.14–6.12 (m, 1H), 5.99 (s, 1H), 5.16 (s, 2H), 4.46

(br s, 2H), 3.67 (s, 3H), 3.43 (br m, 2H), 2.94 (m, 2H); ESI MS *m/z* 404 $[M + H]^+$; HPLC (Method A) 95.7% (AUC), t_R = 14.8 min

Example 142

Preparation of 4-(Benzyloxy)-1-(2-ethyl-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

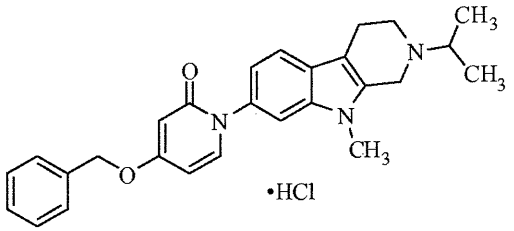


Chemical Formula: $C_{26}H_{28}ClN_3O_2$
Exact Mass: 449.19
Molecular Weight: 449.97

To a solution of 4-(benzyloxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride (120 mg, 0.28 mmol) in dichloromethane/acetic acid (1% acetic acid, 10 mL) were sequentially added acetaldehyde (0.50 mL, 13 mmol) and $NaBH(OAc)_3$ (1.0 g, 4.7 mmol). The reaction mixture was stirred at ambient temperature for 1h. The mixture was concentrated, and the residue was purified by flash chromatography (silica gel silica gel, (1:1 hexanes/EtOAc)/(10:1:0.1 dichloromethane/methanol/concentrated ammonium hydroxide), 1:0 to 0:1) to provide 4-(benzyloxy)-1-(2-ethyl-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one (120 mg, 72%) as a white solid. The free base was converted to the HCl salt using 1.25 M HCl in methanol, providing the title compound (120 mg, 95%) as an off-white solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.57 (d, J = 7.5 Hz, 1H), 7.54–7.34 (m, 7H), 6.97 (d, J = 8.0 Hz, 1H), 6.10 (dd, J = 7.5, 2.0 Hz, 1H), 5.97 (s, 1H), 5.16 (s, 2H), 3.67 (s, 3H), 3.45–3.18 (4H, overlapping with solvent peak), 3.26 (br m, 2H), 2.96 (m, 2H), 1.33 (br m, 3H); ESI MS *m/z* 414 $[M + H]^+$; HPLC (Method A) 95.7% (AUC), t_R = 14.6 min.

Example 143

Preparation of 4-(Benzyloxy)-1-(2-isopropyl-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride

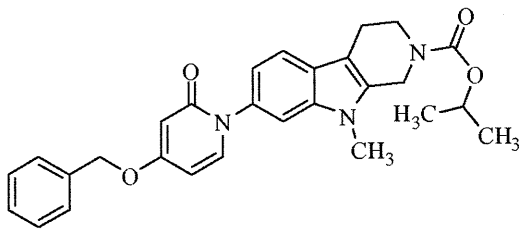


Chemical Formula: $C_{27}H_{30}ClN_3O_2$
Exact Mass: 463.20
Molecular Weight: 464.00

2-Bromopropane (1.5 mL, 16 mmol) was added to a mixture of 4-(benzyloxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one hydrochloride (138 mg, 0.327 mmol) and Cs_2CO_3 (1.2 g, 3.7 mmol) in acetonitrile (25 mL). The mixture was stirred at 55 °C for 72 h. The resulting mixture was cooled, and the precipitate was filtered off. The mother liquor was concentrated under vacuum. The residue was purified by preparatory TLC (silica gel, 10:1:0.1 dichloromethane/methanol/concentrated ammonium hydroxide) to afford 4-(benzyloxy)-1-(2-isopropyl-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one. The free base was converted to the HCl salt using 1.25 M HCl in methanol to provide the title compound (26 mg, 19%) as a off white solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.50 (s, 1H), 7.56 (d, J = 4.5 Hz, 2H), 7.52–7.38 (m, 6H), 7.01 (dd, J = 4.5, 1.0 Hz, 1H), 6.11 (dd, J = 4.5, 1.0 Hz, 1H), 5.97 (s, 1H), 5.16 (s, 2H), 4.60–4.53 (m, 2H), 3.78–3.70 (m, 2H), 3.70 (s, 3H), 3.40–3.28 (m, 1H), 3.18–2.98 (m, 2H), 1.44–1.39 (m, 6H); ESI MS *m/z* 428 $[M + H]^+$; HPLC (Method A) 95.7% (AUC), t_R = 15.1 min.

Example 144

Preparation of Isopropyl 7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate



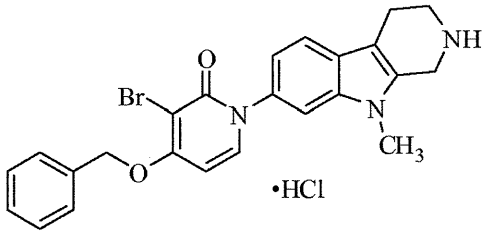
Chemical Formula: $C_{28}H_{29}N_3O_4$
Exact Mass: 471.22
Molecular Weight: 471.55

Following the procedure of Example 143, the title compound (12 mg, 8%) was obtained as a second product as an off-white powder after lyophilization from acetonitrile/water: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 8.5 Hz, 1H), 7.50–7.32 (m,

7H), 6.99 (d, J = 8.5 Hz, 1H), 6.90 (s, 1H), 6.34 (d, J = 6.5 Hz, 1H), 5.17 (s, 2H), 5.05–5.00 (m, 1H), 4.72–4.58 (m, 2H), 3.79 (br m, 2H), 3.76 (s, 3H), 2.82 (m, 2H), 1.42–1.32 (m, 6H); ESI MS m/z 472 $[M + H]^+$; HPLC (Method A) 95.7% (AUC), t_R = 19.9 min.

Example 145

Preparation of 4-(Benzyloxy)-3-bromo-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridine-2(1*H*)-one hydrochloride



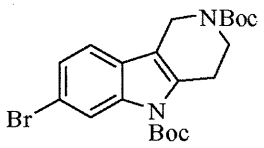
Chemical Formula: $C_{24}H_{23}BrClN_3O_2$
Exact Mass: 499.07
Molecular Weight: 500.82

2-Bromopropane (0.25 mL, 2.7 mmol) was added to a solution of 4-(benzyloxy)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one in DMSO (5 mL). The reaction mixture was stirred at 55 °C for 3 d. The mixture was diluted with a saturated solution of sodium bicarbonate and extracted with dichloromethane (3 × 50 mL). The combined organics were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by preparatory TLC (silica gel, 10:1:0.1 dichloromethane/methanol/concentrated ammonium hydroxide) provided the free base of the title compound. The free base was converted to the HCl salt using 2.5 M HCl in methanol to afford, after lyophilization from acetonitrile/water, the title compound (15 mg, 14%) as a yellow solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.71 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 8.4, Hz, 1H), 7.53–7.30 (m, 6H), 7.05 (dd, J = 7.8, 1.2 Hz, 1H), 6.60 (d, J = 7.6 Hz, 1H), 5.40 (s, 2H), 4.54 (s, 2H), 3.71 (s, 3H), 3.62–3.55 (m, 2H), 3.22–3.02 (m, 2H); ESI MS m/z 465 $[M + H]^+$; HPLC (Method A) 95.7% (AUC), t_R = 15.3 min.

Example 146

Preparation of 4-(Benzyloxy)-1-(2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

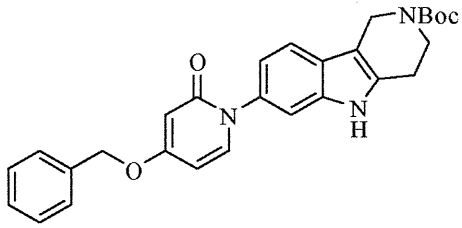
a) Di-*tert*-butyl 7-bromo-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2,5-dicarboxylate



Chemical Formula: $C_{21}H_{27}BrN_2O_4$
Exact Mass: 450.12
Molecular Weight: 451.35

To a solution of *tert*-butyl 7-bromo-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (1.00 g, 2.85 mmol), Boc_2O (683 mg, 3.13 mol) and triethylamine (0.73 mL, 5.7 mmol) in methylene chloride (30 mL) at room temperature was added DMAP (50 mg, 0.41 mmol), and the reaction progressed for 18 h. The mixture was washed with 0.5 N HCl, and the organic phase was removed, dried over Na_2SO_4, filtered and concentrated to dryness. The crude title product (1.25 g, 98%) was recovered as an orange solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (br s, 1H), 7.34 (dd, J = 8.2, 1.6 Hz, 1H), 7.24 (d, J = 8.25 Hz, 1H), 4.54 (br s, 2H), 3.73 (m, 2H), 3.07 (t, J = 5.6 Hz, 2H), 1.66 (s, 9H), 1.50 (s, 9H).

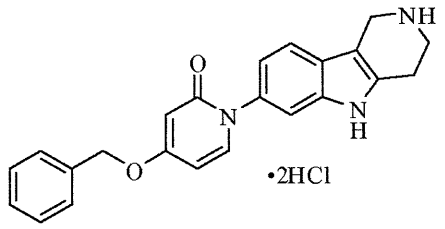
b) *tert*-Butyl 7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-b]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{28}H_{29}N_3O_4$
Exact Mass: 471.22
Molecular Weight: 471.55

Prepared from di-*tert*-butyl 7-bromo-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2,5-dicarboxylate (1.24 g, 2.72 mmol) and 4-benzyloxypyridone (547 mg, 2.72 mmol) according to the procedure of Example 1 (step c). Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, 100:0 to 80:20 to 50:50 to 25:75 then 0:100) gave the title compound (155 mg, 10%) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (br s, 1H), 7.44–7.38 (m, 5H), 7.30 (d, J = 7.5 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 7.16 (s, 1H), 6.82 (dd, J = 8.2, 1.4 Hz, 1H), 6.12–6.09 (m, 2H), 5.09 (s, 2H), 4.46 (br s, 2H), 3.70 (br m, 2H), 2.54 (br m, 2H), 1.50 (s, 9H).

c) 4-(Benzyloxy)-1-(2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride



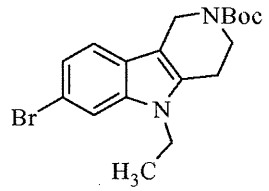
Chemical Formula: $C_{23}H_{23}Cl_2N_3O_2$
Exact Mass: 443.12
Molecular Weight: 444.35

Prepared from *tert*-butyl 7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (150 mg, 0.32 mmol) according to the procedure of Example 1 (step d). Purification by flash column chromatography (4 g ISCO column eluting with methylene chloride and a methanol/ammonia mixture (10:1); gradient 100% methylene chloride to 85% methylene chloride over 30 min) provided the free-base as a yellow solid. This was converted to the bis-HCl salt (2 N HCl/Et_2O in CH_2Cl_2) providing the title compound (36 mg, 26%) as a yellow solid: mp 240 °C dec.; ^{1}H NMR (500 MHz, CD_3OD) δ 7.65 (d, J = 7.5 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.47 (d, J = 7.2 Hz, 2H), 7.42–7.36 (m, 4H), 7.03 (d, J = 8.5 Hz, 1H), 6.39 (dd, J = 7.6, 2.5 Hz, 1H), 6.21 (d, J = 2.5 Hz, 1H), 5.21 (s, 2H), 4.47 (s, 2H), 3.64 (t, J = 6.0 Hz, 2H), 3.20 (t, J = 6.1 Hz, 2H); ESI MS *m/z* 372 $[M + H]^+$; HPLC (Method A) 95.0% (AUC), t_R = 12.2 min.

Example 147

Preparation of 4-(Benzyloxy)-1-(5-ethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

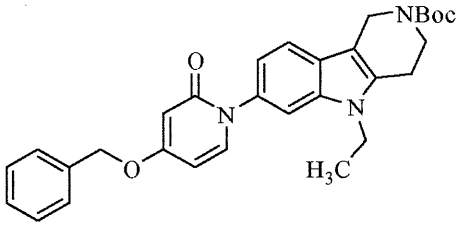
a) *tert*-Butyl 7-bromo-5-ethyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{18}H_{23}BrN_2O_2$
Exact Mass: 378.09
Molecular Weight: 379.29

Prepared from *tert*-butyl 7-bromo-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (500 mg, 1.43 mmol) according to the procedure of Example 1 (step b). This provided the title compound (520 mg, 96%) as a yellow/orange solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.23 (d, J = 8.3 Hz, 1H), 7.10 (d, J = 8.2 Hz, 1H), 4.54 (s, 2H), 3.96 (q, J = 7.2 Hz, 2H), 3.76 (br m, 2H), 2.71 (br m, 2H), 1.43 (s, 9H), 1.25 (t, J = 7.2 Hz, 3H).

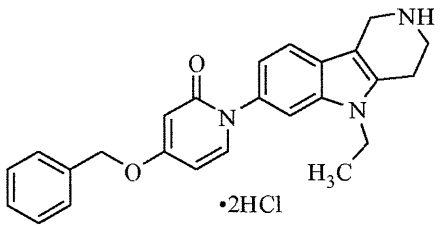
b) *tert*-Butyl 7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-5-ethyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate



Chemical Formula: $C_{30}H_{33}N_3O_4$
Exact Mass: 499.25
Molecular Weight: 499.60

Prepared from *tert*-butyl 7-bromo-5-ethyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (500 mg, 1.32 mmol) and 4-benzyloxypyridone (265 mg, 1.32 mmol), according to the procedure of Example 1 (step c). Purification by flash column chromatography (silica gel, hexanes/EtOAc, 100:0 to 80:20 to 50:50 to 25:75 then 0:100) gave the title compound (317 mg, 48%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 8.2 Hz, 1H), 7.44–7.37 (m, 5H), 7.32–7.29 (m, 2H), 7.04 (d, J = 8.0 Hz, 1H), 6.10–6.03 (m, 2H), 5.08 (s, 2H), 4.66 (br s, 2H), 4.10 (q, J = 7.1 Hz, 2H), 3.86 (br m, 2H), 2.84 (br m, 2H), 1.53 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H).

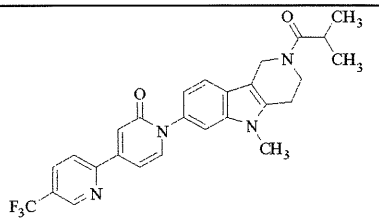
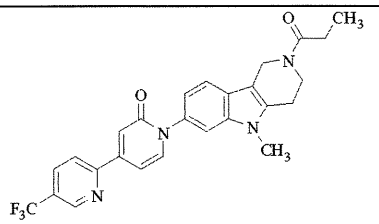
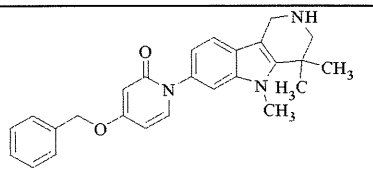
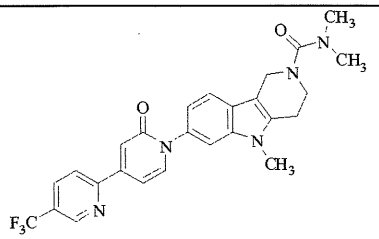
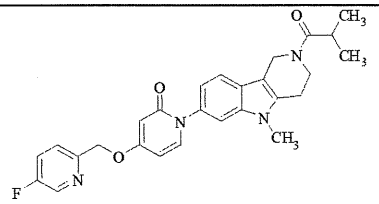
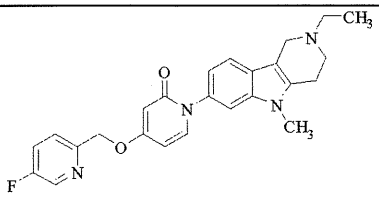
c) 4-(Benzyloxy)-1-(5-ethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one dihydrochloride

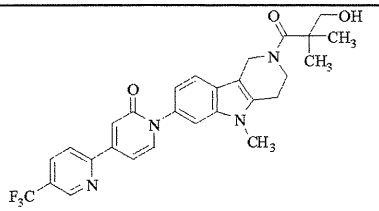
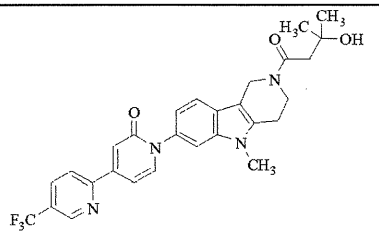
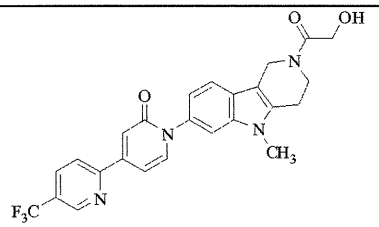
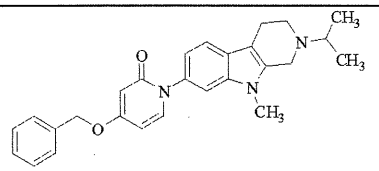
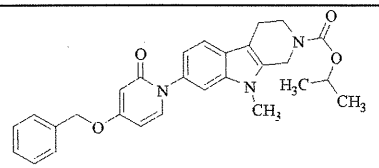
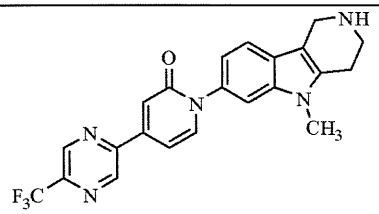
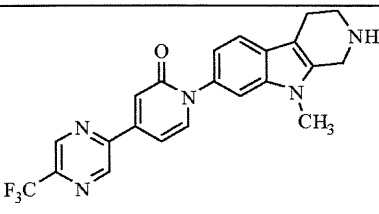


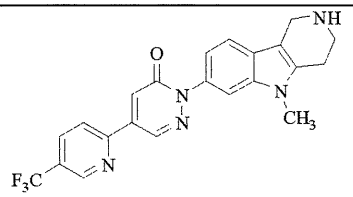
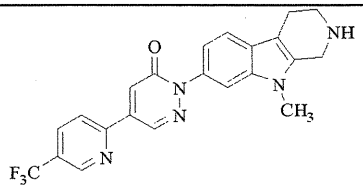
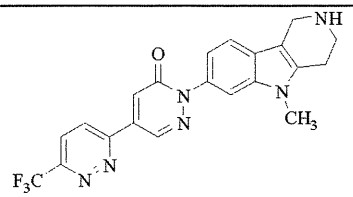
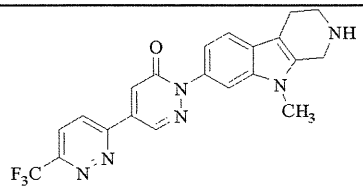
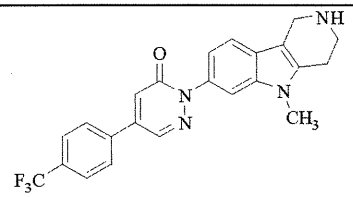
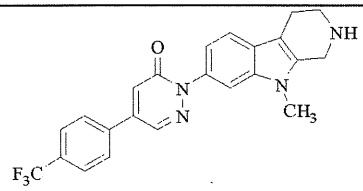
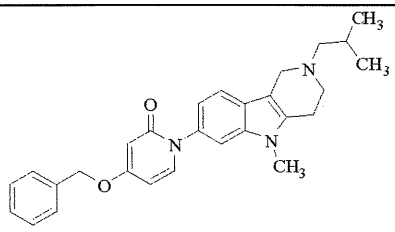
Chemical Formula: $C_{25}H_{27}Cl_2N_3O_2$
Exact Mass: 471.15
Molecular Weight: 472.41

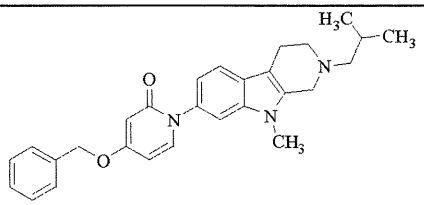
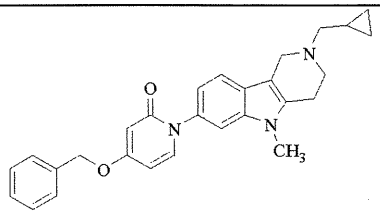
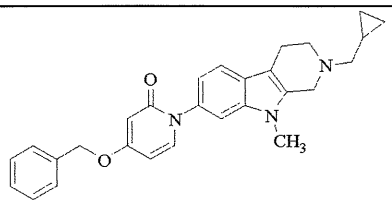
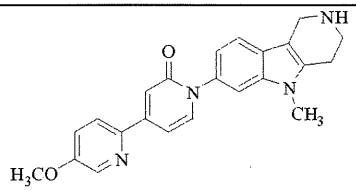
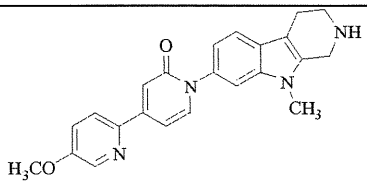
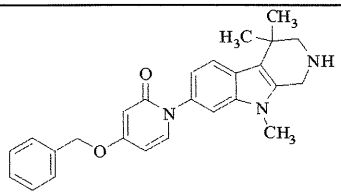
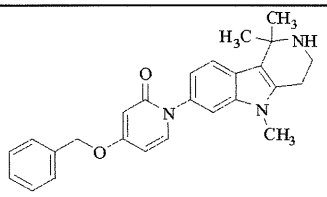
Prepared from *tert*-butyl 7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-5-ethyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (315 mg, 0.631 mmol) according to the procedure of Example 1 (step d) providing the title compound (207 mg, 74%) as a yellow solid: mp 176–181 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.83 (d, J = 7.5 Hz, 1H), 7.62–7.57 (m, 2H), 7.45–7.40 (m, 5H), 7.09 (dd, J = 8.4, 1.6 Hz, 1H), 6.59 (dd, J = 7.5, 2.3 Hz, 1H), 6.36 (d, J = 2.3 Hz, 1H), 5.28 (s, 2H), 4.49 (s, 2H), 4.23 (q, J = 7.2 Hz, 2H), 3.68 (t, J = 6.1 Hz, 2H), 3.22 (t, J = 5.9 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H); ESI MS *m/z* 400 $[M + H]^+$; HPLC (Method A) >99% (AUC), t_R = 13.2 min.

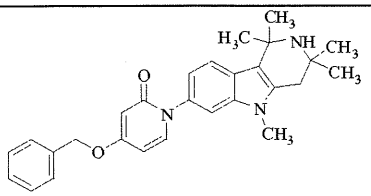
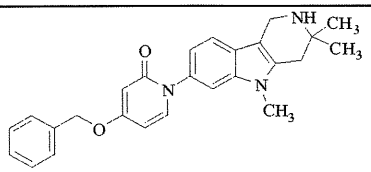
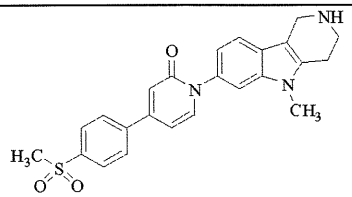
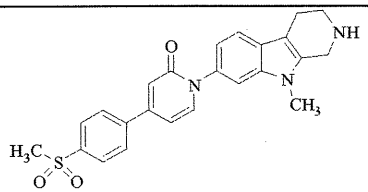
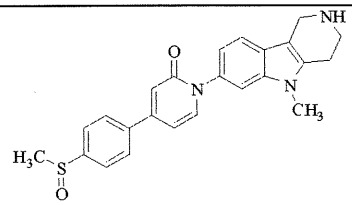
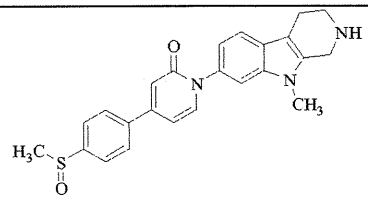
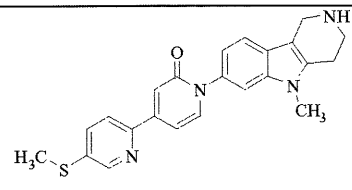
In accordance with further embodiments of the invention, there are provided the following compounds, which may be synthesized by analogy by the methods shown and described above:

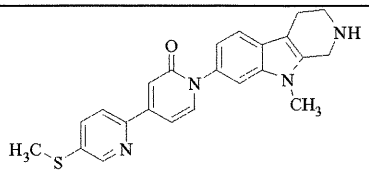
Name	**Structure**
1-(2-Isobutyryl-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one	
1-(5-Methyl-2-propionyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one	
4-(Benzyloxy)-1-(4,4,5-trimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one	
N,*N*,5-Trimethyl-7-(2-oxo-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-1(2*H*)-yl)-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxamide	
4-((5-Fluoropyridin-2-yl)methoxy)-1-(2-isobutyryl-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one	
1-(2-Ethyl-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-((5-fluoropyridin-2-yl)methoxy)pyridin-2(1*H*)-one	

Name	Structure
1-(2-(3-Hydroxy-2,2-dimethylpropanoyl)-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one	
1-(2-(3-Hydroxy-3-methylbutanoyl)-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one	
1-(2-(2-Hydroxyacetyl)-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1*H*)-one	
4-(Benzyloxy)-1-(2-isopropyl-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one	
Isopropyl 7-(4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate	
1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyrazin-2-yl)pyridin-2(1*H*)-one	
1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(5-(trifluoromethyl)pyrazin-2-yl)pyridin-2(1*H*)-one	

Name	Structure
2-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-5-(5-(trifluoromethyl)pyridin-2-yl)pyridazin-3(2*H*)-one	
2-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-5-(5-(trifluoromethyl)pyridin-2-yl)pyridazin-3(2*H*)-one	
2-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-5-(6-(trifluoromethyl)pyridazin-3-yl)pyridazin-3(2*H*)-one	
2-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-5-(6-(trifluoromethyl)pyridazin-3-yl)pyridazin-3(2*H*)-one	
2-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-5-(4-(trifluoromethyl)phenyl)pyridazin-3(2*H*)-one	
2-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-5-(4-(trifluoromethyl)phenyl)pyridazin-3(2*H*)-one	
4-(Benzyloxy)-1-(2-isobutyl-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one	

Name	Structure
4-(Benzyloxy)-1-(2-isobutyl-9-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-7-yl)pyridin-2(1H)-one	
4-(Benzyloxy)-1-(2-(cyclopropylmethyl)-5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one	
4-(Benzyloxy)-1-(2-(cyclopropylmethyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one	
4-(5-Methoxypyridin-2-yl)-1-(5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one	
4-(5-Methoxypyridin-2-yl)-1-(9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one	
4-(Benzyloxy)-1-(4,4,9-trimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)pyridin-2(1*H*)-one	
4-(Benzyloxy)-1-(1,1,5-trimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one	

Name	Structure
4-(Benzyloxy)-1-(1,1,3,3,5-pentamethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one	
4-(Benzyloxy)-1-(3,3,5-trimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)pyridin-2(1*H*)-one	
1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(4-(methylsulfonyl)phenyl)pyridin-2(1*H*)-one	
1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(4-(methylsulfonyl)phenyl)pyridin-2(1*H*)-one	
1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(4-(methylsulfinyl)phenyl)pyridin-2(1*H*)-one	
1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(4-(methylsulfinyl)phenyl)pyridin-2(1*H*)-one	
1-(5-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-7-yl)-4-(5-(methylthio)pyridin-2-yl)pyridin-2(1*H*)-one	

Name	Structure
1-(9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-7-yl)-4-(5-(methylthio)pyridin-2-yl)pyridin-2(1*H*)-one	

Binding Assay I for Human Melanin-Concentrating Hormone (MCH_1) receptor

Evaluation of the affinity of compounds for the human MCH_1 receptor was accomplished in transfected Chinese Hamster Ovary (CHO) cells determined in a radioligand binding assay, as described in MacDonald et al., "Molecular characterization of the melanin-concentrating hormone/receptor complex: identification of critical residues involved in binding and activation", Mol Pharmacol., 58:217 (2000). Cell membrane homogenates (5 μg protein) were incubated for 60 min at 22°C with 0.1 nM [^{125}I][Phe^{13},Tyr^{19}]-MCH in the absence or presence of the test compound in a buffer containing 25 mM Hepes/Tris (pH 7.4), 5 mM $MgCl_2$, 1 mM $CaCl_2$ and 0.5% bovine serum albumin (BSA). Nonspecific binding was determined in the presence of 0.1 μM MCH. Following incubation, the samples were filtered rapidly under vacuum through glass fiber filters (GF/B, Packard) and rinsed several times with an ice-cold buffer containing 25 mM Hepes/Tris (pH 7.4), 500 mM NaCl, 5 mM $MgCl_2$, 1 mM $CaCl_2$ and 0.1% BSA using a 96-sample cell harvester (Unifilter, Packard). The filters were dried, then counted for radioactivity in a scintillation counter (Topcount, Packard) using a scintillation cocktail (Microscint 0, Packard).

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).

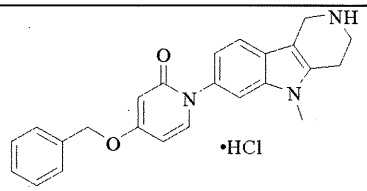
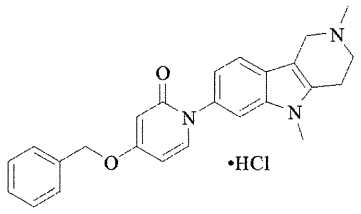
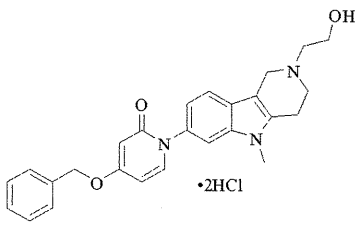
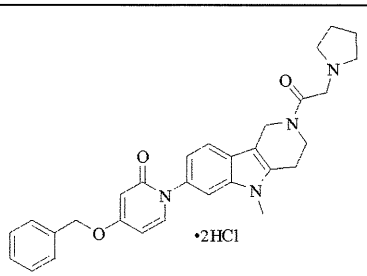
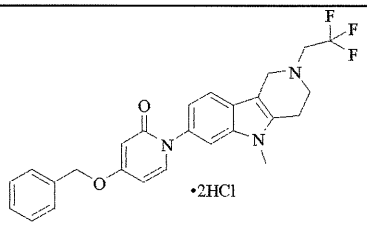
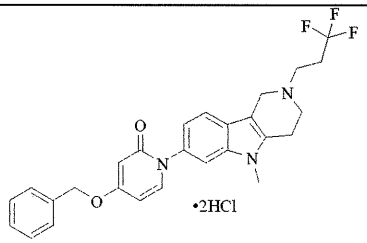
Binding Assay II for Human Melanin-Concentrating Hormone (MCH_1) receptor

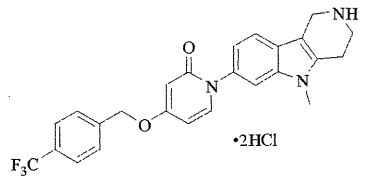
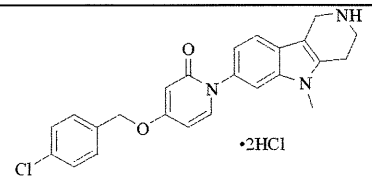
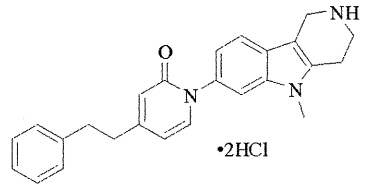
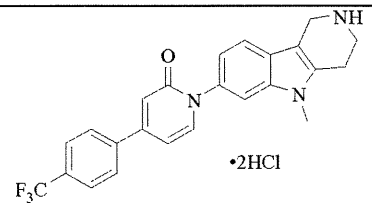
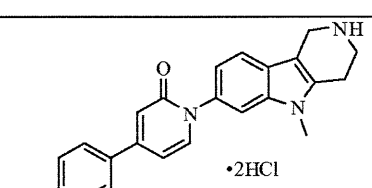
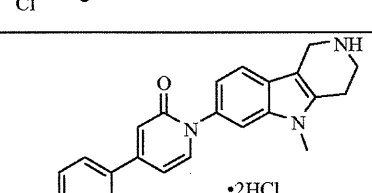
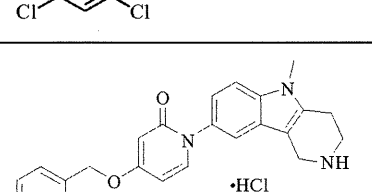
Evaluation of the affinity of compounds for the human MCH_1 receptor was accomplished using 4-(3,4,5-tritritiumbenzyloxy)-1-(1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-indazol-5-yl)pyridin-2(1*H*)-one and membranes prepared from stable CHO-K1 cells expressing the human MCH_1 receptor obtained from Euroscreen (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).

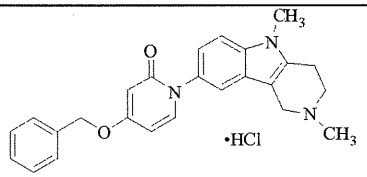
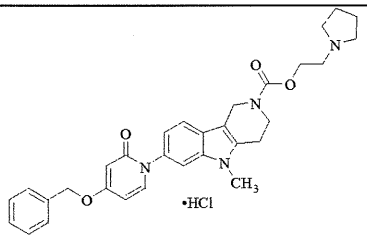
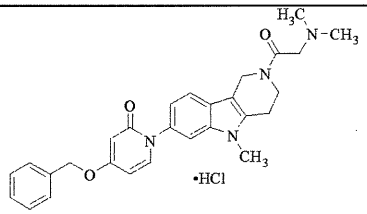
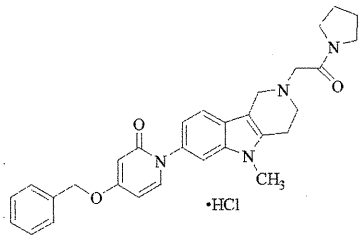
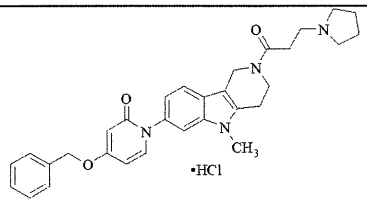
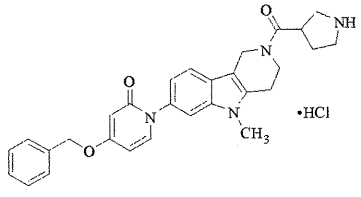
The results are expressed as a percent inhibition of the control radioligand specific binding. The IC_{50} value (concentration causing a half-maximal inhibition of control specific binding) and Hill coefficient (n_H) were determined by non-linear regression analysis of the competition curve using Hill 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.

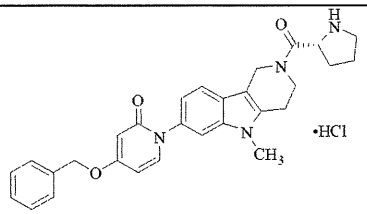
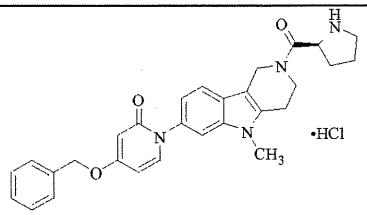
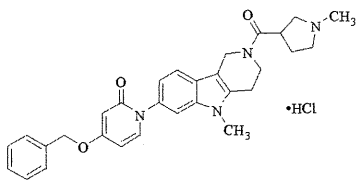
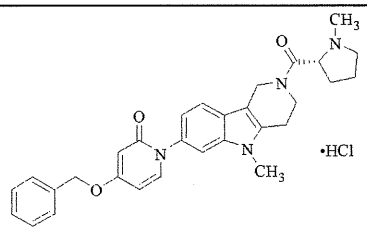
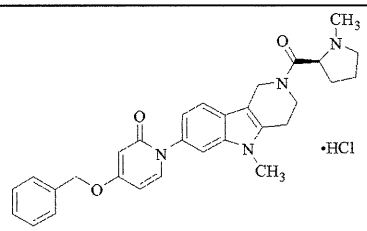
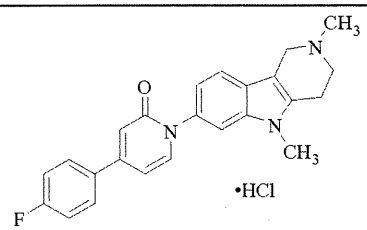
By methods as described above, the compounds listed in TABLE 1 were synthesized and tested for biological activity. All of the compounds in TABLE 1 exhibited K_i of less than or equal to 3.5 μM in MCH_1 binding assays I or II.

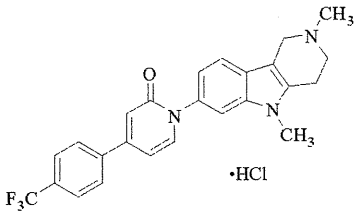
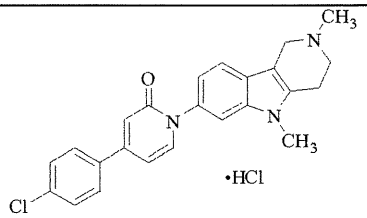
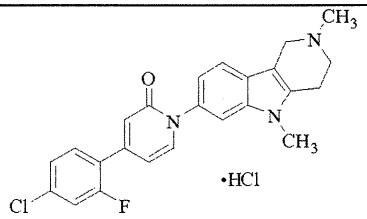
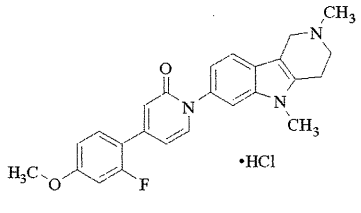
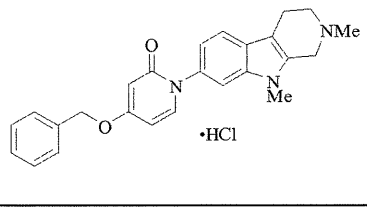
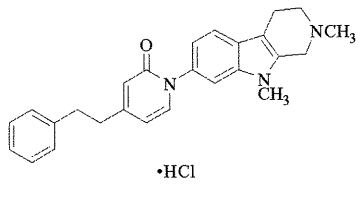
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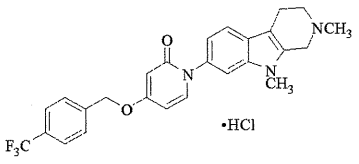
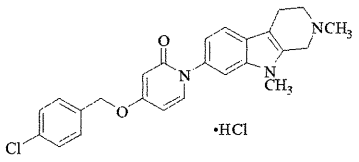
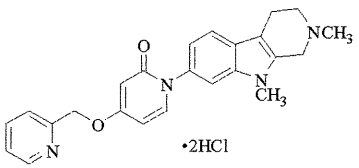
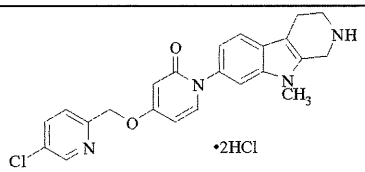
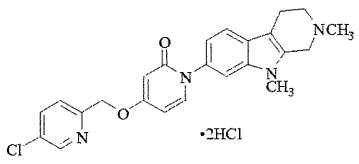
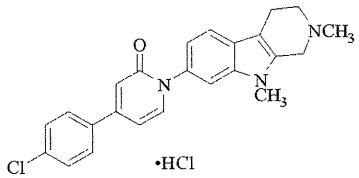
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2		400	^{1}H NMR (500 MHz, CD_3OD) δ 7.57 (dd, J = 7.6, 1.7 Hz, 2H), 7.47–7.46 (m, 3H) 7.43–7.34 (m, 3H), 7.06 (dd, J = 8.4, 1.9 Hz, 1H), 6.29 (dd, J = 7.6, 2.7 Hz, 1H), 6.13 (d, J = 2.6 Hz, 1H), 5.18 (s, 2H), 4.75 (d, J = 14.3 Hz, 1H), 4.38 (d, J = 14.2 Hz, 1H), 3.90 (m, 1H), 3.73 (s, 3H), 3.64–3.58 (m, 1H), 3.29–3.26 (m, 2H, partially masked by solvent), 3.13 (s, 3H)
3		430	^{1}H NMR (500 MHz, CD_3OD) δ 7.63 (dd, J = 7.6, 2.0 Hz, 2H), 7.51–7.50 (m, 3H) 7.46–7.43 (m, 2H), 7.41–7.38 (m, 1H), 7.09 (dd, J = 8.3, 1.7 Hz, 1H), 6.36 (dd, J = 7.6, 2.7 Hz, 1H), 6.18 (d, J = 2.7 Hz, 1H), 5.23 (s, 2H), 4.82 (d, 1H, partially masked by solvent), 4.520 (d, J = 14.3 Hz, 1H), 4.06–4.02 (m, 3H), 3.77 (s, 3H), 3.70–3.68 (m, 1H), 3.55–3.51 (m, 2H), 3.33–3.31 (m, 2H, partially masked by solvent)
4		497	^{1}H NMR (500 MHz, CD_3OD) δ 7.62 (dd, J = 7.7, 1.9 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H) 7.46–7.44 (m, 2H), 7.41–7.35 (m, 4H), 7.06 (dd, J = 8.0, 1.7 Hz, 1H), 6.36 (d, J = 7.6 Hz, 1H), 6.18 (s, 1H), 5.25 (s, 2H), 4.90 (m, 1H, masked by solvent), 4.82 (s, 1H), 4.53 (d, J = 14.2 Hz, 2H), 4.09 (t, J = 6.5 Hz, 1H), 3.91 (t, J = 6.4 Hz, 1H), 3.89–3.86 (m, 2H), 3.77 (s, 3H), 3.20–3.18 (m, 2H), 3.05–3.03 (m, 1H), 2.99–2.97 (m, 1H), 2.12–2.10 (m, 2H), 2.08–2.05 (m, 2H)
5		468	^{1}H NMR (300 MHz, CD_3OD) δ 7.48 (d, J = 7.5 Hz, 1H), 7.40–7.24 (m, 7H), 6.87 (dd, J = 8.3, 1.9 Hz, 1H), 6.19 (dd, J = 7.6, 2.7 Hz, 1H), 6.03 (d, J = 2.7 Hz, 1H), 5.08 (s, 2H), 3.96 (s, 2H), 3.58 (s, 3H), 3.37 (q, J = 9.7 Hz, 2H), 3.15–3.14 (m, 2H, partially masked by solvent), 2.87 (t, J = 5.5 Hz, 2H)
6		482	^{1}H NMR (500 MHz, CD_3OD) δ 7.66 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.52–7.51 (m, 3H), 7.48–7.45 (m, 2H), 7.43 (d, J = 7.2 Hz, 1H), 7.11 (dd, J = 8.3, 1.7 Hz, 1H), 6.36 (dd, J = 7.6, 2.7 Hz, 1H), 6.19 (d, J = 2.7 Hz, 1H), 5.24 (s, 2H), 4.96 (m, 6H, masked by solvent), 3.79–3.74 (m, 5H), 3.03–3.02 (m, 2H)

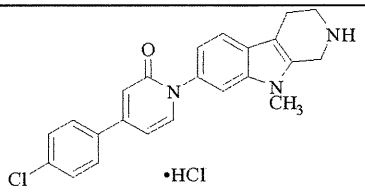
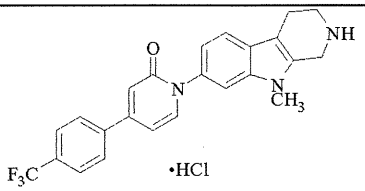
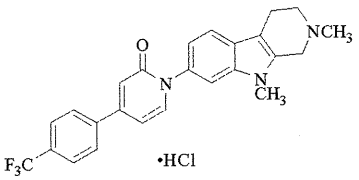
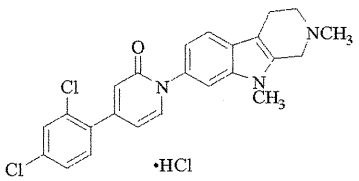
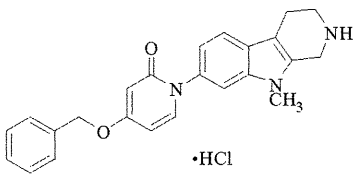
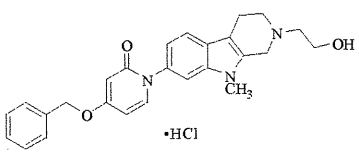
Ex. No.	Structure	Mass Spec	^{1}H NMR Data
7		454	^{1}H NMR (500 MHz, CD_3OD) δ 7.77 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.50 (s, 1H), 7.09 (dd, J = 8.3, 1.8 Hz, 1H), 6.38 (dd, J = 7.6, 2.7 Hz, 1H), 6.17 (d, J = 2.7 Hz, 1H), 5.33 (s, 2H), 4.51 (s, 2H), 3.77 (s, 3H), 3.71 (t, J = 6.2 Hz, 2H), 3.24 (t, J = 6.1 Hz, 2H)
8		420	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (br s, 2H), 7.57 (m, 2H), 7.51 (s, 5H), 6.99 (d, J = 7.8 Hz, 1H), 6.12 (dd, J = 7.8, 2.7 Hz, 1H), 5.99 (d, J = 2.7 Hz, 1H), 5.16 (s, 2H), 4.33 (br s, 2H), 3.68 (s, 3H), 3.52–3.48 (m, 2H), 3.12–3.08 (m, 2H)
9		384	^{1}H NMR (500 MHz, CD_3OD) δ 7.70 (d, J = 6.9 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.52 (s, 1H), 7.33–7.26 (m, 4H), 7.22 (t, J = 7.2 Hz, 1H), 7.09 (dd, J = 8.3, 1.6 Hz, 1H), 6.59–6.56 (m, 2H), 4.50 (s, 2H), 3.76 (s, 3H), 3.70 (t, J = 6.2 Hz, 2H), 3.24 (t, J = 6.0 Hz, 2H), 3.04–3.01 (m, 2H), 2.98–2.95 (m, 2H)
10		424	^{1}H NMR (500 MHz, CD_3OD) δ 7.95 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H), 7.81 (d, J = 7.1 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.57 (s, 1H), 7.14 (dd, J = 8.3, 1.3 Hz, 1H), 6.96 (d, J = 1.6 Hz, 1H), 6.87 (dd, J = 7.1, 1.7 Hz, 1H), 4.50 (s, 2H), 3.76 (s, 3H), 3.68 (t, J = 6.1 Hz, 2H), 3.22 (t, J = 6.1 Hz, 2H)
11		390	^{1}H NMR (500 MHz, CD_3OD) δ 7.80–7.78 (m, 3H), 7.66 (d, J = 8.5 Hz, 1H), 7.58–7.57 (m, 3H), 7.16 (dd, J = 8.3, 1.7 Hz, 1H), 6.94 (d, J = 1.8 Hz, 1H), 6.87 (dd, J = 7.1, 1.9 Hz, 1H), 6.17 (d, J = 2.7 Hz, 1H), 4.53 (s, 2H), 3.79 (s, 3H), 3.72 (t, J = 5.9 Hz, 2H), 3.25 (t, J = 5.9 Hz, 2H)
12		424	^{1}H NMR (500 MHz, CD_3OD) δ 7.80 (d, J = 7.0 Hz, 1H), 7.70 (s, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.62 (s, 1H), 7.54 (s, 2H), 7.13 (d, J = 7.0 Hz, 1H), 6.73 (s, 1H), 6.61 (d, J = 7.2 Hz, 1H), 4.54 (s, 2H), 3.80 (s, 3H), 3.72 (t, J = 6.0 Hz, 2H), 3.26 (t, J = 5.9 Hz, 2H)
13		386	^{1}H NMR (500 MHz, CD_3OD) δ 7.59 (d, J = 7.5 Hz, 1H), 7.54 (d, J = 9.0 Hz, 1H), 7.48–7.40 (m, 5H), 7.38–7.36 (m, 1H), 7.17 (dd, J = 8.5, 1.5 Hz, 1H), 6.33 (dd, J = 7.5, 2.5 Hz, 1H), 6.16 (d, J = 2.5 Hz, 1H), 5.20 (s, 2H), 4.45 (s, 2H), 3.77 (s, 3H), 3.67 (t, J = 6.0 Hz, 2H), 3.21 (t, J = 6.0 Hz, 2H)

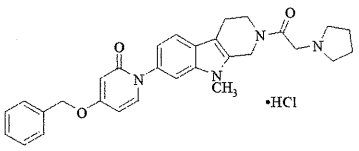
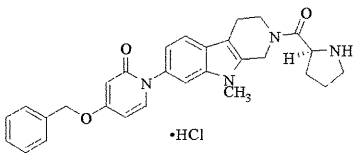
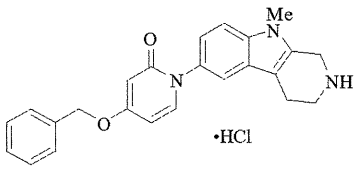
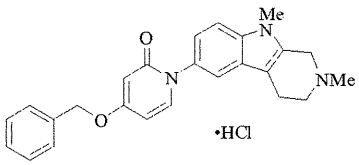
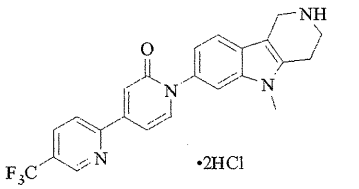
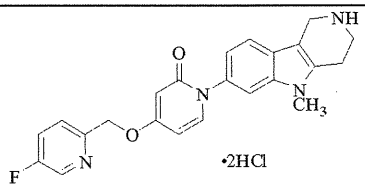
Ex. No.	Structure	Mass Spec	^{1}H NMR Data
14		400	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.26 (s, 1H), 7.56–7.36 (m, 8H), 7.10 (dd, J = 8.5, 1.5 Hz, 1H), 6.10 (dd, J = 7.5, 3.0 Hz, 1H), 5.97 (d, J = 3.0 Hz, 1H), 5.15 (s, 2H), 4.58 (m, 1H), 4.27 (m, 1H), 3.78 (m, 1H), 3.72 (s, 3H), 3.50 (m, 1H), 3.18 (m, 2H), 2.97 (s, 3H)
15		527	^{1}H NMR (500 MHz, CD_3OD) δ 7.78–7.75 (m, 1H), 7.57–7.54 (m, 1H), 7.49–7.37 (m, 6H), 7.04–7.01 (m, 1H), 6.55–6.52 (m, 1H), 6.33–6.31 (m, 1H), 5.26 (s, 2H), 4.80–4.73 (m, 2H), 4.49–4.48 (m, 2H), 3.94–3.93 (m, 2H), 3.82–3.72 (m, 2H), 3.69 (s, 3H), 3.58–3.57 (m, 2H), 3.20–3.14 (m, 2H), 2.98–2.94 (m, 2H), 2.15–1.99 (m, 4H)
16		471	^{1}H NMR (500 MHz, CD_3OD) δ 7.75–7.71 (m, 1H), 7.59–7.55 (m, 1H), 7.49–7.37 (m, 6H), 7.05–7.01 (m, 1H), 6.49–6.45 (m, 1H), 6.28–6.26 (m, 1H), 5.24 (s, 2H), 4.87 (br s, 1H), 4.69 (br s, 1H), 4.44–4.41 (m, 2H), 4.11–4.07 (m, 1H), 3.85–3.82 (m, 1H), 3.70 (2 × s, 3H), 3.06–2.92 (m, 2H), 2.97–2.94 (2 × s, 6H)
17		497	^{1}H NMR (500 MHz, CD_3OD) δ 7.60 (d, J = 7.5 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.49–7.35 (m, 6H), 7.06 (dd, J = 8.5, 1.5 Hz, 1H), 6.33 (dd, J = 7.5, 3.0 Hz, 1H), 6.16 (d, J = 3.0 Hz, 1H), 5.20 (s, 2H), 4.80 (d, J = 14.5 Hz, 1H), 4.54 (d, J = 14.5 Hz, 1H), 4.36 (s, 2H), 4.00–3.98 (m, 1H), 3.75 (s, 3H), 3.68–3.65 (m, 1H), 3.54 (t, J = 7.0 Hz, 2H), 3.49–3.45 (m, 2H), 3.35–3.33 (m, 2H), 2.05–1.92 (m, 4H)
18		511	^{1}H NMR (500 MHz, CD_3OD) δ 7.79–7.76 (m, 1H), 7.61–7.55 (m, 1H), 7.49–7.36 (m, 6H), 7.05–7.02 (m, 1H), 6.55–6.52 (m, 1H), 6.33–6.32 (m, 1H), 5.26 (s, 2H), 4.06 (t, J = 5.5 Hz, 1H), 3.94 (t, J = 5.5 Hz, 1H), 3.70–3.69 (m, 5H), 3.54–3.50 (m, 2H), 3.18–2.89 (m, 8H), 2.18–2.04 (m, 4H)
19		483	^{1}H NMR (500 MHz, CD_3OD) δ 7.75–7.72 (m, 1H), 7.63–7.55 (m, 1H), 7.49–7.36 (m, 6H), 7.05–7.02 (m, 1H), 6.51–6.46 (m, 1H), 6.29–6.27 (m, 1H), 5.25 (s, 2H), 4.79–4.76 (m, 2H), 4.14–3.97 (m, 2H), 3.87–3.82 (m, 1H), 3.71–3.69 (m, 4H), 3.60–3.50 (m, 1H), 3.45–3.36 (m, 3H), 3.04–3.03 (m, 1H), 2.94–2.92 (m, 1H), 2.52–2.36 (m, 1H), 2.18–2.00 (m, 1H)

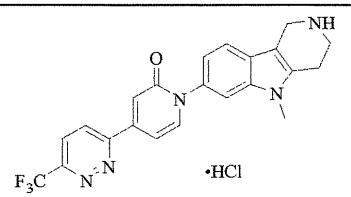
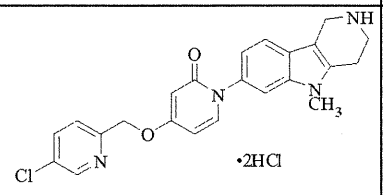
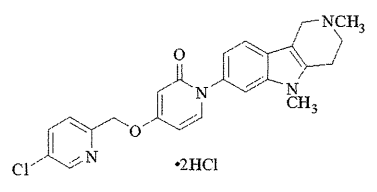
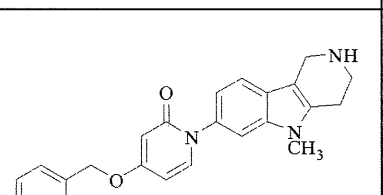
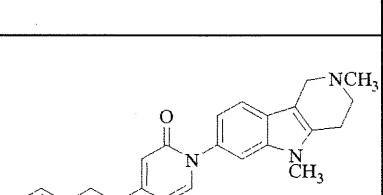
Ex. No.	Structure	Mass Spec	^{1}H NMR Data
20		483	^{1}H NMR (500 MHz, CD_3OD) δ 7.82–7.79 (m, 1H), 7.66–7.56 (m, 1H), 7.49–7.36 (m, 6H), 7.07–7.03 (m, 1H), 6.59–6.56 (m, 1H), 6.36 (dd, *J* = 5.0, 2.5 Hz, 1H), 5.28 (s, 2H), 4.82–4.81 (m, 2H), 4.14–4.05 (m, 1H), 3.97–3.95 (m, 1H), 3.71–3.69 (2 × s, 3H), 3.58–3.34 (m, 3H), 3.07–2.94 (m, 2H), 2.70–2.57 (m, 1H), 2.17–1.85 (m, 3H)
21		483	^{1}H NMR (500 MHz, CD_3OD) δ 7.82–7.79 (m, 1H), 7.66–7.56 (m, 1H), 7.49–7.36 (m, 6H), 7.07–7.03 (m, 1H), 6.59–6.56 (m, 1H), 6.36 (dd, *J* = 5.0, 2.5 Hz, 1H), 5.28 (s, 2H), 4.82–4.81 (m, 2H), 4.14–4.05 (m, 1H), 3.97–3.95 (m, 1H), 3.71–3.69 (2 × s, 3H), 3.58–3.34 (m, 3H), 3.07–2.94 (m, 2H), 2.70–2.57 (m, 1H), 2.17–1.85 (m, 3H)
22		497	^{1}H NMR (500 MHz, CD_3OD) δ 7.61–7.33 (m, 8H), 7.02–6.98 (m, 1H), 6.29–6.27 (m, 1H), 6.12–6.11 (m, 1H), 5.17 (s, 2H), 4.79–4.76 (m, 2H), 4.09–3.97 (m, 2H), 3.81–3.79 (m, 1H), 3.69–3.67 (m, 4H), 3.49–3.42 (m, 1H), 3.22–3.16 (m, 2H), 3.00 (m, 1H), 2.92–2.91 (m, 1H), 2.81–2.78 (2 × s, 3H), 2.52–2.36 (m, 1H), 2.18–2.00 (m, 1H)
23		497	^{1}H NMR (500 MHz, CD_3OD) δ 7.61–7.33 (m, 8H), 7.03–6.99 (m, 1H), 6.30 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.13 (d, *J* = 2.5 Hz, 1H), 5.18 (s, 2H), 4.80–4.70 (m, 2H), 4.12–4.09 (m, 1H), 3.92–3.90 (m, 1H), 3.78–3.72 (m, 1H), 3.69–3.68 (2s, 3H), 3.49–3.42 (m, 1H), 3.28–3.20 (m, 1H), 3.07–3.00 (m, 2H), 2.96–2.94 (2s, 3H), 2.79–2.65 (m, 1H), 2.21–2.09 (m, 1H), 2.09–1.86 (m, 2H)
24		497	^{1}H NMR (500 MHz, CD_3OD) δ 7.61–7.33 (m, 8H), 7.03–6.99 (m, 1H), 6.30 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.13 (d, *J* = 2.5 Hz, 1H), 5.18 (s, 2H), 4.80–4.70 (m, 2H), 4.12–4.09 (m, 1H), 3.92–3.90 (m, 1H), 3.78–3.72 (m, 1H), 3.69–3.68 (2s, 3H), 3.49–3.42 (m, 1H), 3.28–3.20 (m, 1H), 3.07–3.00 (m, 2H), 2.96–2.94 (2 × s, 3H), 2.79–2.65 (m, 1H), 2.21–2.09 (m, 1H), 2.09–1.86 (m, 2H)
25		388	^{1}H NMR (500 MHz, CD_3OD) δ 7.82–7.79 (m, 2H), 7.75 (d, *J* = 7.0 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.56 (d, *J* = 1.5 Hz, 1H), 7.29–7.25 (m, 2H), 7.14 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 6.82 (dd, *J* = 7.0, 2.0 Hz, 1H), 4.77 (d, *J* = 14.0 Hz, 1H), 4.41 (d, *J* = 14.0 Hz, 1H), 3.93–3.90 (m, 1H), 3.76 (s, 3H), 3.66–3.60 (m, 1H), 3.27 (m, 2H), 3.15 (s, 3H)

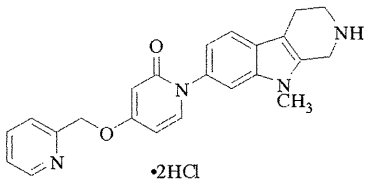
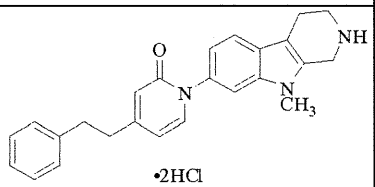
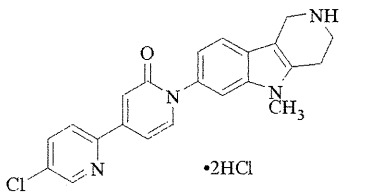
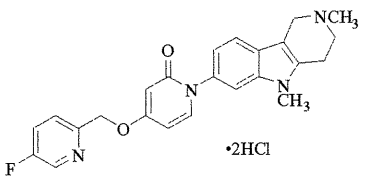
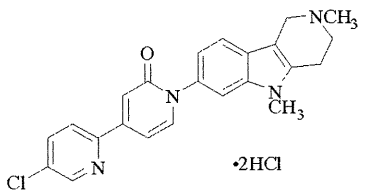
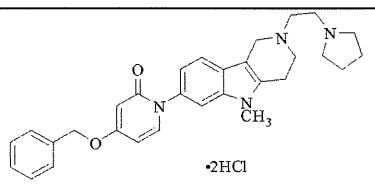
Ex. No.	Structure	Mass Spec	^{1}H NMR Data
26		438	^{1}H NMR (500 MHz, CD_3OD) δ 7.95 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 1.5 Hz, 1H), 7.15 (dd, J = 8.5, 2.0 Hz, 1H), 6.96 (d, J = 1.5 Hz, 1H), 6.87 (dd, J = 7.5, 2.0 Hz, 1H), 4.78 (d, J = 14.0 Hz, 1H), 4.41 (d, J = 14.0 Hz, 1H), 3.93–3.90 (m, 1H), 3.77 (s, 3H), 3.66–3.60 (m, 1H), 3.27 (m, 2H), 3.15 (s, 3H)
27		404	^{1}H NMR (500 MHz, CD_3OD) δ 7.77–7.75 (m, 3H), 7.62 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.56–7.54 (m, 2H), 7.15 (dd, J = 8.5, 2.0 Hz, 1H), 6.91 (d, J = 2.0 Hz, 1H), 6.84 (dd, J = 7.0, 2.0 Hz, 1H), 4.78 (d, J = 14.0 Hz, 1H), 4.41 (d, J = 14.0 Hz, 1H), 3.93–3.90 (m, 1H), 3.77 (s, 3H), 3.66–3.60 (m, 1H), 3.27 (m, 2H), 3.15 (s, 3H)
28		422	^{1}H NMR (500 MHz, CD_3OD) δ 7.76 (d, J = 7.0 Hz, 1H), 7.66–7.57 (m, 2H), 7.57 (d, J = 2.0 Hz, 1H), 7.42–7.39 (m, 2H), 7.15 (dd, J = 8.5, 2.0 Hz, 1H), 6.84 (s, 1H), 6.73–6.71 (m, 1H), 4.77 (d, J = 14.0 Hz, 1H), 4.41 (d, J = 14.0 Hz, 1H), 3.93–3.90 (m, 1H), 3.76(s, 3H), 3.64–3.61 (m, 1H), 3.27 (m, 2H), 3.15 (s, 3H)
29		418	^{1}H NMR (500 MHz, CD_3OD) δ 7.72 (d, J = 7.0 Hz, 1H), 7.63–7.56 (m, 3H), 7.15 (dd, J = 8.5, 1.5 Hz, 1H), 6.92 (dd, J = 8.5, 2.5 Hz, 1H), 6.87 (dd, J = 13.0, 2.0 Hz, 1H), 6.83 (s, 1H), 6.76 (d, J = 7.0 Hz, 1H), 4.77 (d, J = 14.0 Hz, 1H), 4.41 (d, J = 14.0 Hz, 1H), 3.94–3.90 (m, 1H), 3.88 (s, 3H), 3.76 (s, 3H), 3.66–3.60 (m, 1H), 3.27 (m, 2H), 3.15 (s, 3H)
30		400	^{1}H NMR (500 MHz, CD_3OD) δ 7.67–7.63 (m, 2H), 7.50–7.40 (m, 3H), 7.43–7.35 (m, 3H), 7.08 (dd, J = 8.3, 1.6 Hz, 1H), 6.40 (dd, J = 7.5, 2.6 Hz, 1H), 6.21 (d, J = 2.6 Hz, 1H), 5.22 (s, 2H), 4.81–4.80 (m, 1H), 4.58 (d, J = 15.3 Hz, 1H), 3.88–3.84 (m, 1H), 3.72 (s, 3H), 3.55–3.49 (m, 1H), 3.21–3.16 (m, 5H)
31		398	^{1}H NMR (500 MHz, CD_3OD) δ 7.67–7.64 (m, 2H), 7.51 (d, J = 1.8 Hz, 1H), 7.30–7.24 (m, 4H), 7.20–7.17 (m, 1H), 7.08 (dd, J = 8.4, 1.9 Hz, 1H), 6.56 (dd, J = 6.9, 1.9 Hz, 1H), 6.53 (s, 1H), 4.85 (m, 1H), 4.49 (d, J = 15.3 Hz, 1H), 3.89–3.84 (m, 1H), 3.72 (s, 3H), 3.55–3.50 (m, 1H), 3.21–3.19 (m, 2H), 3.16 (s, 3H), 3.02–2.99 (m, 2H), 2.96–2.93 (m, 2H)

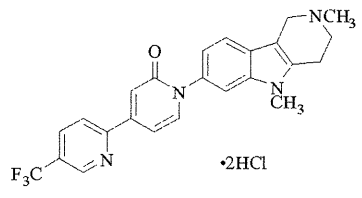
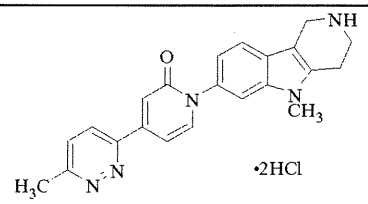
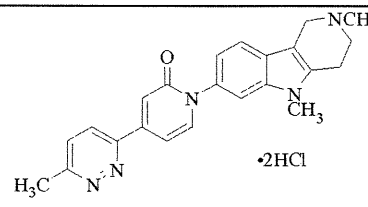
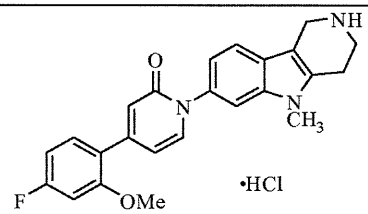
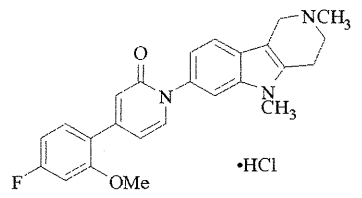
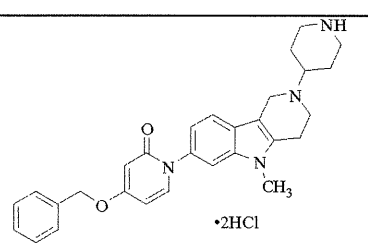
Ex. No.	Structure	Mass Spec	^{1}H NMR Data
32		468	^{1}H NMR (500 MHz, CD_3OD) δ 7.78–7.73 (m, 3H), 7.69–7.64 (m, 3H), 7.52 (d, *J* = 1.8 Hz, 1H), 7.18–7.08 (m, 1H), 6.55–6.52 (m, 1H), 6.28 (d, *J* = 2.6 Hz, 1H), 5.35 (s, 2H), 4.82–4.80 (m, 1H), 4.50 (d, *J* = 15.4 Hz, 1H), 3.89–3.85 (m, 1H), 3.73 (s, 3H), 3.55–3.50 (m, 1H), 3.22–3.16 (m, 5H)
33		434	^{1}H NMR (500 MHz, CD_3OD) δ 7.83 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.50–7.46 (m, 3H), 7.44–7.42 (m, 2H), 7.08 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.41 (dd, *J* = 7.6, 2.6 Hz, 1H), 6.21 (d, *J* = 2.6 Hz, 1H), 5.21 (s, 2H), 4.86–4.84 (m, 1H), 4.49 (d, *J* = 15.4 Hz, 1H), 3.88–3.84 (m, 1H), 3.72 (s, 3H), 3.55–3.50 (m, 1H), 3.21–3.16 (m, 5H)
34		401	^{1}H NMR (500 MHz, CD_3OD) δ 8.90 (dd, *J* = 5.8, 1.8 Hz, 1H), 8.65 (overlapping ddd, *J* = 7.9, 1.6 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 8.07 (overlapping dd, *J* = 6.4 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 6.4 Hz, 1H), 7.49 (d, *J* = 1.7 Hz, 1H), 7.07 (dd, *J* = 6.8, 1.8 Hz, 1H), 6.63 (dd, *J* = 7.6, 2.7 Hz, 1H), 6.21 (d, *J* = 2.7 Hz, 1H), 5.59 (s, 2H), 4.80 (m, 1H), 4.50 (d, *J* = 15.3 Hz, 1H), 3.88–3.85 (m, 1H), 3.73 (s, 3H), 3.55–3.50 (m, 1H), 3.21–3.16 (m, 5H)
35		421	^{1}H NMR (500 MHz, CD_3OD) δ 8.61 (s, 1H), 7.77 (dd, *J* = 8.3, 3.8 Hz, 1H), 7.64–7.62 (m, 3H), 7.47 (d, *J* = 1.6 Hz, 1H), 7.03 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.37 (dd, *J* = 7.6, 3.8 Hz, 1H), 6.15 (d, *J* = 2.7 Hz, 1H), 5.28 (s, 2H), 4.54 (s, 2H), 3.71 (s, 3H), 3.60 (t, *J* = 6.1 Hz, 2H), 3.12 (t, *J* = 6.0 Hz, 2H)
36		435	^{1}H NMR (500 MHz, CD_3OD) δ 8.68 (br s, 1H), 8.05 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.51 (d, *J* = 1.6 Hz, 1H), 7.09 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.53 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.28 (d, *J* = 1.6 Hz, 1H), 5.36 (s, 2H), 4.85–4.80 (m, 1H), 4.49 (d, *J* = 15.3 Hz, 1H), 3.89–3.84 (m, 1H), 3.72 (s, 3H), 3.53–3.47 (m, 1H), 3.22–3.19 (m, 2H), 3.16 (s, 3H)
37		404	^{1}H NMR (500 MHz, DMSO-d_6) δ 11.0 (br s, 1H), 7.83 (dd, *J* = 6.8, 1.9 Hz, 2H), 7.76 (d, *J* = 7.1 Hz, 1H), 7.62–7.57 (m, 4H), 7.07 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.69 (dd, *J* = 7.2, 2.1 Hz, 1H), 4.79 (d, *J* = 15.2 Hz, 1H), 4.44 (dd, *J* = 15.2, 6.0 Hz, 1H), 3.74–3.68 (m, 4H), 3.48–3.38 (m, 1H), 3.10–2.99 (m, 5H)

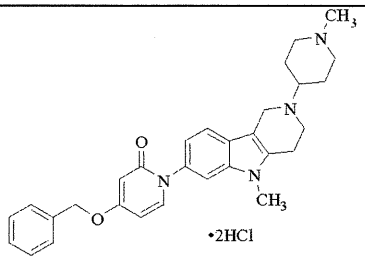
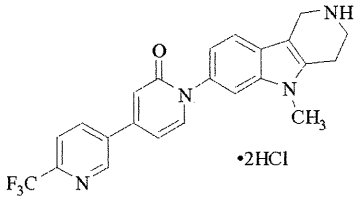
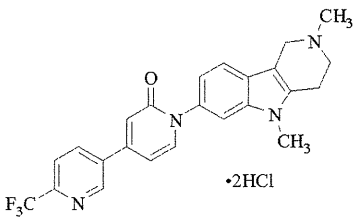
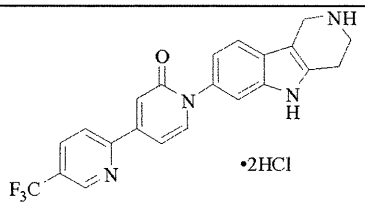
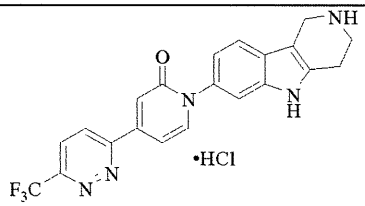
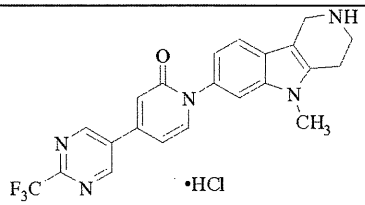
Ex. No.	Structure	Mass Spec	^{1}H NMR Data
38		390	^{1}H NMR (500 MHz, CD_3OD) δ 7.78–7.75 (m, 3H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.55–7.53 (m, 3H), 7.13 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.91 (d, *J* = 1.9 Hz, 1H), 6.84 (dd, *J* = 7.1, 2.0 Hz, 1H), 4.56 (s, 2H), 3.74 (s, 3H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.14 (t, *J* = 6.0 Hz, 2H)
39		424	^{1}H NMR (300 MHz, CD_3OD) δ 7.97 (d, *J* = 8.1 Hz, 2H), 7.87–7.80 (m, 3H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 1.5 Hz, 1H), 7.14 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.96 (d, *J* = 1.8 Hz, 1H), 6.87 (dd, *J* = 7.2, 1.8 Hz, 1H), 4.56 (s, 2H), 3.74 (s, 3H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.14 (t, *J* = 6.0 Hz, 2H)
40		438	^{1}H NMR (500 MHz, CD_3OD) δ 7.96 (d, *J* = 8.2 Hz, 2H), 7.85–7.83 (m, 3H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.58 (d, *J* = 1.6 Hz, 1H), 7.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.98 (d, *J* = 1.8 Hz, 1H), 6.90 (dd, *J* = 7.1, 1.9 Hz, 1H), 4.87–4.86 (m, 1H), 4.51 (d, *J* = 15.3 Hz, 1H), 3.90–3.86 (m, 1H), 3.74 (s, 3H), 3.57–3.51 (m, 1H), 3.23–3.20 (m, 2H), 3.17 (s, 3H)
41		438	^{1}H NMR (500 MHz, CD_3OD) δ 7.77 (d, *J* = 7.0 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.65 (overlapping dd, *J* = 1.1 Hz, 1H), 7.58 (d, *J* = 1.7 Hz, 1H), 7.49 (s, 2H), 7.16 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.70 (d, *J* = 1.5 Hz, 1H), 6.62 (dd, *J* = 7.0, 1.9 Hz, 1H), 4.86 (m, 1H), 4.50 (d, *J* = 15.3 Hz, 1H), 3.89–3.85 (m, 1H), 3.74 (s, 3H), 3.56–3.55 (m, 1H), 3.23–3.20 (m, 2H), 3.16 (s, 3H)
42		386	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.71 (br s, 2H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.50–7.47 (m, 3H), 7.44–7.41 (m, 2H), 7.38–7.37 (m, 1H), 6.99 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.11 (dd, *J* = 7.6, 2.8 Hz, 1H), 5.97 (d, *J* = 2.6 Hz, 1H), 5.15 (s, 2H), 4.45 (s, 2H), 3.81 (s, 3H), 3.42–3.41 (m, 2H), 2.98–2.97 (m, 2H)
43		430	^{1}H NMR (500 MHz, CD_3OD) δ 7.63 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.47–7.46 (m, 3H), 7.42–7.39 (m, 2H), 7.36 (d, *J* = 7.1 Hz, 1H), 7.06 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.33 (dd, *J* = 7.6, 2.6 Hz, 1H), 6.15 (d, *J* = 2.6 Hz, 1H), 5.19 (s, 2H), 4.81–4.79 (m, 1H), 4.59 (d, *J* = 15.3 Hz, 1H), 4.01 (t, *J* = 5.1 Hz, 2H), 3.97–3.94 (m, 1H), 3.73 (s, 3H), 3.58–3.50 (m, 3H), 3.21–3.16 (m, 2H)

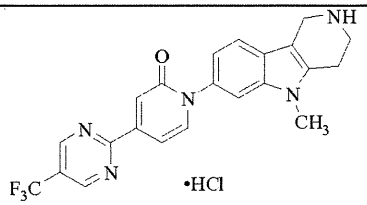
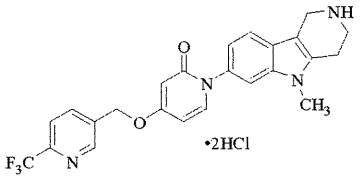
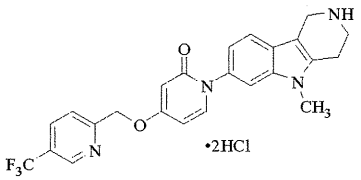
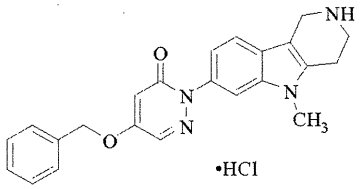
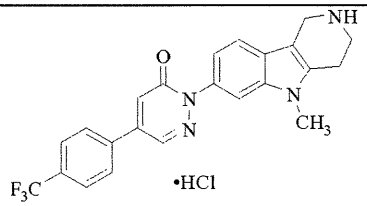
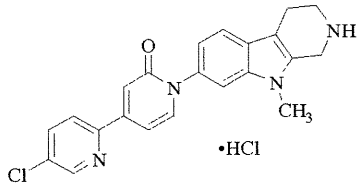
Ex. No.	Structure	Mass Spec	^{1}H NMR Data
44		497	^{1}H NMR (500 MHz, CD_3OD) δ 7.86 (d, J = 7.5 Hz, 1H), 7.62 (dd, J = 8.2, 2.7 Hz, 1H), 7.51–7.50 (m, 3H), 7.46–7.43 (m, 2H), 7.41–7.40 (m, 1H), 7.08–7.06 (m, 1H), 6.63 (dd, J = 7.8, 2.6 Hz, 1H), 6.40 (d, J = 1.4 Hz, 1H), 5.31 (s, 2H), 4.93 (s, 1.3H), 4.77 (s, 0.7H), 4.56–4.55 (m, 2H), 4.04–4.02 (m, 0.6H), 3.81–3.78 (m, 3.4H), 3.76 (s, 3H), 3.24–3.19 (m, 2H), 2.79–2.97 (m, 1.3H), 2.92–2.85 (m, 0.7H), 2.22–2.19 (m, 2H), 2.11–2.19 (m, 2H)
45		483	^{1}H NMR (500 MHz, CD_3OD) δ 7.79 (dd, J = 7.5, 1.4 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.49–7.46 (m, 3H), 7.44–7.46 (m, 2H), 7.39–7.36 (m, 1H), 7.04 (dd, J = 8.3, 1.6 Hz, 1H), 6.57–6.55 (m, 1H), 6.34 (d, J = 2.5 Hz, 1H), 5.27 (s, 2H), 4.96–4.87 (m, 2H), 3.90–8.86 (m, 2H), 3.77 (s, 3H), 3.48–3.34 (m, 3H), 3.00–2.86 (m, 2H), 2.67–2.61 (m, 1H), 2.17–2.02 (m, 3H)
46		386	^{1}H NMR (500 MHz, CD_3OD) δ 7.66 (d, J = 7.5 Hz, 1H), 7.57–7.52 (m, 2H), 7.46 (d, J = 7.7 Hz, 2H), 7.41 (overlapping dd, J = 7.3 Hz, 2H), 7.36 (d, J = 7.5 Hz, 1H), 7.19 (dd, J = 8.6, 2.0 Hz, 1H), 6.42 (dd, J = 7.5, 2.7 Hz, 1H), 6.22 (d, J = 2.6 Hz, 1H), 5.22 (s, 2H), 4.55 (s, 2H), 3.75 (s, 3H), 3.58 (t, J = 6.0 Hz, 2H), 3.10 (t, J = 6.0 Hz, 2H)
47		400	^{1}H NMR (500 MHz, CD_3OD) δ 7.56–7.53 (m, 2H), 7.51 (d, J = 1.8, 1H), 7.46 (d, J = 7.3 Hz, 2H), 7.41 (overlapping dd, J = 7.4 Hz, 2H), 7.36 (d, J = 7.2 Hz, 1H), 7.19 (dd, J = 8.6, 2.0 Hz, 1H), 6.27 (dd, J = 7.6, 2.7 Hz, 1H), 6.11 (d, J = 2.6 Hz, 1H), 5.18 (s, 2H), 4.64 (br s, 2H), 3.75 (s, 3H), 3.67 (br s, 2H), 3.18–3.13 (m, 5H)
48		425	^{1}H NMR (500 MHz, CD_3OD) δ 9.06 (s, 1H), 8.28 (dd, J = 8.4, 2.1 Hz, 1H), 8.23 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 7.1 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 1.6 Hz, 1H), 7.43 (d, J = 1.6 Hz, 1H), 7.29 (dd, J = Hz, 1H), 7.17 (dd, J = 8.3, 1.8 Hz, 1H), 4.50 (s, 2H), 3.76 (s, 3H), 3.69 (t, J = 6.0 Hz, 2H), 3.22 (t, J = Hz, 2H)
49		405	^{1}H NMR (500 MHz, CD_3OD) δ 8.70 (s, 1H), 8.00 (dt, J = 8.4, 2.8 Hz, 1H), 7.91–7.88 (m, 2H), 7.63 (d, J = 8.4 Hz, 1H), 7.55 (s, 1H), 7.11 (dd, J = 8.3, 1.7 Hz, 1H), 6.69 (dd, J = 7.5, 2.7 Hz, 1H), 6.45 (d, J = 2.6 Hz, 1H), 5.46 (s, 2H), 4.49 (s, 2H), 3.75 (s, 3H), 3.68 (t, J = 6.1 Hz, 2H), 3.22 (t, J = 6.1 Hz, 2H)

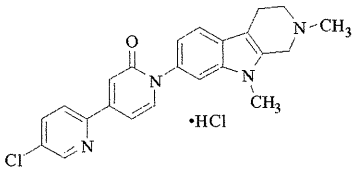
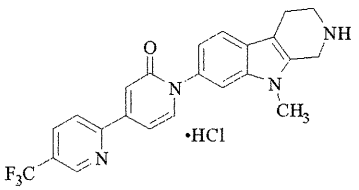
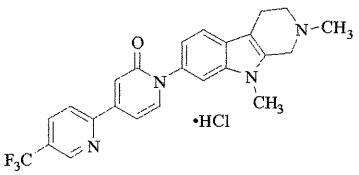
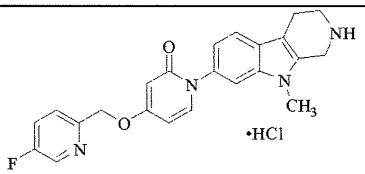
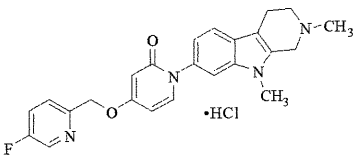
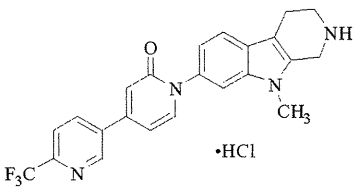
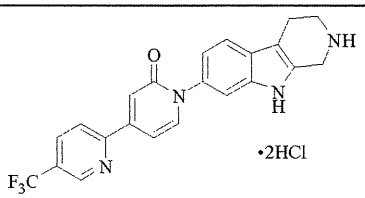
Ex. No.	Structure	Mass Spec	^{1}H NMR Data
50		426	^{1}H NMR (500 MHz, CD_3OD) δ 8.54 (d, J = 8.8 Hz, 1H), 8.28 (d, J = 8.9 Hz, 1H), 7.91 (d, J = 7.0 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 1.5 Hz, 1H), 7.44 (d, J = 1.5 Hz, 1H), 7.35 (dd, J = 7.2, 1.9 Hz, 1H), 7.16 (dd, J = 8.3, 1.8 Hz, 1H), 4.50 (s, 2H), 3.77 (s, 3H), 3.69 (t, J = 6.1 Hz, 2H), 3.22 (t, J = 6.0 Hz, 2H)
51		421	^{1}H NMR (300 MHz, CD_3OD) δ 8.61 (d, J = 2.1 Hz, 1H), 7.95 (dd, J = 8.4, 2.4 Hz, 1H), 7.62 (d, J = 7.6 Hz, 2H), 7.58 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 1.6 Hz, 1H), 7.05 (dd, J = 8.3, 1.8 Hz, 1H), 6.36 (dd, J = 7.6, 2.2 Hz, 1H), 6.13 (d, J = 2.6 Hz, 1H), 5.28 (s, 2H), 4.48 (s, 2H), 3.73 (s, 3H), 3.67 (t, J = 6.2 Hz, 2H), 3.02 (t, J = 6.2 Hz, 2H)
52		435	^{1}H NMR (300 MHz, CD_3OD) δ 8.60 (d, J = 2.0 Hz, 1H), 7.96–7.92 (m, 1H), 7.61 (d, J = 7.7 Hz, 2H), 7.57 (d, J = 8.3 Hz, 1H), 7.47 (d, J = 1.4 Hz, 1H), 7.06 (dd, J = 8.4, 1.7 Hz, 1H), 6.34 (dd, J = 7.6, 2.6 Hz, 1H), 6.12 (d, J = 2.6 Hz, 1H), 5.27 (s, 2H), 4.75 (d, J = 14.2 Hz, 1H), 4.38 (d, J = 14.1 Hz, 1H), 3.95–3.85 (m, 1H), 3.73 (s, 3H), 3.63 (m, 1H), 3.31 (m overlapping with solvent, 2H), 3.13 (s, 3H)
53		387	^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (d, J = 5.2 Hz, 1H), 8.59 (dd, J = 7.9, 1.5 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.01 (overlapping dd, J = 6.6 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 1.6 Hz, 1H), 7.06 (dd, J = 8.4, 1.8 Hz, 1H), 6.44 (dd, J = 7.6, 2.7 Hz, 1H), 6.21 (d, J = 2.7 Hz, 1H), 5.57 (s, 2H), 4.48 (s, 2H), 3.74 (s, 3H), 3.68 (t, J = 6.2 Hz, 2H), 3.21 (t, J = 6.2 Hz, 2H)
54		401	^{1}H NMR (500 MHz, CD_3OD) δ 8.87 (d, J = 5.7 Hz, 1H), 8.58 (overlapping dd, J = 8.2 Hz, 1H), 8.14 (d, J = 7.9 Hz, 1H), 8.00 (overlapping dd, J = 6.6 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.49 (s, 1H), 7.07 (dd, J = 8.3, 1.7 Hz, 1H), 6.44 (dd, J = 7.5, 2.6 Hz, 1H), 6.20 (d, J = 2.0 Hz, 1H), 5.56 (s, 2H), 4.76 (d, J = 14.2 Hz, 1H), 4.40 (d, J = 14.2 Hz, 1H), 3.91 (m, 1H), 3.74 (s, 3H), 3.61 (m, 1H), 3.29–3.17 (m overlapping with solvent, 2H), 3.13 (s, 3H)

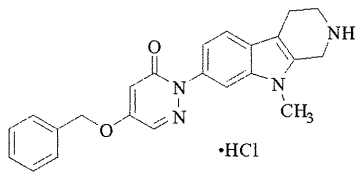
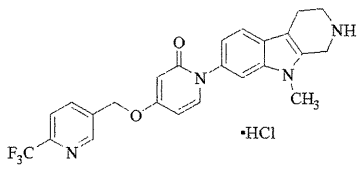
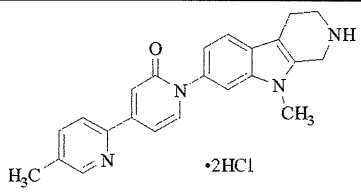
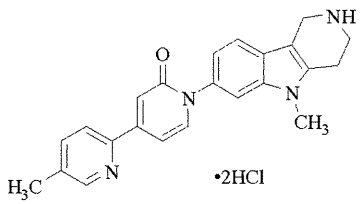
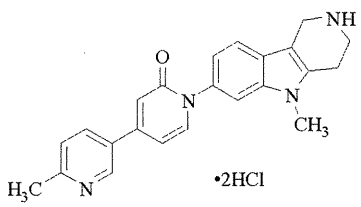
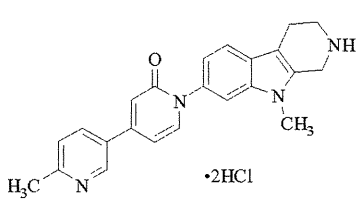
Ex, No.	Structure	Mass Spec	^{1}H NMR Data
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56		384	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.67 (s, 2H), 7.59–7.52 (m, 3H), 7.35–7.27 (m, 4H), 7.24–7.17 (m, 1H), 7.01 (dd, J = 7.4, 2.0 Hz, 1H), 6.38–6.27 (m, 2H), 4.45 (s, 2H), 3.67 (s, 3H), 3.42 (t, J = 6.4 Hz, 2H), 2.97–2.89 (m, 4H), 2.81–2.76 (m, 2H)
57		391	^{1}H NMR (500 MHz, CD_3OD) δ 8.74 (d, J = 2.4 Hz, 1H), 8.06 (d, J = 8.5 Hz, 1H), 8.02 (dd, J = 8.7, 2.4 Hz, 1H), 7.86 (d, J = 7.2 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 1.9 Hz, 1H), 7.37 (d, J = 1.5 Hz, 1H), 7.27 (dd, J = 8.5, 1.8 Hz, 1H), 7.15 (dd, J = 8.4, 1.8 Hz, 1H), 4.50 (s, 2H), 3.75 (s, 3H), 3.68 (t, J = 6.5 Hz, 2H), 3.22 (t, J = 6.5 Hz, 2H)
59		419	^{1}H NMR (500 MHz, CD_3OD) δ 8.65 (d, J = 2.6 Hz, 1H), 7.91 (overlapping ddd, J = 9.6, 2.1 Hz, 1H), 7.83–7.20 (m, 2H), 7.61 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 1.8 Hz, 1H), 7.09 (dd, J = 8.4, 1.8 Hz, 1H), 6.59 (dd, J = 7.5, 2.6 Hz, 1H), 6.36 (d, J = 2.6 Hz, 1H), 5.41 (s, 2H), 4.76 (d, J = 14.2 Hz, 1H), 4.39 (d, J = 14.2 Hz, 1H), 3.94–3.82 (m, 2H), 3.74 (s, 3H), 3.65–3.58 (m, 2H), 3.13 (s, 3H)
60		405	^{1}H NMR (500 MHz, CD_3OD) δ 8.72 (d, J = 1.7 Hz, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.99 (dd, J = 8.2, 2.2 Hz, 1H), 7.79 (d, J = 7.1 Hz, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 1.3 Hz, 1H), 7.34 (d, J = 1.5 Hz, 1H), 7.19 (dd, J = 7.2, 1.8 Hz, 1H), 7.14 (dd, J = 8.3, 1.8 Hz, 1H), 4.80–4.72 (br m, 1H), 4.46–4.34 (m, 1H), 3.96–3.86 (m, 1H), 3.75 (s, 3H), 3.65–3.55 (br m, 1H), 3.28 (s, 2H), 3.14 (s, 3H)
61		483	^{1}H NMR (300 MHz, D_2O) δ 7.50 (d, J = 8.3 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.42–7.31 (m, 6H), 6.96 (dd, J = 8.3, 1.6 Hz, 1H), 6.27 (dd, J = 7.7, 2.6 Hz, 1H), 6.10 (d, J = 2.6 Hz, 1H), 5.90 (s, 2H), 4.59 (br s, 2H), 3.81–3.59 (m, 8H), 3.55 (s, 3H), 3.20 (t, J = 5.7 Hz, 2H), 3.18–3.05 (br m, 2H), 2.15–1.90 (m, 4H)

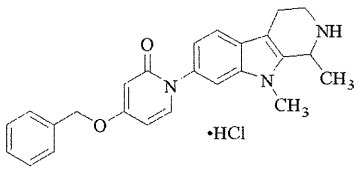
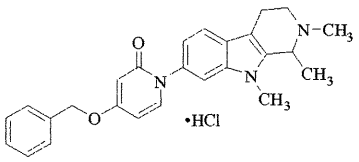
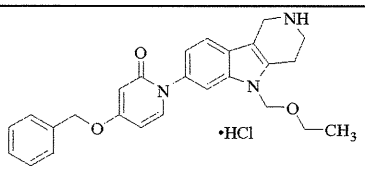
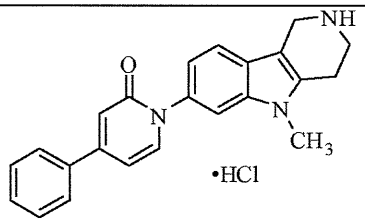
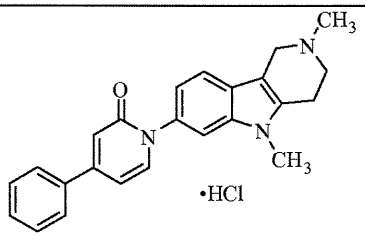
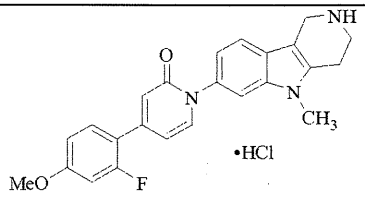
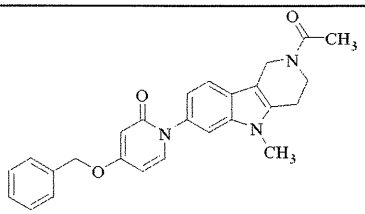
Ex, No.	Structure	Mass Spec	^{1}H NMR Data
62		439	^{1}H NMR (500 MHz, CD_3OD) δ 9.04 (s, 1H), 8.28 (dd, J = 8.7, 1.9 Hz, 1H), 8.21 (d, J = 2.1 Hz, 1H), 7.83 (d, J = 7.1 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 1.3 Hz, 1H), 7.39 (d, J = 1.6 Hz, 1H), 7.24 (dd, J = 7.1, 1.9 Hz, 1H), 7.15 (dd, J = 8.3, 1.7 Hz, 1H), 4.80–4.71 (br m, 1H), 4.44–4.35 (br m, 1H), 3.96–3.86 (br m, 1H), 3.75 (s, 3H), 3.67–3.57 (br m, 1H), 3.28 (s, 2H), 3.14 (s, 3H)
63		372	^{1}H NMR (500 MHz, CD_3OD) δ 8.47 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 7.4 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 1.6 Hz, 1H), 7.35 (d, J = 1.6 Hz, 1H), 7.25 (dd, J = 7.1, 1.9 Hz, 1H), 7.15 (dd, J = 8.3, 1.9 Hz, 1H), 4.49 (s, 2H), 3.75 (s, 3H), 3.68 (t, J = 6.2 Hz, 2H), 3.24 (t, J = 6.2 Hz, 2H), 2.85 (s, 3H)
64		386	^{1}H NMR (300 MHz, DMSO-d_6) δ 10.9 (s, 1H), 8.32 (d, J = 8.8 Hz, 1H), 7.85 (d, J = 7.2 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.64 (d, J = 1.5 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.25 (d, J = 1.7 Hz, 1H), 7.14–7.11 (m, 2H), 4.65 (d, J = 12.1 Hz, 1H), 4.31 (dd, J = 14.2, 7.5 Hz, 1H), 3.81–3.74 (m, 1H), 3.71 (s, 3H), 3.55–3.45 (m, 1H), 3.26–3.15 (m, 2H), 2.98 (s, 3H), 2.72 (s, 3H)
65		404	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.56 (br s, 2H), 7.64 (d, J = 7.1 Hz, 1H), 7.62–7.55 (m, 2H), 7.47 (dd, J = 8.4, 6.9 Hz, 1H), 7.12–7.06 (m, 2H), 6.90 (overlapping ddd, J = 8.4, 2.4 Hz, 1H), 6.55 (d, J = 1.6 Hz, 1H), 6.47 (dd, J = 7.1, 1.8 Hz, 1H), 4.37–4.30 (br m, 2H), 3.81 (s, 3H), 3.69 (s, 3H), 3.56–3.45 (br m, 2H), 3.10 (t, J = 5.5 Hz, 2H)
66		418	^{1}H NMR (300 MHz, DMSO-d_6) δ 10.83 (br s, 1H), 7.65 (d, J = 7.1 Hz, 1H), 7.61 (d, J = 1.4 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.46 (dd, J = 8.4, 6.9 Hz, 1H), 7.12–7.10 (m, 1H), 7.08 (d, J = 1.4 Hz, 1H), 6.91 (overlapping ddd, J = 8.4, 2.4 Hz, 1H), 6.55 (d, J = 1.6 Hz, 1H), 6.48 (dd, J = 7.1, 1.6 Hz, 1H), 4.62 (d, J = 12.2 Hz, 1H), 4.30 (dd, J = 14.2, 7.5 Hz, 1H), 3.86 (s, 3H), 3.80–3.76 (m, 1H), 3.75 (s, 3H), 3.52–3.42 (m, 1H), 3.24–3.15 (m, 2H), 2.79 (d, J = 4.6 Hz, 3H)
67		469	^{1}H NMR (500 MHz, D_2O) δ 7.56–7.53 (m, 2H), 7.48–7.40 (m, 6H), 7.02 (dd, J = 8.4, 1.4 Hz, 1H), 6.33 (dd, J = 7.5, 2.4 Hz, 1H), 6.17 (d, J = 2.4 Hz, 1H), 5.16 (s, 2H), 4.63 (br s, 2H), 4.09–3.79 (br m, 2H), 3.69–3.53 (m, 6H), 3.26–3.23 (m, 2H), 3.14 (t, J = 12.8 Hz, 2H), 2.49 (d, J = 1.3 Hz, 2H), 2.16–2.04 (m, 2H)

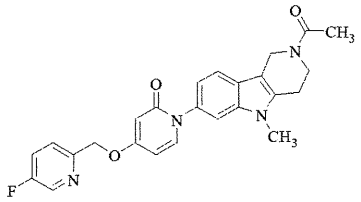
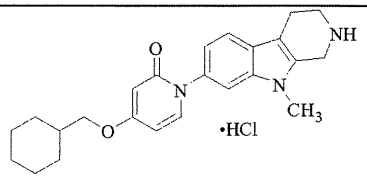
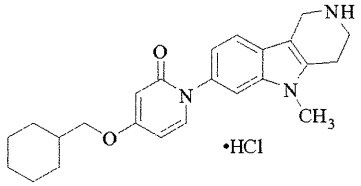
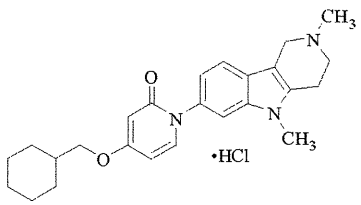
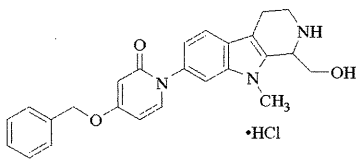
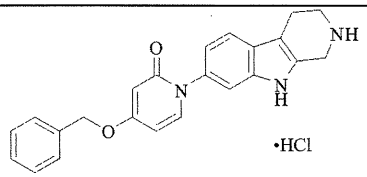
Ex, No.	Structure	Mass Spec	^{1}H NMR Data
68		483	^{1}H NMR (500 MHz, D_2O) δ 7.56–7.52 (m, 2H), 7.48–7.38 (m, 6H), 7.02 (dd, *J* = 8.3, 1.6 Hz, 1H), 6.33 (dd, *J* = 7.5, 2.6 Hz, 1H), 6.16 (d, *J* = 2.5 Hz, 1H), 5.16 (s, 2H), 4.63 (s, 2H), 3.85–3.83 (m, 2H), 3.74–3.71 (m, 2H), 3.62 (s, 3H), 3.26–3.14 (m, 5H), 2.89 (s, 3H), 2.55–2.50 (m, 2H), 2.19–2.12 (m, 2H)
69		425	^{1}H NMR (300 MHz, CD_3OD) δ 9.10 (d, *J* = 2.0 Hz, 1H), 8.41 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 1.6 Hz, 1H), 7.14 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.02 (d, *J* = 1.6 Hz, 1H), 6.89 (dd, *J* = 7.1, 2.0 Hz, 1H), 4.49 (s, 2H), 3.76 (s, 3H), 3.68 (t, *J* = 6.2 Hz, 2H), 3.22 (t, *J* = 6.2 Hz, 2H)
70		439	^{1}H NMR (500 MHz, CD_3OD) δ 9.09 (d, *J* = 1.7 Hz, 1H), 8.42 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 7.1 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.58 (d, *J* = 1.5 Hz, 1H), 7.15 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.02 (d, *J* = 1.8 Hz, 1H), 6.89 (dd, *J* = 7.1, 2.0 Hz, 1H), 4.79–4.37 (br m, 2H), 3.90–3.60 (br m, 5H), 3.30 (br m, 2H), 3.14 (s, 3H)
71		411	^{1}H NMR (500 MHz, CD_3OD) δ 9.04 (s, 1H), 8.28 (dd, *J* = 8.3, 2.2 Hz, 1H), 8.22 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 7.0 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.46 (d, *J* = 1.8 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 7.24 (dd, *J* = 7.1, 2.0 Hz, 1H), 7.11 (dd, *J* = 8.3, 2.0 Hz, 1H), 4.49 (s, 2H), 3.65 (t, *J* = 6.2 Hz, 2H), 3.21 (t, *J* = 6.2 Hz, 2H)
72		412	^{1}H NMR (300 MHz, CD_3OD) δ 8.52 (d, *J* = 8.9 Hz, 1H), 8.28 (d, *J* = 8.9 Hz, 1H), 7.89 (d, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.48 (d, *J* = 1.5 Hz, 1H), 7.43 (d, *J* = 1.5 Hz, 1H), 7.33 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.14 (dd, *J* = 7.4, 2.0 Hz, 1H), 4.49 (s, 2H), 3.65 (t, *J* = 6.2 Hz, 2H), 3.21 (t, *J* = 6.2 Hz, 2H)
73		426	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.51 (s, 2H), 9.37 (br s, 2H), 7.90 (d, *J* = 7.2 Hz, 1H), 7.62–7.60 (m, 2H), 7.13 (d, *J* = 1.9 Hz, 1H), 7.10 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.88 (dd, *J* = 7.1, 2.0 Hz, 1H), 4.38–4.34 (br m, 2H), 3.70 (s, 3H), 3.56–3.50 (br m, 2H), 3.11 (t, *J* = 5.8 Hz, 2H)

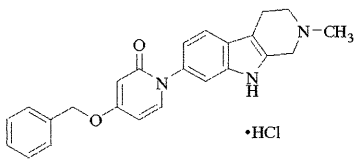
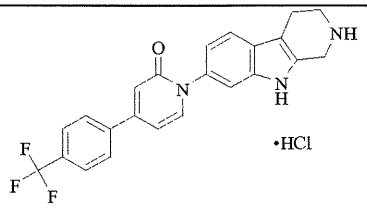
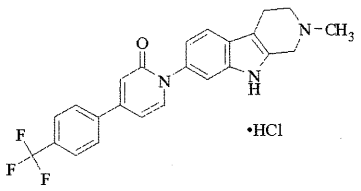
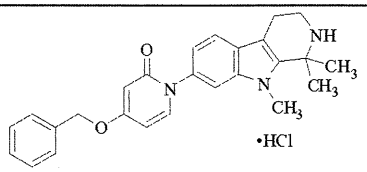
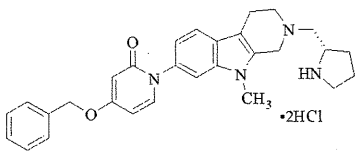
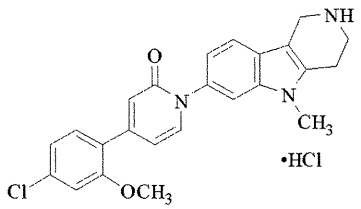
Ex. No.	Structure	Mass Spec	^{1}H NMR Data
74		426	^{1}H NMR (500 MHz, DMSO–d_6) δ 9.48 (s, 2H), 9.37 (br s, 2H), 7.89 (d, J = 7.2 Hz, 1H), 7.65 (d, J = 1.6 Hz, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.50 (d, J = 1.6 Hz, 1H), 7.21 (dd, J = 7.6, 1.9 Hz, 1H), 7.12 (dd, J = 8.3, 1.8 Hz, 1H), 4.41–4.31 (br m, 2H), 3.71 (s, 3H), 3.51–3.48 (br m, 2H), 3.10 (t, J = 5.6 Hz, 2H)
75		455	^{1}H NMR (500 MHz, DMSO–d_6) δ 9.54 (br s, 2H), 8.89 (s, 1H), 8.19 (dd, J = 7.9, 1.4 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.50 (d, J = 1.7 Hz, 1H), 6.98 (dd, J = 8.3, 1.8 Hz, 1H), 6.15 (dd, J = 7.5, 2.7 Hz, 1H), 6.02 (d, J = 2.7 Hz, 1H), 5.35 (s, 2H), 4.35–4.30 (br m, 2H), 3.67 (s, 3H), 3.53–3.47 (br m, 2H), 3.09 (t, J = 5.8 Hz, 2H)
76		455	^{1}H NMR (300 MHz, CD_3OD) δ 8.93 (s, 1H), 8.23 (dd, J = 8.2, 2.1 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 1.7 Hz, 1H), 7.06 (dd, J = 8.3, 1.8 Hz, 1H), 6.47 (dd, J = 7.5, 2.7 Hz, 1H), 6.20 (d, J = 2.6 Hz, 1H), 5.42 (s, 2H), 4.48 (s, 2H), 3.73 (s, 3H), 3.67 (t, J = 6.1 Hz, 2H), 3.20 (t, J = 6.1 Hz, 2H)
77		387	^{1}H NMR (500 MHz, DMSO–d_6) δ 9.23 (s, 2H), 7.96 (d, J = 2.8 Hz, 1H), 7.59 (d, J = 1.6 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.51–7.48 (m, 2H), 7.46–7.42 (m, 2H), 7.40 (d, J = 7.5 Hz, 1H), 7.13 (dd, J = 8.4, 1.7 Hz, 1H), 6.51 (d, J = 2.8 Hz, 1H), 5.22 (s, 2H), 4.34 (s, 2H), 3.69 (s, 3H), 3.52 (t, J = 5.8 Hz, 2H), 3.09 (t, J = 5.8 Hz, 2H)
78		425	^{1}H NMR (300 MHz, DMSO–d_6) δ 9.37 (s, 2H), 8.56 (d, J = 2.2 Hz, 1H), 8.13 (d, J = Hz, 2H), 7.93 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 1.6 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.4, 1.8 Hz, 1H), 4.36 (s, 2H), 3.70 (s, 3H), 3.58–3.48 (br m, 2H), 3.11 (t, J = 5.7 Hz, 2H)
79		391	^{1}H NMR (500 MHz, CD_3OD) δ 8.73 (dd, J = 2.4, 0.6 Hz, 1H), 8.03 (dd, J = 8.5, 0.5 Hz, 1H), 8.00 (dd, J = 8.5, 2.4 Hz, 1H), 7.80 (d, J = 7.1 Hz, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 1.7 Hz, 1H), 7.31 (d, J = 1.7 Hz, 1H), 7.19 (dd, J = 7.1, 2.0 Hz, 1H), 7.14 (dd, J = 8.4, 1.8 Hz, 1H), 4.56 (s, 2H), 3.74 (s, 3H), 3.61 (t, J = 6.1 Hz, 2H), 3.14 (t, J = 6.1 Hz, 2H)

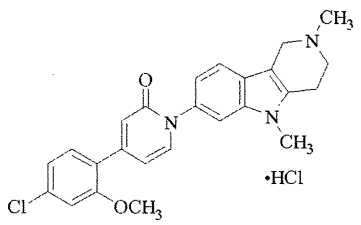
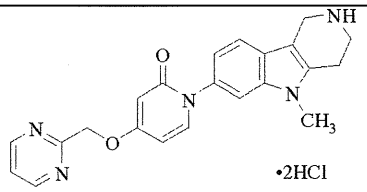
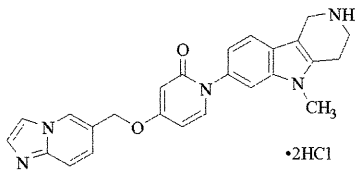
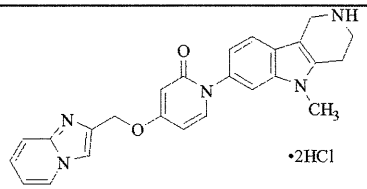
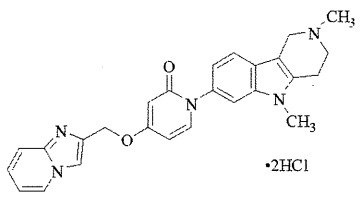
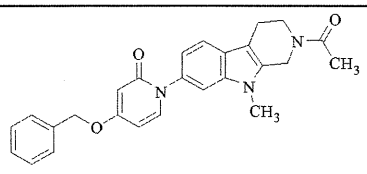
Ex, No.	Structure	Mass Spec	^{1}H NMR Data
80		405	^{1}H NMR (500 MHz, CD_3OD) δ 8.73 (d, J = 2.3 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H) 7.99 (dd, J = 8.5, 2.3 Hz, 1H), 7.79 (d, J = 7.2 Hz, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.57 (s, 1H), 7.31 (d, J = 1.6 Hz, 1H), 7.19 (dd, J = 7.1, 1.8 Hz, 1H), 7.15 (dd, J = 8.3, 1.7 Hz, 1H), 4.65 (br s, 2H), 3.74 (m, 5H), 3.21 (t, J = 5.7 Hz, 2H), 3.17 (s, 3H)
81		425	^{1}H NMR (500 MHz, CD_3OD) δ 9.05 (s, 1H), 8.28 (dd, J = 8.3, 2.2 Hz, 1H), 8.22 (d, J = 8.3, Hz, 1H), 7.84 (d, J = 7.1 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 1.8 Hz, 1H), 7.40 (d, J = 1.8 Hz, 1H), 7.25 (dd, J = 7.2, 2.0 Hz, 1H), 7.15 (dd, J = 8.4, 1.8 Hz, 1H), 4.57 (s, 2H), 3.74 (s, 3H), 3.62 (t, J = 6.1 Hz, 2H), 3.15 (t, J = 5.9 Hz, 2H)
82		439	^{1}H NMR (500 MHz, CD_3OD) δ 9.05 (s, 1H), 8.28 (dd, J = 8.3, 2.1 Hz, 1H) 8.22 (d, J = 8.4, Hz, 1H), 7.84 (d, J = 7.1 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.59 (d, J = 1.6, 1H), 7.40 (d, J = 1.7 Hz, 1H), 7.25 (dd, J = 7.2, 1.9 Hz, 1H), 7.16 (dd, J = 8.3, 1.8 Hz, 1H), 4.87 (s, 1H), 4.51 (s, 1H), 3.87 (s, 1H), 3.75 (br s, 3H), 3.55 (br s, 1H), 3.21–3.17 (m, 5H)
84		405	^{1}H NMR (500 MHz, CD_3OD) δ 8.51 (s, 1H), 7.72–7.59 (m, 4H), 7.46 (d, J = 1.0 Hz, 1H), 7.05 (dd, J = 8.3, 1.5 Hz, 1H), 6.32 (dd, J = 7.6, 2.6 Hz, 1H), 7.05 (d, J = 2.6 Hz, 1H), 5.26 (s, 2H), 4.54 (s, 2H), 3.71 (s, 3H), 3.60 (t, J = 6.0 Hz, 2H), 3.12 (t, J = 5.8 Hz, 2H)
85		419	^{1}H NMR (500 MHz, CD_3OD) δ 8.51 (d, J = 2.6 Hz, 1H), 7.72–7.59 (m, 4H), 7.47 (s, 1H), 7.06 (dd, J = 8.3, 1.7 Hz, 1H), 6.32 (dd, J = 7.6, 2.6 Hz, 1H), 6.13 (d, J = 2.6 Hz, 1H), 5.26 (s, 2H), 4.68 (m, 2H), 3.71 (m, 5H), 3.18 (t, J = 5.9 Hz, 2H), 3.15 (s, 3H)
86		425	^{1}H NMR (500 MHz, CD_3OD) δ 9.10 (d, J = 1.9 Hz, 1H), 8.41 (dd, J = 8.2, 2.2 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H), 7.85 (d, J = 7.0 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.57 (d, J = 1.7 Hz, 1H), 7.15 (dd, J = 8.3, 1.8 Hz, 1H), 7.03 (d, J = 1.8 Hz, 1H), 6.89 (dd, J = 7.1, 2.0 Hz, 1H), 4.57 (br m, 2H), 3.75 (s, 3H), 3.62 (br m, 2H), 3.15 (br m, 2H)
87		411	^{1}H NMR (500 MHz, CD_3OD) δ 9.05 (s, 1H), 8.28 (dd, J = 8.4, 2.1 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 7.2 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 7.1 Hz, 1H), 7.39 (d, J = 1.7 Hz, 1H), 7.24 (dd, J = 7.2, 1.9 Hz, 1H), 7.13 (dd, J = 8.4, 1.8 Hz, 1H), 4.50 (s, 2H), 3.63 (t, J = 6.1 Hz, 2H), 3.14 (t, J = 6.1 Hz, 2H)

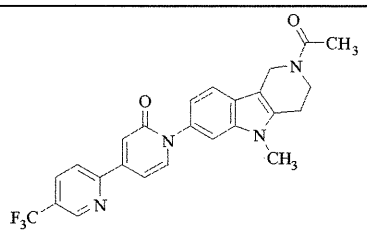
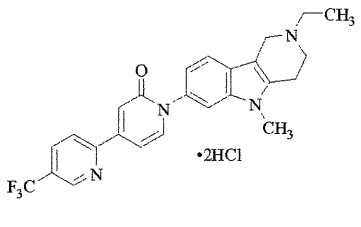
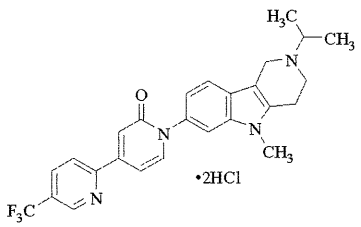
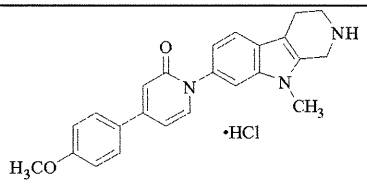
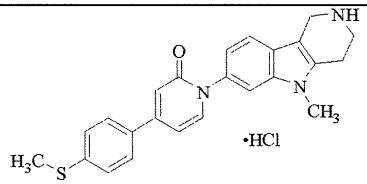
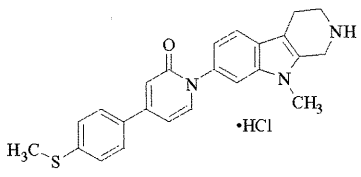
Ex, No.	Structure	Mass Spec	^{1}H NMR Data
88		387	^{1}H NMR (500 MHz, CD_3OD) δ 7.93 (d, J = 2.7 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 1.5 Hz, 1H), 7.50–7.48 (m, 2H), 7.43 (overlapping dd, J = 7.8 Hz, 2H), 7.39 (d, J = 1.7 Hz, 1H), 7.18 (dd, J = 8.4, 1.7 Hz, 1H), 6.48 (d, J = 2.7 Hz, 1H), 5.22 (s, 2H), 4.54 (s, 2H), 3.71 (s, 3H), 3.59 (t, J = 5.6 Hz, 2H), 3.12 (t, J = 5.9 Hz, 2H)
89		455	^{1}H NMR (500 MHz, CD_3OD) δ 8.75 (s, 1H), 8.08 (d, J = 7.9 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.53 (dd, J = 7.9, 2.0 Hz, 2H), 7.38 (d, J = 1.7 Hz, 1H), 6.97 (dd, J = 8.4, 1.8 Hz, 1H), 6.25 (dd, J = 7.6, 2.7 Hz, 1H), 6.08 (d, J = 2.6 Hz, 1H), 5.26 (s, 2H), 4.46 (s, 2H), 3.63 (s, 3H), 3.51 (t, J = 6.1 Hz, 2H), 3.03 (t, J = 6.1 Hz, 2H)
90		371	^{1}H NMR (500 MHz, CD_3OD) δ 8.59 (s, 1H), 7.95 (d, J = 8.1Hz, 1H), 7.87 (d, J = 6.5 Hz, 1H), 7.80 (d, J = 7.0 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 1.4 Hz, 1H), 7.24 (d, J = 1.6 Hz, 1H), 7.15–7.12 (m, 2H), 4.57 (s, 2H), 3.74 (s, 3H), 3.61 (t, J = 6.0 Hz, 2H), 3.14 (t, J = 6.1 Hz, 2H), 2.46 (s, 3H)
91		371	^{1}H NMR (500 MHz, CD_3OD) δ 8.76 (d, J = 1.8 Hz, 1H), 8.34 (d, J = 6.9 Hz, 1H), 8.24 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 7.2 Hz, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.61 (d, J = 1.7 Hz, 1H), 7.23 (d, J = 1.8 Hz, 1H), 7.17 (dd, J = 8.3, 1.8 Hz, 1H), 7.04 (dd, J = 7.1, 2.1 Hz, 1H), 4.53 (s, 2H), 3.79 (s, 3H), 3.71 (t, J = 6.2 Hz, 2H), 3.25 (t, J = 6.2 Hz, 2H), 2.61 (s, 3H)
92		371	^{1}H NMR (500 MHz, CD_3OD) δ 8.80 (d, J = 2.2 Hz, 1H), 8.12 (dd, J = 8.1, 2.5 Hz, 1H), 7.79 (d, J = 7.0 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 1.7 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.10 (dd, J = 8.3, 1.9 Hz, 1H), 6.93 (d, J = 1.8 Hz, 1H), 6.85 (dd, J = 7.1, 2.0 Hz, 1H), 4.34 (s, 2H), 3.73 (s, 3H), 3.52 (t, J = 6.1 Hz, 2H), 3.10 (t, J = 6.1 Hz, 2H), 2.62 (s, 3H)
93		371	^{1}H NMR (500 MHz, CD_3OD) δ 8.80 (d, J = 8.1Hz, 1H), 8.11 (dd, J = 8.2, 2.5 Hz, 1H), 7.79 (d, J = 7.0 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 1.7 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.11 (dd, J = 8.3, 1.8 Hz, 1H), 6.93 (d, J = 1.9 Hz, 1H), 6.85 (dd, J = 7.1, 2.0 Hz, 1H), 4.40 (s, 2H), 3.71 (s, 3H), 3.46 (t, J = 5.9 Hz, 2H), 3.04 (t, J = 5.9 Hz, 2H), 2.62 (s, 3H)

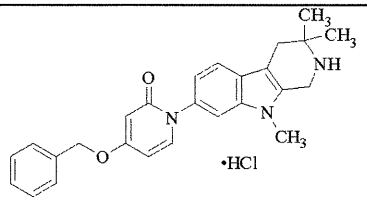
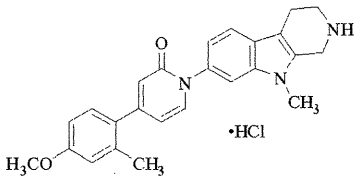
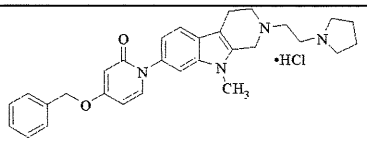
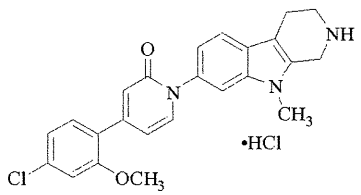
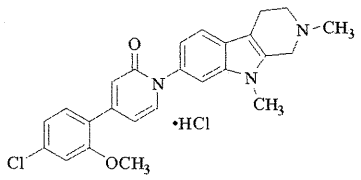
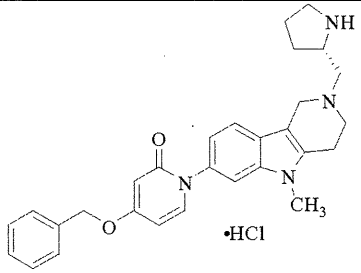
Ex, No.	Structure	Mass Spec	^{1}H NMR Data
94		400	^{1}H NMR (500 MHz, CD_3OD) δ 7.79 (d, J = 7.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.53 (s, 1H), 7.48–7.36 (m, 5H), 7.10 (d, J = 8.5 Hz, 1H), 6.55 (d, J = 6.5 Hz, 1H), 6.33 (s, 1H), 5.27 (s, 2H), 4.98 (q, J = 6.5 Hz, 1H), 3.76 (s, 3H), 3.67–3.59 (m, 2H), 3.13–3.08 (m, 2H), 1.76 (d, J = 7.0 Hz, 3H)
95		414	^{1}H NMR (500 MHz, CD_3OD) δ 7.58–7.55 (m, 2H), 7.47–7.34 (m, 6H), 6.99 (d, J = 8.5, 1.0 Hz, 1H), 6.28 (dd, J = 7.5, 2.5 Hz, 1H), 6.11 (d, J = 2.5 Hz, 1H), 5.18 (s, 2H), 4.27 (q, J = 6.5 Hz, 1H), 3.69 (s, 3H), 3.36–3.33 (m, 1H), 3.10–2.96 (m, 2H), 2.84–2.80 (m, 1H), 2.65 (s, 3H), 1.51 (d, J = 6.5 Hz, 3H)
96		430	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.12 (s, 2H), 7.66 (d, J = 2.0 Hz, 1H), 7.59–7.56 (m, 2H), 7.49–7.37 (m, 5H), 7.08–7.05 (m, 1H), 6.14–6.12 (m, 1H), 5.99 (d, J = 2.5 Hz, 1H), 5.57 (s, 2H), 5.17 (s, 2H), 4.38 (m, 2H), 3.55 (m, 2H), 3.45–3.40 (m, 2H), 3.13 (m, 2H), 1.08–1.05 (m, 3H)
97		356	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.26 (s, 2H), 7.79 (dd, J = 8.0, 1.5 Hz, 2H), 7.75 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 1.5 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.55–7.50 (m, 3H), 7.10 (dd, J = 8.5, 2.0 Hz, 1H), 6.78 (d, J = 1.5 Hz, 1H), 6.70 (dd, J = 7.0, 2.0 Hz, 1H), 4.37 (m, 2H), 3.71 (s, 3H), 3.54–3.53 (m, 2H), 3.10 (t, J = 6.0 Hz, 2H)
98		370	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.46 (s, 1H), 7.80–7.74 (m, 3H), 7.63 (s, 1H), 7.56–7.52 (m, 4H), 7.11 (d, J = 8.0 Hz, 1H), 6.78 (s, 1H), 6.70 (d, J = 7.0 Hz, 1H), 4.68–4.65 (m, 1H), 4.34–4.30 (m, 1H), 3.82–3.79 (m, 1H), 3.71 (s, 3H), 3.53–3.51 (m, 1H), 3.20 (m, 2H), 3.00 (d, J = 4.0 Hz, 3H)
99		404	^{1}H NMR (500 MHz, CD_3OD) δ 7.72 (d, J = 7.0 Hz, 1H), 7.63–7.56 (m, 3H), 7.14 (dd, J = 8.5, 1.5 Hz, 1H), 6.92 (dd, J = 8.5, 2.5 Hz, 1H), 6.87 (dd, J = 13.0, 2.5 Hz, 1H), 6.84 (s, 1H), 6.77–6.75 (m, 1H), 4.50 (s, 2H), 3.88 (s, 3H), 3.76 (s, 3H), 3.68 (t, J = 6.0 Hz, 2H), 3.22 (t, J = 6.0 Hz, 2H)
100		428	^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.36 (m, 6H), 7.32–7.30 (m, 2H), 7.06–7.00 (m, 1H), 6.09 (d, J = 3.0 Hz, 1H), 6.07–6.04 (m, 1H), 5.06 (s, 2H), 4.82 (s, 1H), 4.67 (s, 1H), 4.03 (t, J = 5.5 Hz, 1H), 3.84 (t, J = 5.5 Hz, 1H), 3.64 (s, 3H), 2.90 (t, J = 5.5 Hz, 1H), 2.84 (t, J = 5.5 Hz, 1H), 2.24, 2.22 (2 × s, 3H)

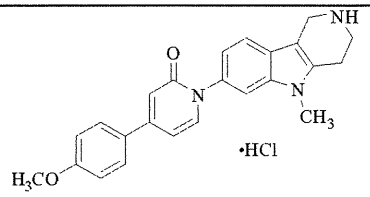
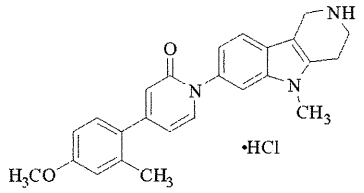
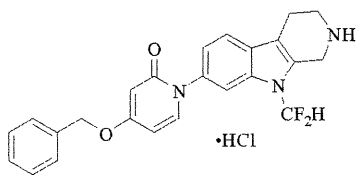
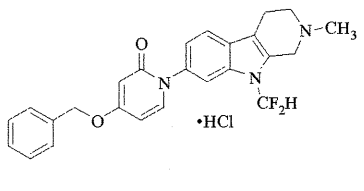
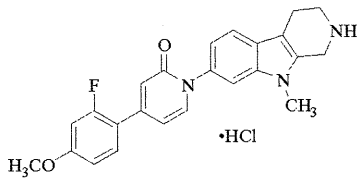
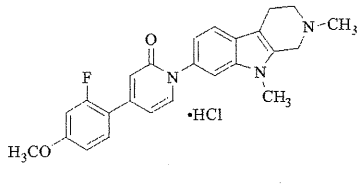
Ex. No.	Structure	Mass Spec	^{1}H NMR Data
101		447	^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, J = 1.5 Hz, 1H), 7.54–7.46 (m, 3H), 7.35 (d, J = 7.5 Hz, 1H), 7.32 (d, J = 2.0 Hz, 1H), 7.03 (ddd, J = 20, 8.0, 1.5 Hz, 1H), 6.15–6.08 (m, 2H), 5.18 (s, 2H), 4.83, 4.70 (2 × s, 2H), 4.04 (t, J = 5.5 Hz, 1H), 3.85 (t, J = 5.5 Hz, 1H), 3.65, 3.64 (2 × s, 3H), 2.91 (t, J = 5.5 Hz, 1H), 2.85 (t, J = 5.5 Hz, 1H), 2.23, 2.25 (2 × s, 3H)
102		392	^{1}H NMR (500 MHz, CD_3OD) δ 7.67–7.65 (m, 2H), 7.50 (s, 1H), 7.09 (d, J = 8.5 Hz, 1H), 6.35 (d, J = 6.0 Hz, 1H), 6.10 (s, 1H), 4.58 (s, 2H), 3.92 (d, J = 5.5 Hz, 2H), 3.75 (s, 3H), 3.63 (t, J = 6.0 Hz, 2H), 3.15 (d, J = 6.0 Hz, 2H), 1.92–1.74 (m, 6H), 1.39–1.19 (m, 5H)
103		392	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (s, 2H), 7.55 (d, J = 8.5 Hz, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.50 (s, 1H), 6.99 (dd, J = 8.5, 1.5 Hz, 1H), 6.04 (dd, J = 7.5, 2.5 Hz, 1H), 5.85 (d, J = 2.5 Hz, 1H), 4.35 (s, 2H), 3.82 (d, J = 6.0 Hz, 2H), 3.68 (s, 3H), 3.54–3.53 (m, 2H), 3.09 (t, J = 5.5 Hz, 2H), 1.80–1.65 (m, 6H), 1.30–1.01 (m, 5H)
104		406	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.53 (s, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 1.5 Hz, 1H), 7.00 (dd, J = 8.5, 1.5 Hz, 1H), 6.04 (dd, J = 7.5, 2.5 Hz, 1H), 5.85 (d, J = 3.0 Hz, 1H), 4.64 (d, J = 13 Hz, 1H), 4.30 (dd, J = 14, 7.5 Hz, 1H), 3.82 (d, J = 6.0 Hz, 2H), 3.80–3.78 (m, 1H), 3.69 (s, 3H), 3.51–3.47 (m, 1H), 3.18 (t, J = 5.5 Hz, 2H), 2.98 (d, J = 4.5 Hz, 3H), 1.80–1.65 (m, 6H), 1.30–1.01 (m, 5H)
105		416	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.48 (br s, 1H), 9.10 (br s, 1H), 7.56 (overlapping dd, J = 8.5 Hz, 2H), 7.52 (s, 1H), 7.49–7.41 (m, 4H), 7.40–7.36 (m, 1H), 7.01 (dd, J = 7.0, 1.5 Hz, 1H), 6.12 (dd, J = 7.5, 1.5 Hz, 1H), 5.98 (d, J = 1.5 Hz, 1H), 5.72 (t, J = 3.3 Hz, 1H), 5.16 (s, 2H), 4.89–4.82 (m, 1H), 4.07–4.01 (m, 1H), 3.80–3.71 (m, 1H), 3.72 (s, 3H), 3.61–3.50 (m, 1H), 3.49–3.43 (m, 1H), 3.02–2.94 (m, 2H)
106		372	^{1}H NMR (500 MHz, DMSO-d_6) δ 11.22 (s, 1H), 9.29 (br s, 2H), 7.54 (dd, J = 12.0, 8.0 Hz, 2H), 7.50–7.41 (m, 4H), 7.40–7.33 (m, 2H), 6.96 (dd, J = 8.0, 1.5 Hz, 1H), 6.09 (dd, J = 7.5, 2.5 Hz, 1H), 5.97 (d, J = 2.5 Hz, 1H), 5.15 (s, 2H), 4.38 (s, 2H), 3.50–3.42 (m, 2H) 3.00–2.92 (m, 2H)

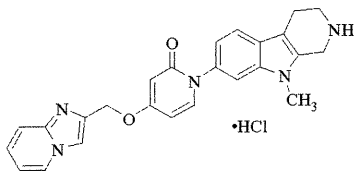
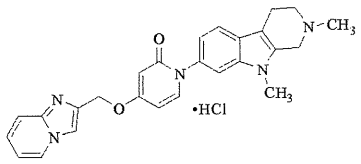
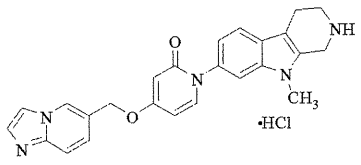
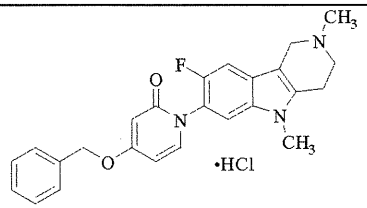
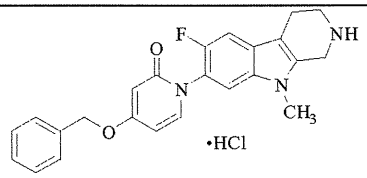
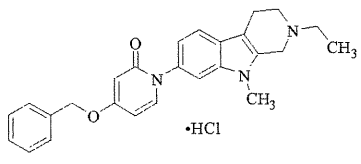
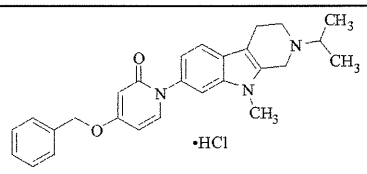
Ex. No.	Structure	Mass Spec	^{1}H NMR Data
107		386	^{1}H NMR (500 MHz, DMSO-d_6) δ 11.30 (s, 1H), 10.50–10.41 (m, 1H), 7.58–7.52 (m, 2H), 7.49–7.40 (m, 4H), 7.39–7.35 (m, 2H), 6.96 (br d, J = 8.0 Hz, 1H), 6.09 (br d, J = 7.5 Hz, 1H), 5.97 (br s, 1H), 5.15 (s, 2H), 4.60 (br d, J = 15.0 Hz, 1H), 4.41 (dd, J = 15.0, 7.5 Hz, 1H), 3.78–3.71 (m, 1H), 3.45–3.38 (m, 1H), 3.09–2.98 (m, 5H)
108		410	^{1}H NMR (500 MHz, DMSO-d_6) δ 11.28 (s, 1H), 9.21 (br s, 2H), 8.01 (d J = 8.3 Hz, 2H), 7.88 (d, J = 8.3 Hz, 2H), 7.80 (d, J = 7.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 1.5 Hz, 1H), 7.07 (dd, J = 8.0, 1.5 Hz, 1H), 6.87 (d, J = 2.0 Hz, 1H), 6.72 (dd, J = 7.0, 2.0 Hz, 1H), 4.40 (s, 2H), 3.52–3.48 (m, 2H), 2.99 (t, J = 6.0 Hz, 2H)
109		424	^{1}H NMR (500 MHz, DMSO-d_6) δ 11.36 (s, 1H), 10.35 (br s, 1H), 8.02 (d, J = 8.3 Hz, 2H), 7.88 (d, J = 8.3 Hz, 2H), 7.80 (d, J = 7.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.49 (br s, 1H), 7.07 (dd, J = 8.0, 1.5 Hz, 1H), 6.87 (d, J = 1.5 Hz, 1H), 6.72 (d, J = 7.0, 1.5 Hz, 1H), 4.62 (br d, J = 16.0 Hz, 1H), 4.49–4.40 (m, 1H), 3.81–3.73 (m, 1H), 3.49–3.39 (m, 1H), 3.12–3.00 (m, 5H)
110		414	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.59 (s, 2H), 7.58–7.51 (m, 3H), 7.49–7.41 (m, 4H), 7.40–7.35 (m, 1H), 7.01 (dd, J = 8.5, 1.5 Hz, 1H), 6.10 (dd, J = 7.5, 2.8 Hz, 1H), 5.97 (d, J = 2.8 Hz, 1H), 5.16 (s, 2H), 3.80 (s, 3H), 3.52–3.48 (m, 2H), 2.99 (t, J = 6.0 Hz, 2H), 1.81 (s, 6H)
111		469	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.25 (br s, 1H), 7.56 (d, J = 7.5 Hz, 1H), 7.54–7.40 (m, 6H), 7.39–7.34 (m, 1H), 7.04–6.93 (m, 1H), 6.11 (dd, J = 7.5, 2.5 Hz, 1H), 5.97 (d, J = 2.5 Hz, 1H), 5.16 (s, 2H), 3.98–3.45 (m, 11H), 3.39 (s, 1H), 3.30–3.21 (m, 2H), 2.25–2.10 (m, 1H), 2.05–1.74 (m, 2H), 1.73–1.60 (m, 1H)
112		420	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.17 (br s, 2H), 7.65 (d, J = 7.0 Hz, 1H), 7.62 (d, J = 1.8 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 1.8 Hz, 1H), 7.14 (dd, J = 8.0, 1.8 Hz, 1H), 7.09 (dd, J = 8.5, 1.8 Hz, 1H), 6.57 (d, J = 2.0 Hz, 1H), 6.47 (dd, J = 7.0, 2.0 Hz, 1H), 4.37 (br s, 2H), 3.87 (s, 3H), 3.70 (s, 3H), 3.57–3.52 (m, 2H), 3.10 (t, J = 6.0 Hz, 2H)

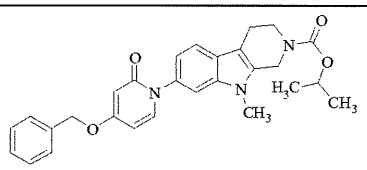
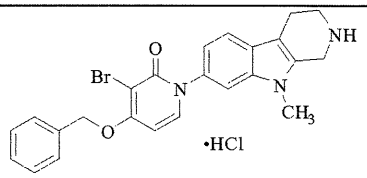
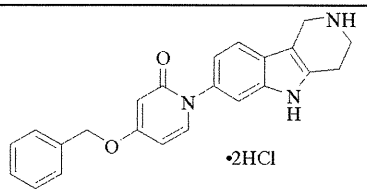
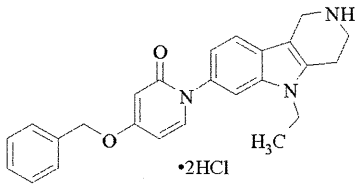
Ex. No.	Structure	Mass Spec	^{1}H NMR Data
113		434	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.15 (br s, 1H), 7.66 (d, J = 7.0 Hz, 1H), 7.63 (d, J = 1.5 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 1.8 Hz, 1H), 7.14 (dd, J = 8.5, 1.5 Hz, 1H), 7.11 (dd, J = 8.0, 1.8 Hz, 1H), 6.57 (d, J = 2.0 Hz, 1H), 6.47 (dd, J = 7.0, 2.0 Hz, 1H), 4.67 (d, J = 13.5 Hz, 1H), 4.33 (dd, J = 14.3, 6.0 Hz, 1H), 3.87 (s, 3H), 3.86–3.79 (m, 1H), 3.71 (s, 3H), 3.55–3.47 (m, 1H), 3.24–3.15 (m, 2H), 3.01 (s, 3H)
114		388	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.10 (br s, 2H), 8.88 (d, J = 5.0 Hz, 2H), 7.58–7.52 (m, 4H), 6.99 (dd, J = 8.0, 1.8 Hz, 1H), 6.14 (dd, J = 7.5, 2.5 Hz, 1H), 5.86 (d, J = 2.5 Hz, 1H), 5.33 (s, 2H), 4.36 (br s, 2H), 3.68 (s, 3H), 3.57–3.52 (m, 2H), 3.11–3.05 (m, 2H)
115		426	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.28 (br s, 2H), 9.06 (s, 1H), 8.38 (s, 1H), 8.19 (s, 1H), 8.05–7.94 (m, 2H), 7.62 (d, J = 7.5 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 1.5 Hz, 1H), 6.99 (dd, J = 8.0, 1.5 Hz, 1H), 6.13 (dd, J = 7.5, 2.5 Hz, 1H), 6.09 (d, J = 2.5 Hz, 1H), 5.33 (s, 2H), 4.35 (br s, 2H), 3.69 (s, 3H), 3.56–3.50 (m, 2H), 3.12–3.05 (m, 2H)
116		426	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.30 (br s, 2H), 8.84 (s, 1H), 8.37 (s, 1H), 7.89–7.70 (m, 2H), 7.64–7.53 (m, 2H), 7.50 (s, 1H), 7.37–7.29 (m, 1H), 7.03–6.97 (m, 1H), 6.20–6.09 (m, 2H), 5.41 (s, 2H), 4.35 (br s, 2H), 3.69 (s, 3H), 3.58–3.50 (m, 2H), 3.13–3.07 (m, 2H)
117		440	^{1}H NMR (500 MHz, DMSO-d_6) 10.79 (br s, 1H), 8.87 (d, J = 6.5 Hz, 1H), 8.41 (s, 1H), 7.90–7.78 (m, 2H), 7.61 (d, J = 7.5 Hz, 1H), 7.53–7.49 (m, 2H), 7.42–7.35 (m, 1H), 7.00 (dd, J = 8.5, 1.5 Hz, 1H), 6.15 (d, J = 2.5Hz, 1H), 6.12 (dd, J = 7.5, 2.5 Hz, 1H), 5.43 (s, 2H), 4.62 (d, J = 14.0 Hz, 1H), 4.29 (dd, J = 14.0, 7.5 Hz, 1H), 3.80–3.75 (m, 1H), 3.69 (s, 3H), 3.55–3.46 (m, 1H), 3.23–3.16 (m, 2H), 2.97 (s, 3H)
118		428	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.56 (d, J = 7.5 Hz, 1H), 7.52–7.35 (m, 7H), 6.94 (dd, J = 8.0, 1.5 Hz, 1H), 6.12–6.08 (m, 1H), 5.97 (d, J = 3.0 Hz, 1H), 5.15 (s, 2H), 4.77–4.72 (m, 2H), 3.82–3.72 (m, 2H), 3.69–3.65 (m, 3H), 3.82–2.78 (m, 1.3H), 2.71–2.68 (m, 0.7H), 2.16 (s, 3H)

Ex. No.	Structure	Mass Spec	^{1}H NMR Data
119		467	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.38 (d, J = 8.3 Hz, 1H), 8.35 (d, J = 8.3 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.59–7.54 (m, 2H), 7.28 (d, J = 1.5 Hz, 1H), 7.08–7.03 (m, 2H), 4.70 (s, 0.8H), 4.68 (s, 1.2H), 3.88 (t, J = 5.5 Hz, 0.8H), 3.83 (t, J = 5.5 Hz, 1.2 H), 3.67 (s, 3H), 2.97–2.91 (m, 1.2H), 2.86–2.81 (m, 0.8H), 2.15 (s, 1.8H), 2.13 (s, 1.2H)
120		453	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.16 (br s, 1H), 9.15 (s, 1H), 8.42–8.35 (m, 2H), 7.85 (d, J = 7.0 Hz, 1H), 7.65 (d, J = 1.5 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H), 7.13 (dd, J = 8.5, 1.5 Hz, 1H), 7.08 (dd, J = 7.5, 2.0 Hz, 1H), 4.70 (d, J = 12.5 Hz, 1H), 4.32 (dd, J = 14.5, 8.0 Hz, 1H), 3.91–3.83 (m, 1H), 3.72 (s, 3H), 3.52–3.43 (m, 1H), 3.41–3.30 (m, 2H), 3.24–3.16 (m, 2H), 1.38 (t, J = 7.3 Hz, 3H)
121		467	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.80 (br s, 1H), 9.15 (d, J = 2.0 Hz, 1H), 8.42–8.35 (m, 2H), 7.85 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 1.5 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H), 7.14 (dd, J = 8.5, 1.5 Hz, 1H), 7.08 (dd, J = 7.5, 2.0 Hz, 1H), 4.58 (d, J = 13.0 Hz, 1H), 4.48–4.40 (m, 1H), 3.90–3.82 (m, 1H), 3.78–3.70 (m, 4H), 3.51–3.42 (m, 1H), 3.38–3.15 (m, 2H), 1.45–1.36 (m, 6H)
122		386	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.43 (br s, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 7.0 Hz, 1H), 7.61–7.58 (m, 2H), 7.11–7.05 (m, 3H), 6.73 (d, J = 2.0 Hz, 1H), 6.68 (dd, J = 7.0, 2.0 Hz, 1H), 4.51–4.45 (m, 2H), 3.83 (s, 3H), 3.70 (s, 3H), 3.48–3.42 (m, 2H), 2.99 (t, J = 6.0 Hz, 2H)
123		402	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.27 (br s, 2H), 7.77–7.71 (m, 3H), 7.61–7.58 (m, 2H), 7.39 (d, J = 8.5 Hz, 2H), 7.09 (dd, J = 8.5, 2.0 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 6.69 (dd, J = 7.5, 2.0 Hz, 1H), 4.36 (br s, 2H), 3.70 (s, 3H), 3.56–3.51 (m, 2H), 3.10 (t, J = 5.5 Hz, 2H), 2.54 (s, 3H)
124		402	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.32 (br s, 2H), 7.75 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 7.3 Hz, 1H), 7.62–7.58 (m, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.10 (dd, J = 8.5, 2.0 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 6.69 (dd, J = 7.3, 2.0 Hz, 1H), 4.49 (br s, 2H), 3.70 (s, 3H), 3.60–3.32 (m, 2H), 2.99 (t, J = 5.5 Hz, 2H), 2.54 (s, 3H)

Ex. No.	Structure	Mass Spec	^{1}H NMR Data
125		414	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.34 (br s, 2H), 7.57 (d, J = 7.5 Hz, 1H), 7.53–7.50 (m, 2H), 7.49–7.41 (m, 4H), 7.40–7.35 (m, 1H), 6.99 (dd, J = 8.0, 2.0 Hz, 1H), 6.11 (dd, J = 8.0, 2.5 Hz, 1H), 5.98 (d, J = 2.5 Hz, 1H), 5.16 (s, 2H), 4.50 (br s, 2H), 3.70 (s, 3H), 2.89 (s, 2H), 1.42 (s, 6H)
126		400	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.44 (br s, 2H), 7.67 (d, J = 7.0 Hz, 1H), 7.63 (d, J = 1.5 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.11 (dd, J = 8.5, 1.5 Hz, 1H), 6.92 (d, J = 2.5 Hz, 1H), 6.88 (dd, J = 8.5, 2.5 Hz, 1H), 6.37 (s, 1H), 6.34 (dd, J = 7.5, 1.5 Hz, 1H), 4.89 (br s, 2H), 3.79 (s, 3H), 3.70 (s, 3H), 3.49–3.43 (m, 2H), 2.99 (t, J = 6.0 Hz, 2H), 2.36 (s, 3H)
127		483	^{1}H NMR (500 MHz, CD_3OD) δ 7.62–7.57 (m, 2H), 7.47–7.34 (m, 6H), 7.03 (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), 4.55–4.43 (m, 2H), 3.72 (s, 3H), 3.38–3.14 (m, 12H), 2.14 (m, 4H)
128		420	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.43 (br s, 2H), 7.65 (d, J = 7.0 Hz, 1H), 7.61 (d, J =1.5 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 2.0 Hz, 1H), 7.13 (dd, J = 8.5, 2.0 Hz, 1H), 7.09 (dd, J = 8.0, 2.0 Hz, 1H), 6.56 (d, J = 2.0 Hz, 1H), 6.47 (dd, J = 7.0, 1.5 Hz, 1H), 4.49–4.47 (m, 2H), 3.87 (m, 3H), 3.69 (s, 3H), 3.47–3.43 (m, 2H), 3.00–2.97 (m, 2H)
129		434	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.82 (br s, 1H), 7.65 (d, J = 7.0 Hz, 1H), 7.62 (d, J = 1.5 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 1.5 Hz, 1H), 7.14–7.09 (m, 2H), 6.56 (d, J = 1.5 Hz, 1H), 6.47 (dd, J = 7.0, 1.5 Hz, 1H), 4.79–4.76 (m, 1H), 4.53–4.42 (m, 1H), 3.87 (s, 3H), 3.72–3.68 (m, 4H), 3.42–3.40 (m, 1H), 3.08–3.06 (m, 2H), 3.00 (s, 3H)
130		469	^{1}H NMR (500 MHz, CD_3OD) δ 7.59–7.56 (m, 2H), 7.47–7.45 (m, 3H), 7.42–7.39 (m, 2H), 7.37–7.34 (m, 1H), 7.06 (dd, J = 8.5, 2.0 Hz, 1H), 6.29 (dd, J = 7.5, 2.5 Hz, 1H), 6.12 (d, J = 3.0 Hz, 1H), 5.18 (s, 2H), 4.70–4.49 (br m, 2H), 4.28–4.26 (m, 1H), 3.75–3.73 (m, 7H), 3.46–3.43 (m, 2H), 3.34–3.33 (m, 2H), 2.46–2.43 (m, 1H), 2.21–2.08 (m, 2H), 1.91–1.86 (m, 1H)

Ex, No.	Structure	Mass Spec	^{1}H NMR Data
131		386	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.26 (br s, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 7.0 Hz, 1H), 7.60–7.57 (m, 2H), 7.09–7.06 (m, 3H), 6.73 (d, J = 2.0 Hz, 1H), 6.68 (dd, J = 7.5, 2.0 Hz, 1H), 4.37–4.35 (m, 2H), 3.83 (s, 3H), 3.70 (s, 3H), 3.54–3.53 (m, 2H), 3.10 (t, J = 6.0 Hz, 2H)
132		400	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.39 (br s, 2H), 7.67 (d, J = 7.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 2.0 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.10 (dd, J = 8.5, 2.0 Hz, 1H), 6.92 (d, J = 2.5 Hz, 1H), 6.88 (dd, J = 8.0, 2.5 Hz, 1H), 6.37 (d, J = 2.0 Hz, 1H), 6.34 (dd, J = 7.0, 2.0 Hz, 1H), 4.36–4.34 (m, 2H), 3.79 (s, 3H), 3.71 (s, 3H), 3.53–3.52 (m, 2H), 3.10 (t, J = 6.0 Hz, 2H), 2.35 (s, 3H)
133		422	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.60 (br s, 2H), 8.11 (t, J = 58.0 Hz, 1H), 7.78 (d, J = 1.5 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.48–7.36 (m, 5H), 7.22 (dd, J = 8.5, 1.5 Hz, 1H), 6.14 (dd, J = 7.5, 2.5 Hz, 1H), 5.99 (d, J = 2.5 Hz, 1H), 5.16 (s, 2H), 4.52 (m, 2H), 3.49–3.48 (m, 2H), 2.99 (m, 2H)
134		436	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.89 (br s, 1H), 8.15 (t, J = 58.0 Hz, 1H), 7.82 (d, J = 1.5 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.47–7.36 (m, 5H), 7.23 (dd, J = 8.4, 1.5 Hz, 1H), 6.14 (dd, J = 7.6, 2.7 Hz, 1H), 6.00 (d, J = 2.7 Hz, 1H), 5.16 (s, 2H), 4.77 (m, 1H), 4.55 (m, 1H), 3.76–3.75 (m, 1H), 3.45–3.40 (m, 1H), 3.07–3.02 (m, 5H)
135		404	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (s, 2H), 7.71 (d, J = 7.2 Hz, 1H), 7.62–7.58 (m, 3H), 7.10 (dd, J = 8.3, 1.8 Hz, 1H), 7.01 (dd, J = 13.2, 2.4 Hz, 1H), 6.94 (dd, J = 8.6, 2.3 Hz, 1H), 6.62 (s, 1H), 6.53–6.52 (m, 1H), 4.48 (s, 2H), 3.95 (s, 3H), 3.69 (s, 3H), 3.45–3.44 (m, 2H), 3.00–2.97 (m, 2H)
136		418	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.71 (s, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.63–7.59 (m, 3H), 7.11 (dd, J = 8.3, 1.6 Hz, 1H), 7.01 (dd, J = 13.2, 2.4 Hz, 1H), 6.94 (dd, J = 8.7, 2.4 Hz, 1H), 6.62 (s, 1H), 6.53–6.52 (m, 1H), 4.80–4.77 (m, 1H), 4.45–4.43 (m, 1H), 3.84 (s, 3H), 3.73 (br s, 1H), 3.68 (s, 3H), 3.42–3.34 (m, 1H), 3.07–3.06 (m, 2H), 3.00 (s, 3H)

Ex. No.	Structure	Mass Spec	^{1}H NMR Data
137		426	^{1}H NMR (500 MHz, CD_3OD) δ 8.81 (d, J = 7.0, 1.0 Hz, 1H), 8.38 (s, 1H), 8.02–7.99 (m, 1H), 7.92 (d, J = 9.5 Hz, 1H), 7.66–7.62 (m, 2H), 7.52–7.49 (m, 1H), 7.46 (s, 1H), 7.05 (d, J = 7.0 Hz, 1H), 6.33 (dd, J = 7.5, 3.0 Hz, 1H), 6.23 (d, J = 3.0 Hz, 1H), 5.50 (s, 2H), 4.55 (s, 2H), 3.72 (s, 3H), 3.60 (t, J = 6.0 Hz, 2H), 3.14–3.12 (m, 2H)
138		440	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.91 (br s, 1H), 8.86 (d, J = 6.0 Hz, 1H), 8.39 (s, 1H), 7.87–7.79 (m, 2H), 7.61 (d, J = 7.5 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.51 (s, 1H), 7.37–7.35 (m, 1H), 7.01 (dd, J = 8.5, 1.0 Hz, 1H), 6.15–6.11 (m, 2H), 5.42 (s, 2H), 4.77 (d, J = 15.0 Hz, 1H), 4.43 (dd, J = 14.0, 6.0 Hz, 1H), 3.80–3.77 (m, 1H), 3.66 (s, 3H), 3.41–3.39 (m, 1H), 3.08–3.04 (m, 2H), 2.99 (s, 3H)
139		426	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.55 (br s, 2H), 9.01 (s, 1H), 8.33 (s, 1H), 8.11 (s, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.89 (d, J = 9.2 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 1.6 Hz, 1H), 7.00 (dd, J = 8.4, 1.7 Hz, 1H), 6.13 (dd, J = 7.6, 2.7 Hz, 1H), 6.08 (d, J = 2.7 Hz, 1H), 5.31 (s, 2H), 4.46 (m, 2H), 3.67 (s, 3H), 3.44 (m, 2H), 2.97 (t, J = 5.7 Hz, 2H)
140		418	^{1}H NMR (300 MHz, CD_3OD) δ 7.53–7.33 (m, 7H), 7.27 (d, J = 10.5 Hz, 1H), 7.28 (dd, J = 7.8, 2.4 Hz, 1H), 6.10 (d, J = 2.7 Hz, 1H), 5.17 (s, 2H), 3.79 (br s, 2H), 3.67 (s, 3H), 3.03–3.00 (m, 4H), 2.64 (s, 3H)
141		404	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.56 (br s, 2H), 7.61 (d, J = 6.0 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.50–7.37 (m, 6H), 6.14–6.12 (m, 1H), 5.99 (s, 1H), 5.16 (s, 2H), 4.46 (br s, 2H), 3.67 (s, 3H), 3.43 (br m, 2H), 2.94 (m, 2H)
142		414	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.57 (d, J = 7.5 Hz, 1H), 7.54–7.34 (m, 7H), 6.97 (d, J = 8.0 Hz, 1H), 6.10 (dd, J = 7.5, 2.0 Hz, 1H), 5.97 (s, 1H), 5.16 (s, 2H), 3.67 (s, 3H), 3.45–3.18 (4H, overlapping with solvent peak), 3.26 (br m, 2H), 2.96 (m, 2H), 1.33 (br m, 3H)
143		428	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.50 (s, 1H), 7.56 (d, J = 4.5 Hz, 2H), 7.52–7.38 (m, 6H), 7.01 (dd, J = 4.5, 1.0 Hz, 1H), 6.11 (dd, J = 4.5, 1.0 Hz, 1H), 5.97 (s, 1H), 5.16 (s, 2H), 4.60–4.53 (m, 2H), 3.78–3.70 (m, 2H), 3.70 (s, 3H), 3.40–3.28 (m, 1H), 3.18–2.98 (m, 2H), 1.44–1.39 (m, 6H)

Ex, No.	Structure	Mass Spec	^{1}H NMR Data
144		472	^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 8.5 Hz, 1H), 7.50–7.32 (m, 7H), 6.99 (d, J = 8.5 Hz, 1H), 6.90 (s, 1H), 6.34 (d, J = 6.5 Hz, 1H), 5.17 (s, 2H), 5.05–5.00 (m, 1H), 4.72–4.58 (m, 2H), 3.79 (br m, 2H), 3.76 (s, 3H), 2.82 (m, 2H), 1.42–1.32 (m, 6H)
145		465	^{1}H NMR (300 MHz, CD_3OD) δ 7.71 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 8.4, Hz, 1H), 7.53–7.30 (m, 6H), 7.05 (dd, J = 7.8, 1.2 Hz, 1H), 6.60 (d, J = 7.6 Hz, 1H), 5.40 (s, 2H), 4.54 (s, 2H), 3.71 (s, 3H), 3.62–3.55 (m, 2H), 3.22–3.02 (m, 2H)
146		372	^{1}H NMR (500 MHz, CD_3OD) δ 7.65 (d, J = 7.5 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.47 (d, J = 7.2 Hz, 2H), 7.42–7.36 (m, 4H), 7.03 (d, J = 8.5 Hz, 1H), 6.39 (dd, J = 7.6, 2.5 Hz, 1H), 6.21 (d, J = 2.5 Hz, 1H), 5.21 (s, 2H), 4.47 (s, 2H), 3.64 (t, J = 6.0 Hz, 2H), 3.20 (t, J = 6.1 Hz, 2H)
147		400	^{1}H NMR (300 MHz, CD_3OD) δ 7.83 (d, J = 7.5 Hz, 1H), 7.62–7.57 (m, 2H), 7.45–7.40 (m, 5H), 7.09 (dd, J = 8.4, 1.6 Hz, 1H), 6.59 (dd, J = 7.5, 2.3 Hz, 1H), 6.36 (d, J = 2.3 Hz, 1H), 5.28 (s, 2H), 4.49 (s, 2H), 4.23 (q, J = 7.2 Hz, 2H), 3.68 (t, J = 6.1 Hz, 2H), 3.22 (t, J = 5.9 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H)

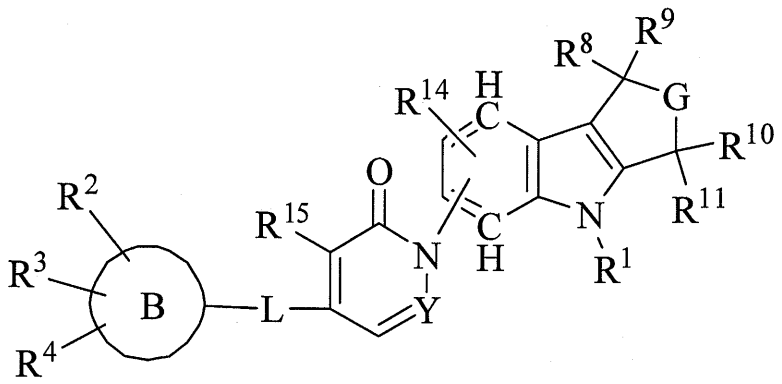
As compounds that bind strongly to MCH_1, compounds of formula I are expected to be effective in reducing obesity.

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.

The invention has been described in detail with particular reference to some embodiments thereof, but it will be understood by those skilled in the art that variations and modifications can be effected within the spirit and scope of the invention.

CLAIMS:

1. A compound of formula I:



(I)

wherein

R^1 is H or optionally substituted alkyl;

R^2, R^3, R^4 are each independently selected from H, -O-alkyl, -S-alkyl, alkyl, halo, $-CF_3$, and –CN;

G is $-CR^{12}R^{13}-NR^5-$ or $-NR^5-CR^{12}R^{13}$;

R^5 is H, optionally substituted alkyl, optionally substituted heterocycle, $-C(=O)-R^6$, $-C(=O)-O-R^7$, or $-C(=O)-NR^{19}R^{20}$;

R^6 and R^7 are each optionally substituted alkyl or optionally substituted heterocycle;

R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{19} and R^{20} are each independently selected from H or optionally substituted alkyl;

R^{14} and R^{15} are each independently H or halogen;

Y is CH or N;

L is $-CH_2-O-$, $-CH_2CH_2-$, -CH=CH- or a bond; and

B is aryl or heteroaryl or cycloalkyl;

with the proviso that, when L is a direct bond, B cannot be unsubstituted heteroaryl or heteroaryl monosubstituted with fluorine.

2. A compound according to claim 1 wherein G is $-CH_2-NR^5-$.

3. A compound according to claim 1 wherein G is -NR^5-CH_2-.

4. A compound according to any of claims 1 to 3 wherein R^5 is H.

5. A compound according to any of claims 1 to 3 wherein R^5 is optionally substituted alkyl.

6. A compound according to claim 5 wherein R^5 is selected from methyl, ethyl, 2-propyl, 2-hydroxyethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl and 2-oxo-2-(pyrrolidin-1-yl)ethyl, 2-(pyrrolidin-1-yl)ethyl and (*S*)-pyrrolidin-2-ylmethyl.

7. A compound according to any of claims 1 to 3 wherein R^5 is optionally substituted heterocycle.

8. A compound according to claim 7 wherein R^5 is selected from piperidin-4-yl and 1-methylpiperidin-4-yl.

9. A compound according to any of claims 1 to 3 wherein R^5 is -C(=O)-R^6.

10. A compound according to any of claims 1 to 3 wherein R^5 is -C(=O)-O-R^7.

11. A compound according to claims 7 or 8 wherein R^6 and R^7 are each optionally substituted alkyl.

12. A compound according to claim 11 wherein R^6 and R^7 are selected from methyl, 2-pyrrolidin-1-ylmethyl and dimethylaminomethyl.

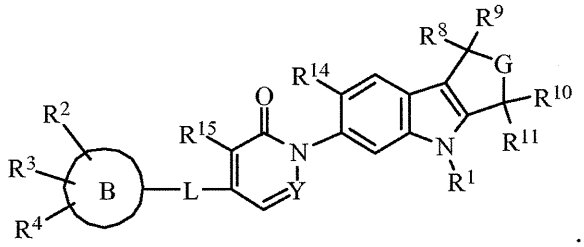
13. A compound according to claims 7 or 8 wherein R^6 and R^7 are each optionally substituted heterocycle.

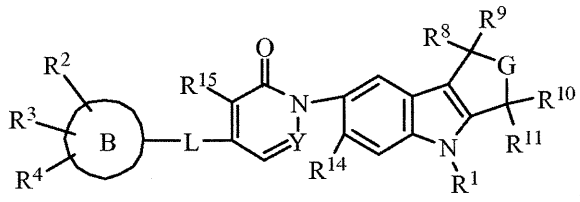
14. A compound according to claim 13 wherein R^6 and R^7 are selected from pyrrolidin-3-yl, (R)-pyrrolidin-2-yl, (S)-pyrrolidin-2-yl, 1-methylpyrrolidin-3-yl, (R)-1-methylpyrrolidin-2-yl and (S)-1-methylpyrrolidin-2-yl.

15. A compound according to any of claims 1 to 14 wherein R^1 is H.

16. A compound according to any of claims 1 to 14 wherein R^1 is alkyl.

17. A compound according to claim 16 wherein R^1 is selected from methyl and ethyl.

18. A compound according to any of claims 1 to 17 wherein the compound has the structure  .

19. A compound according to any of claims 1 to 17 wherein the compound has the structure  .

20. A compound according to any of claims 1 to 19 wherein L is a bond.

21. A compound according to any of claims 1 to 19 wherein L is $-CH_2-O-$.

22. A compound according to any of claims 1 to 19 wherein L is $-CH_2CH_2-$.

23. A compound according to any of claims 1 to 19 wherein L is -CH=CH-.

24. A compound according to any of claims 1 to 23 wherein B is aryl.

25. A compound according to claim 24 wherein B is phenyl.

26. A compound according to any of claims 1 to 23 wherein B is heteroaryl.

27. A compound according to claim 26 wherein B is pyridinyl.

28. A compound according to claim 27 wherein B is pyridin-2-yl.

29. A compound according to claim 27 wherein B is pyridin-3-yl.

30. A compound according to claim 26 wherein B is pyridazinyl.

31. A compound according to claim 30 wherein B is pyridazin-3-yl.

32. A compound according to claim 26 wherein B is pyrimidinyl.

33. A compound according to claim 32 wherein B is pyrimidin-5-yl.

34. A compound according to claim 32 wherein B is pyrimidin-2-yl.

35. A compound according to claim 1 to 23 wherein B is cycloalkyl.

36. A compound according to claim 35 wherein B is cyclohexyl.

37. A compound according to any of claims 1 to 36 wherein R^2, R^3 and R^4 are each H.

38. A compound according to any of claims 1 to 36 wherein two of R^2, R^3 and R^4 are H, and the other of R^2, R^3 and R^4 is selected from trifluoromethyl, chloro, fluoro, methyl, methoxy and methylthio.

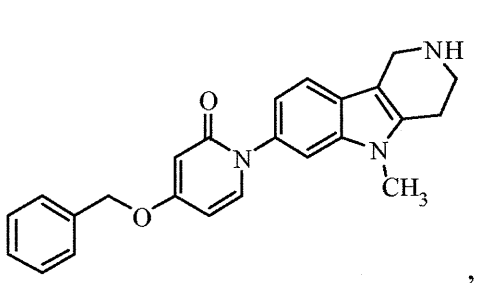
39. A compound according to any of claims 1 to 36 wherein one of R^2, R^3 and R^4 is H, another of R^2, R^3 and R^4 is Cl, and the third of R^2, R^3 and R^4 is F, Cl or methoxy.

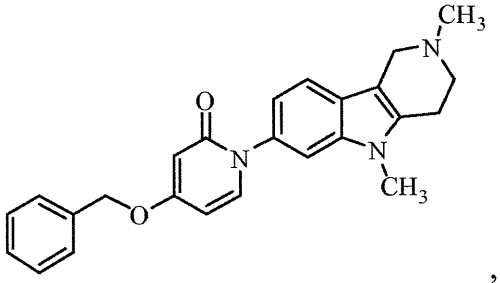
40. A compound according to any of claims 1 to 36 wherein one of R^2, R^3 and R^4 is H, another of R^2, R^3 and R^4 is F, and the third of R^2, R^3 and R^4 is methoxy.

41. A compound according to any of claims 1 to 36 wherein one of R^2, R^3 and R^4 is H, another of R^2, R^3 and R^4 is methoxy, and the third of R^2, R^3 and R^4 is methyl.

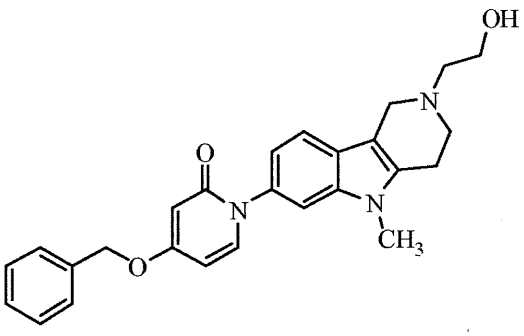
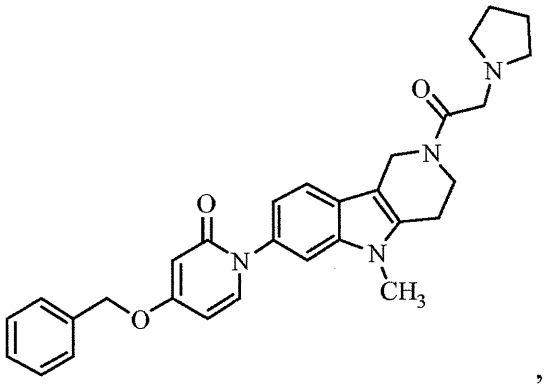
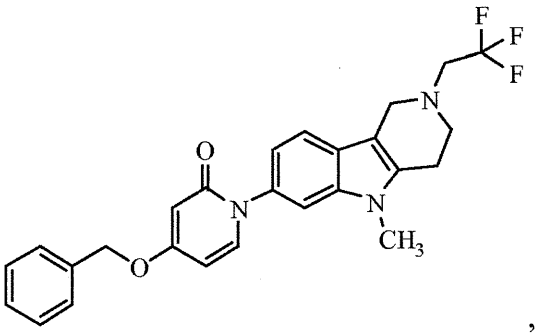
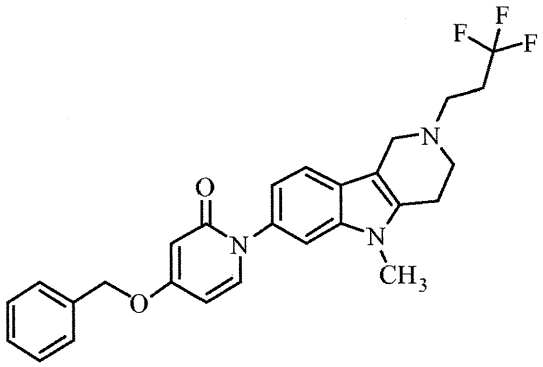
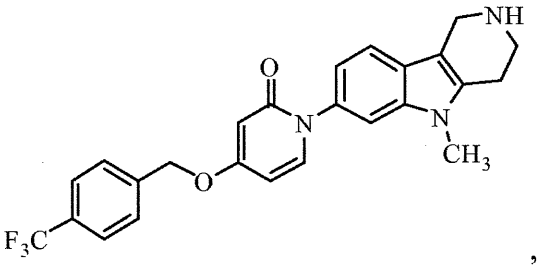
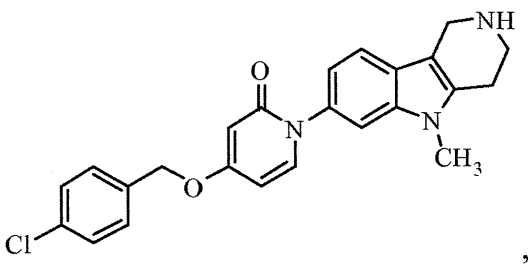
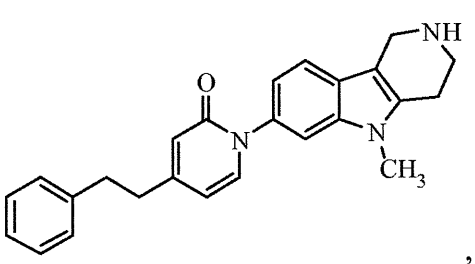
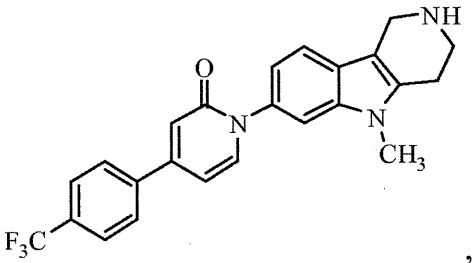
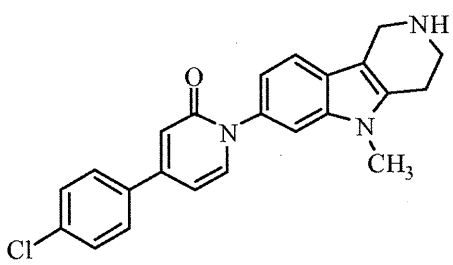
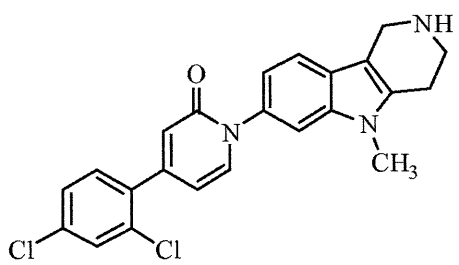
42. A compound according to any of claims 1 to 23 wherein B, together with R^2, R^3 and R^4, is selected from phenyl, 4-trifluoromethylphenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 4-fluorophenyl, 4-chloro-2-fluorophenyl, 2-fluoro-4-methoxyphenyl, pyridin-2-yl, 5-chloropyridin-2-yl, 5-(trifluoromethyl)pyridin-2-yl, 5-fluoropyridin-2-yl, 6-(trifluoromethyl)pyridazin-3-yl, 6-methylpyridazin-3-yl, 4-fluoro-2-methoxyphenyl, 6-(trifluoromethyl)pyridin-3-yl, 2-(trifluoromethyl)pyrimidin-5-yl, 5-(trifluoromethyl)pyrimidin-2-yl, 5-methylpyridin-2-yl, 6-methylpyridin-3-yl, cyclohexyl, 4-chloro-2-methoxyphenyl, pyrimidin-2-yl, imidazo[1,2-*a*]pyridin-6-yl, imidazo[1,2-*a*]pyridin-2-yl, 4-methoxyphenyl, 4-methanethiophenyl and 4-methoxy-2-methylphenyl.

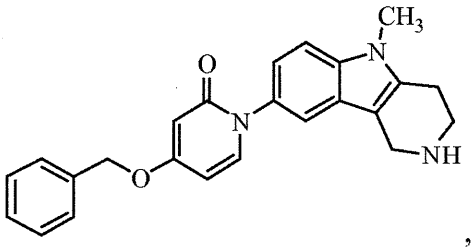
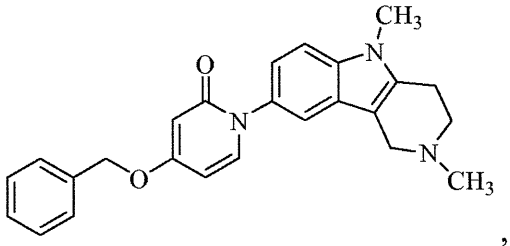
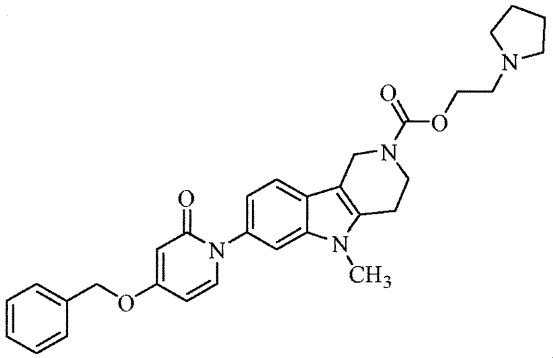
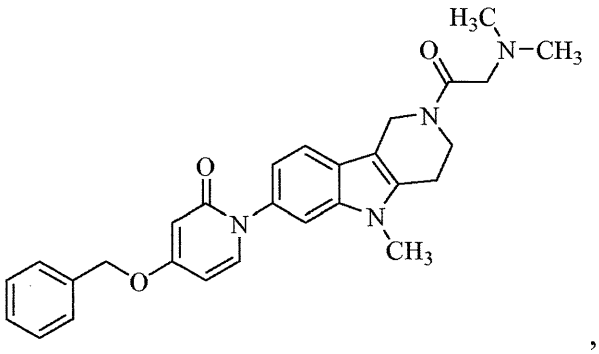
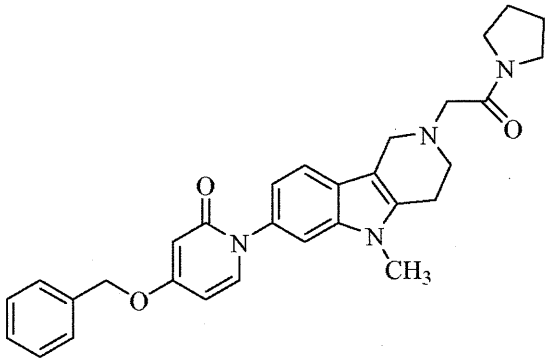
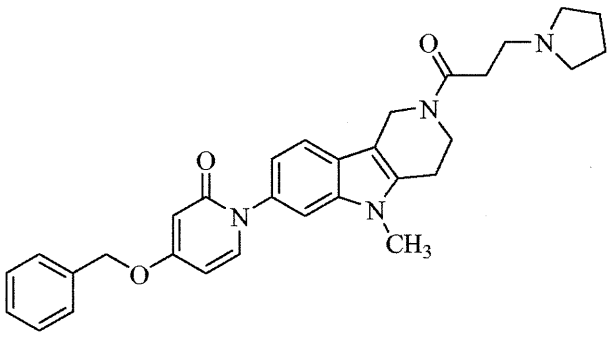
43. A compound according to claim 1 wherein the compound is selected from

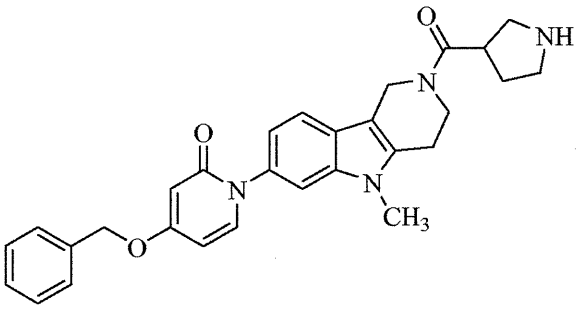
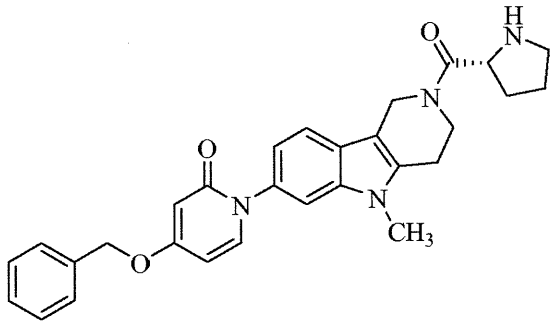
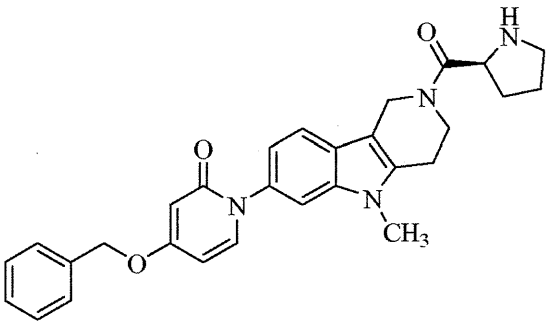
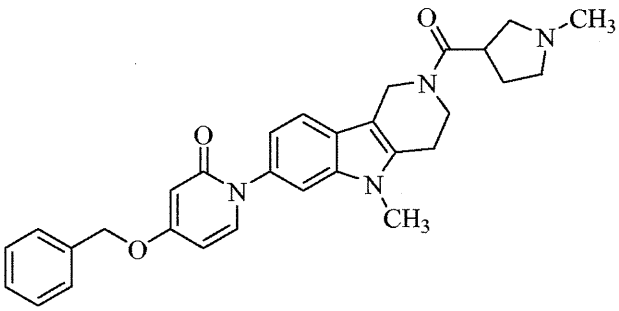
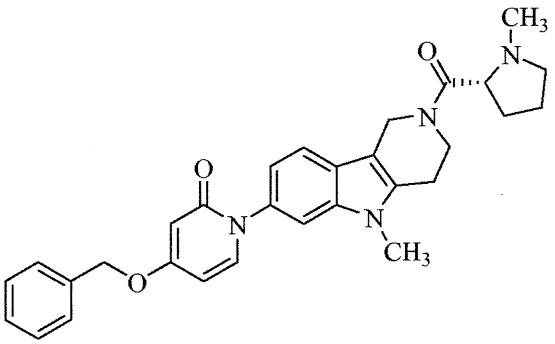
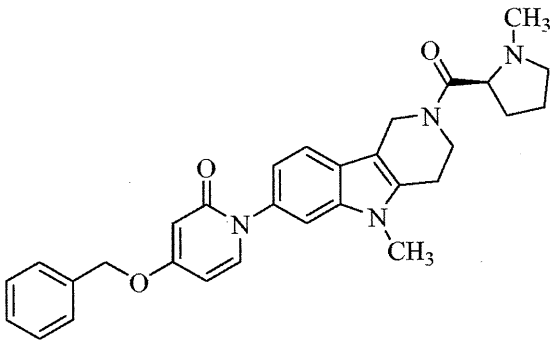


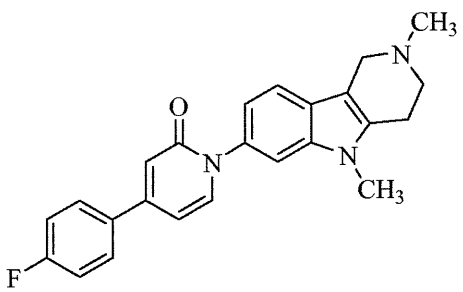
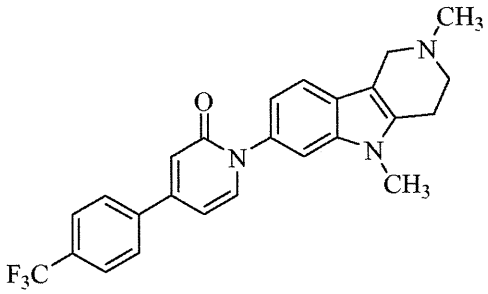
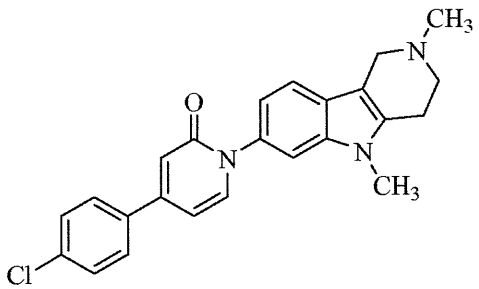
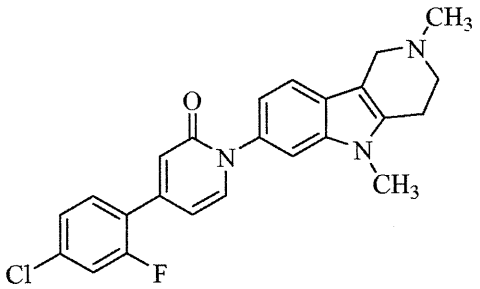
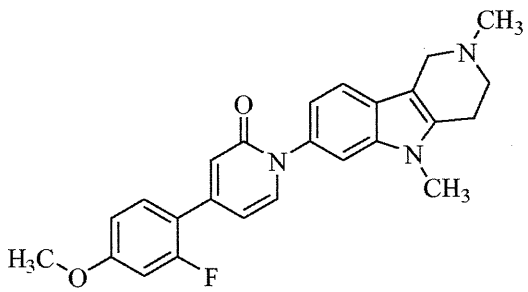
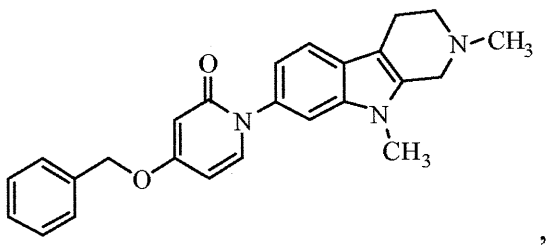
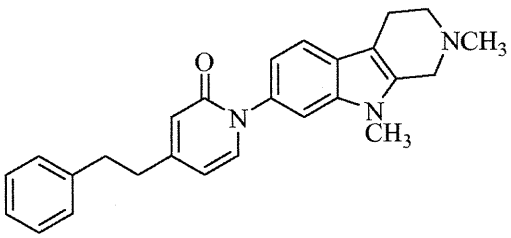
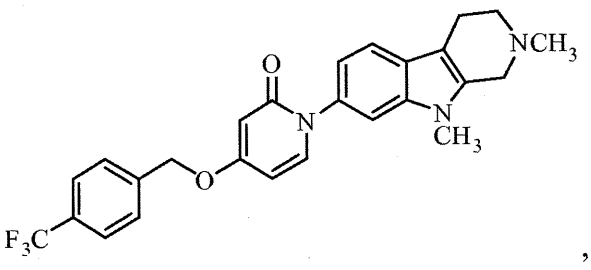
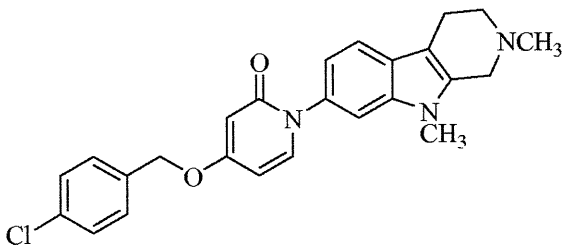
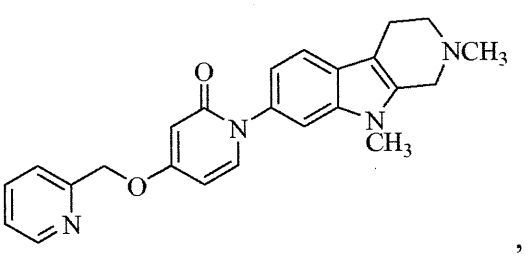
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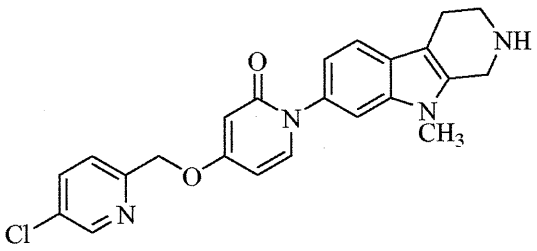

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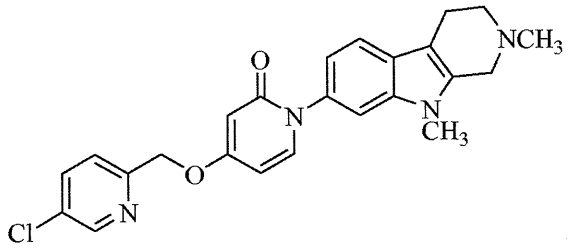

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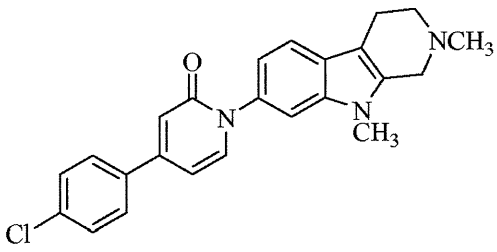
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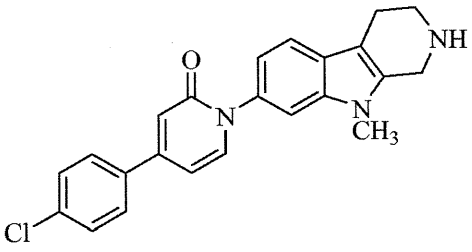
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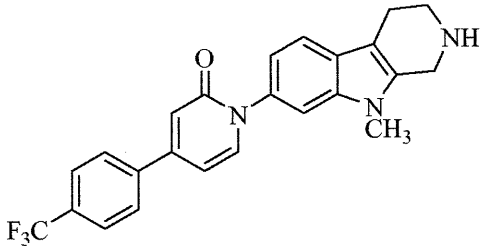
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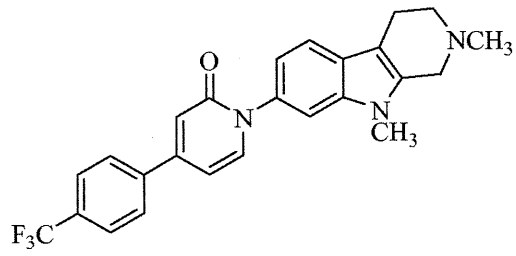
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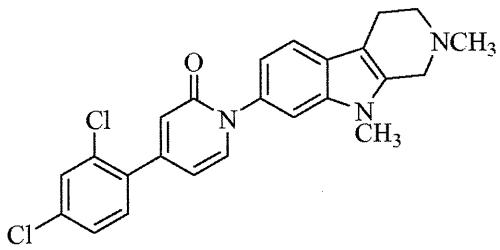
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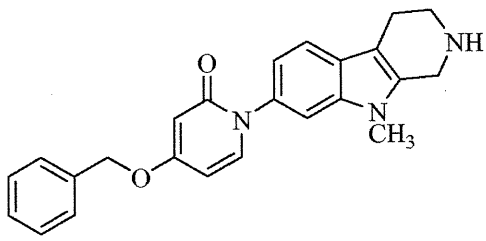
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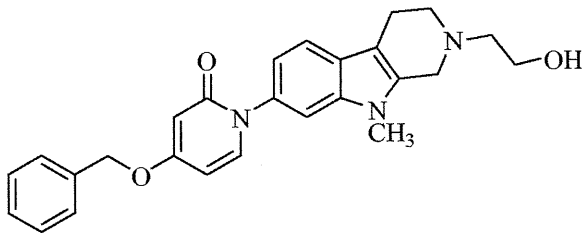
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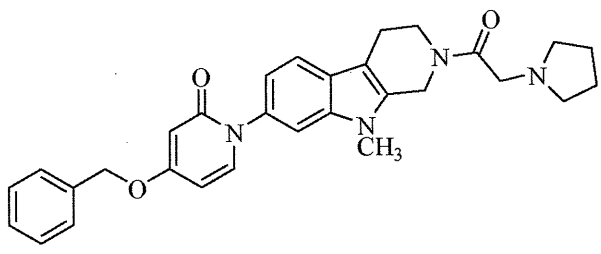
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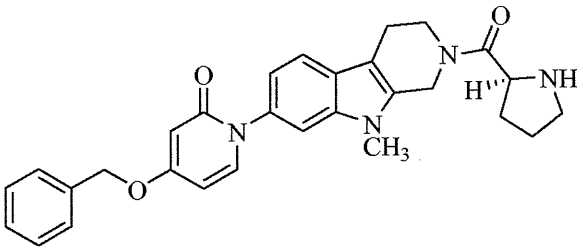
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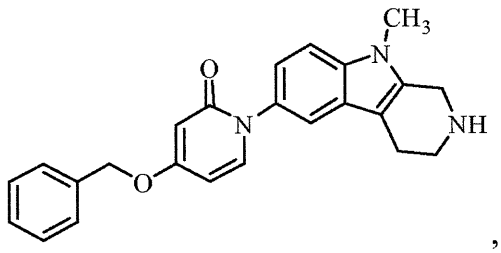
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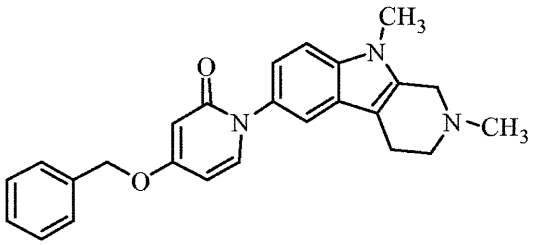
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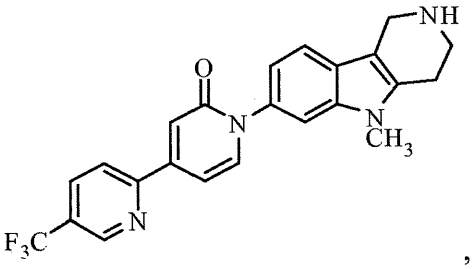
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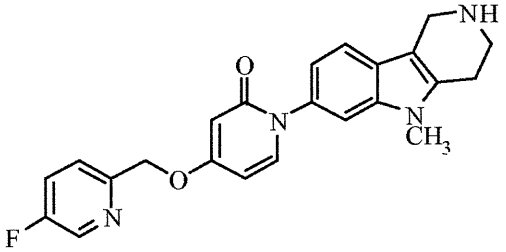
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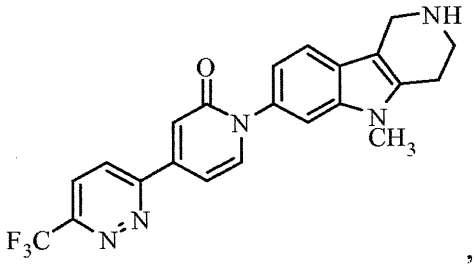
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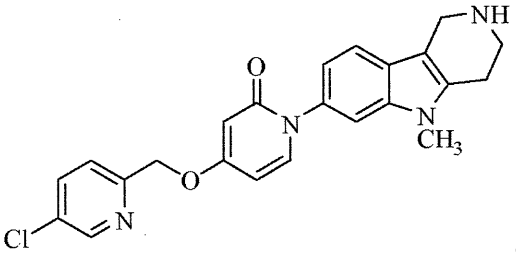
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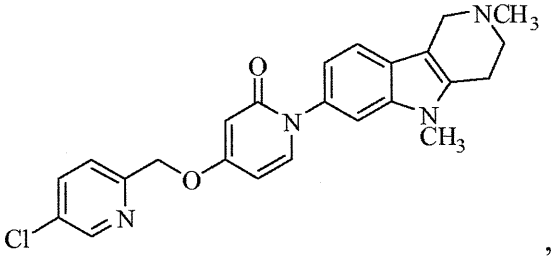
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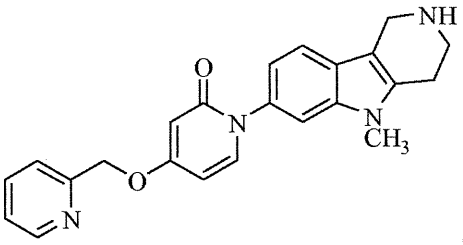
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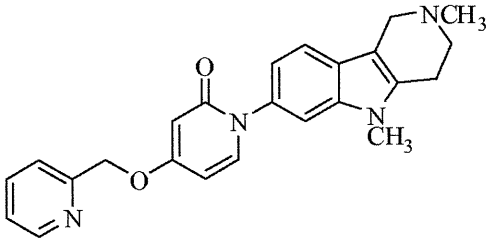
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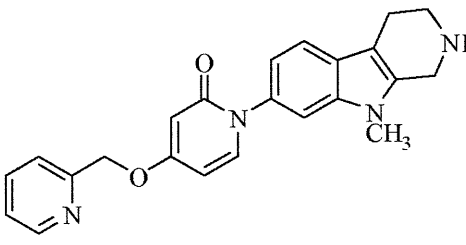
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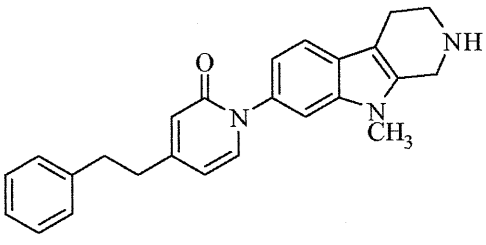
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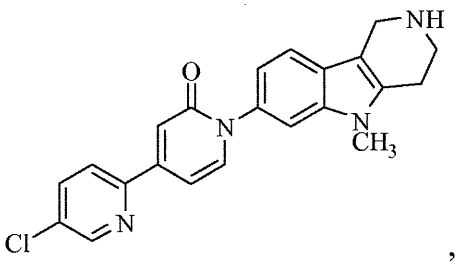
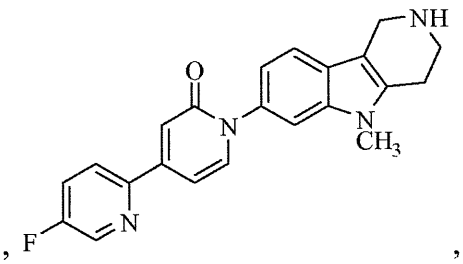
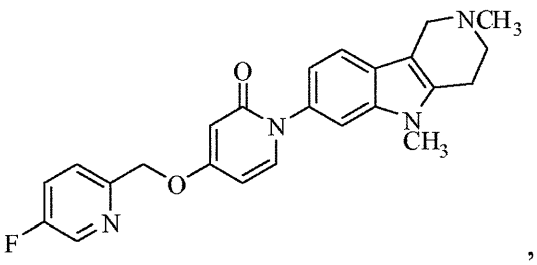
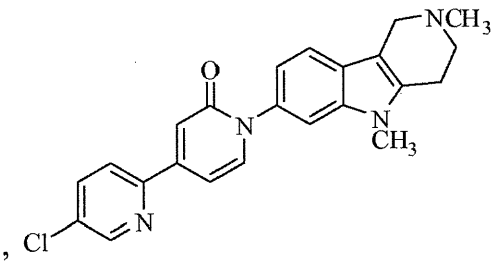
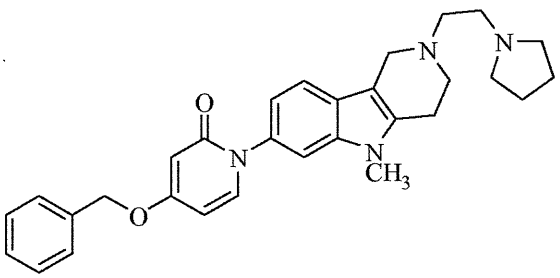
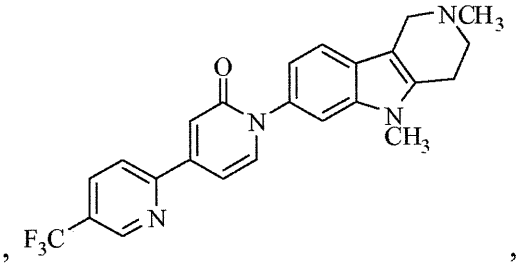
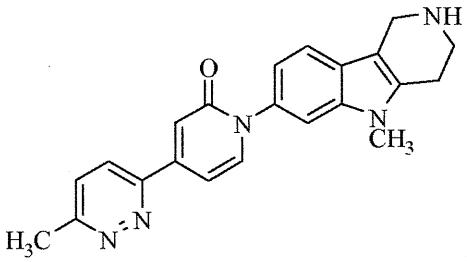
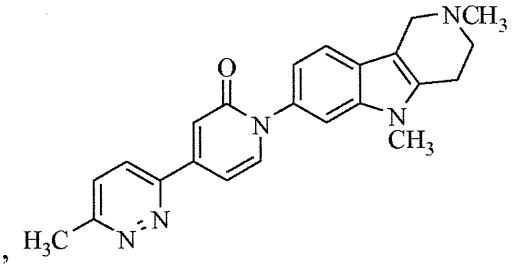
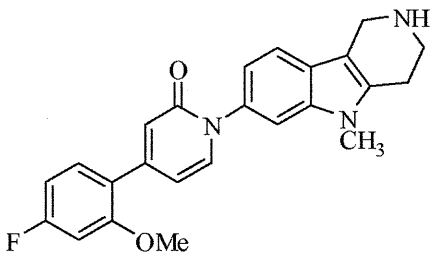
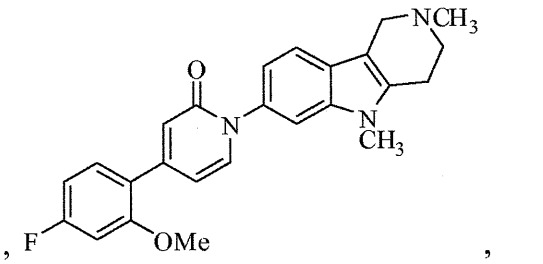


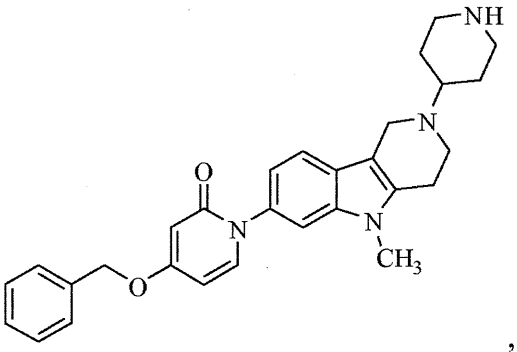
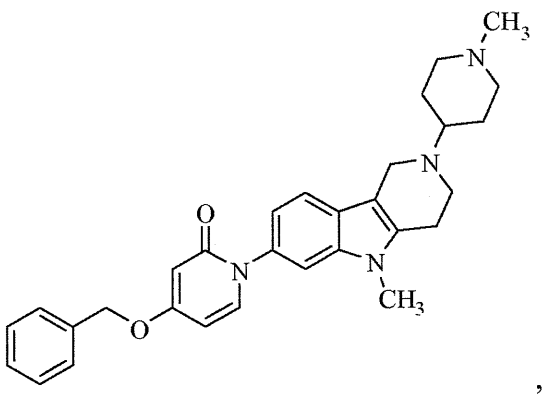
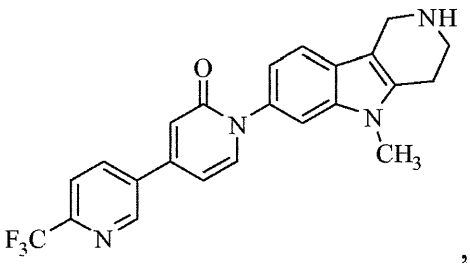
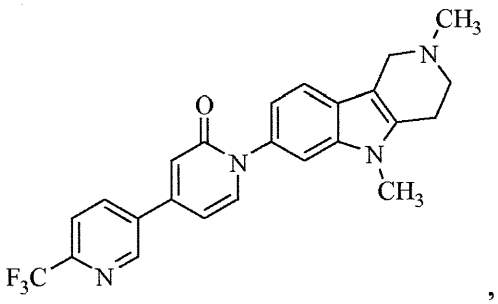
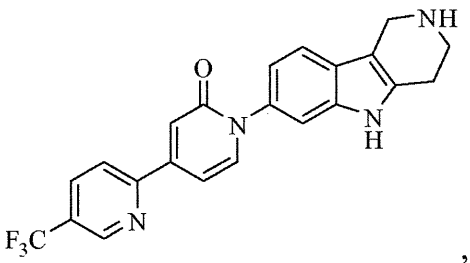
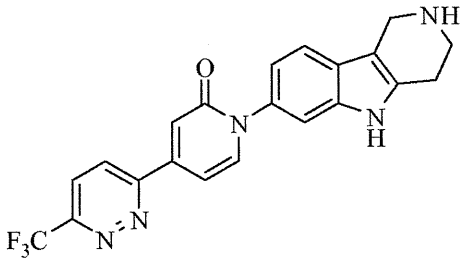
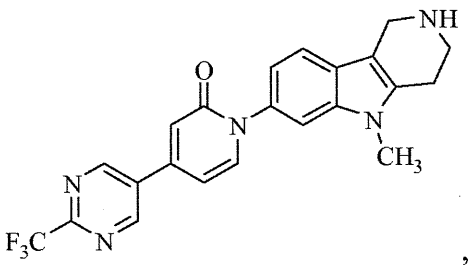
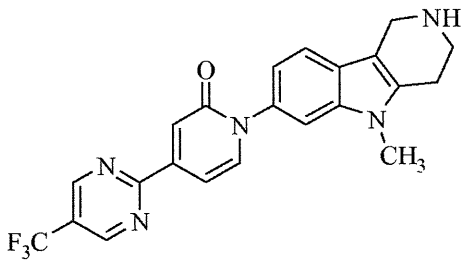
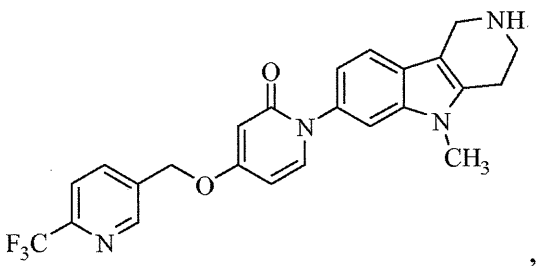
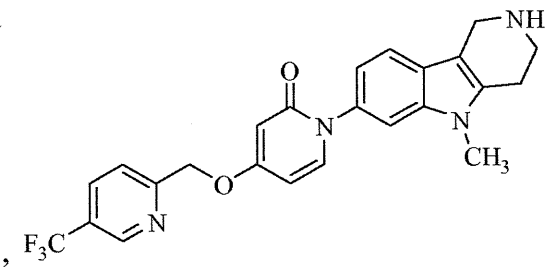
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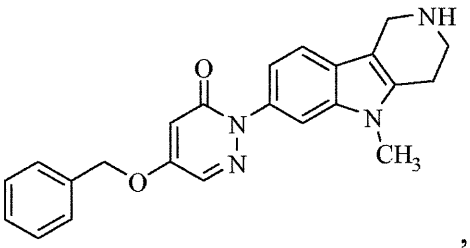
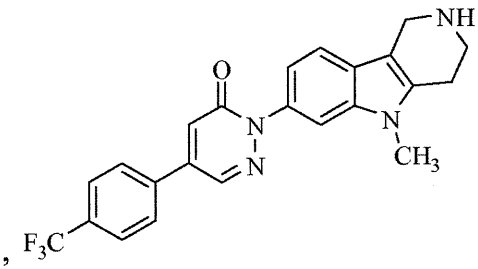
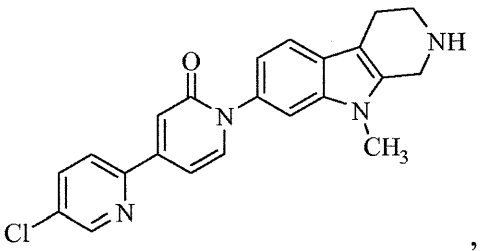
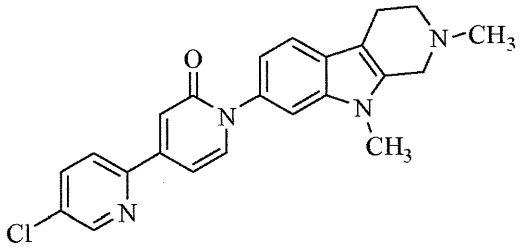
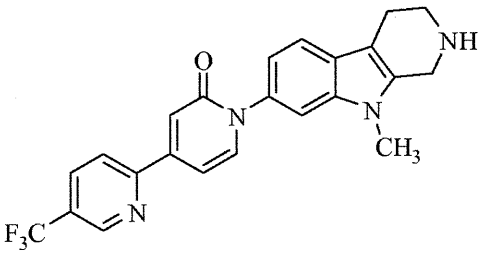
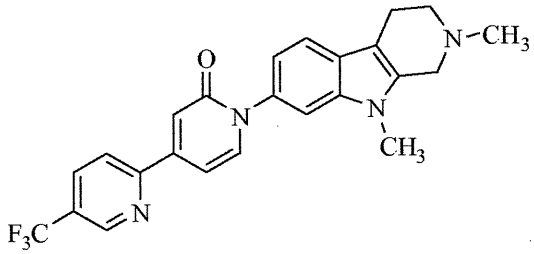
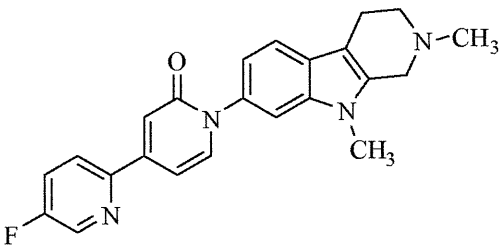
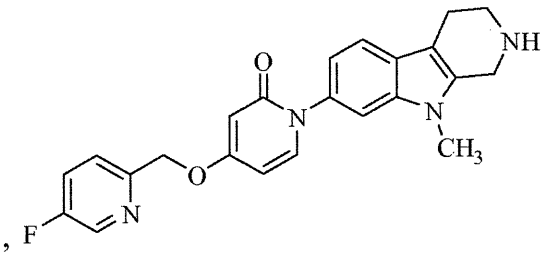
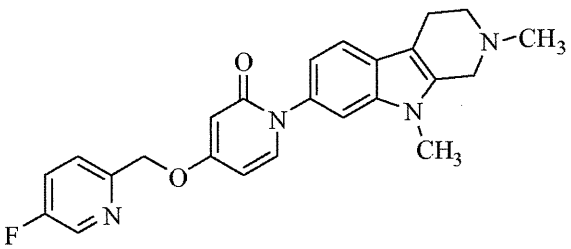
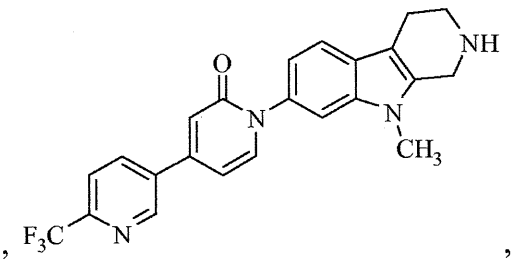
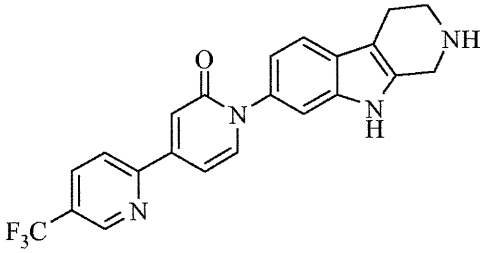
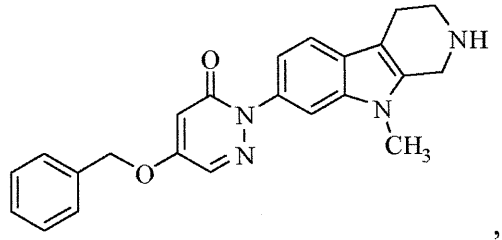
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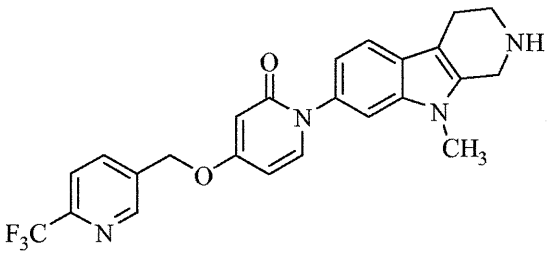
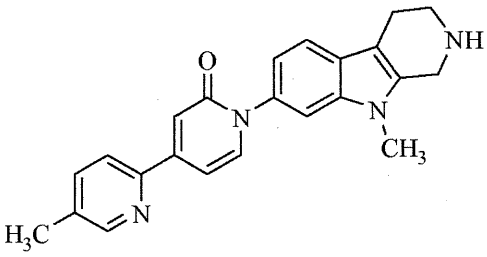
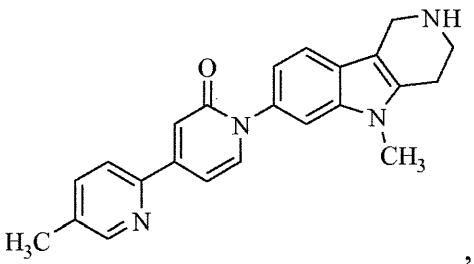
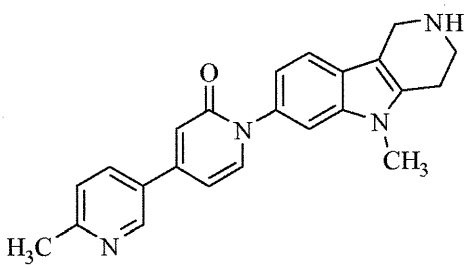
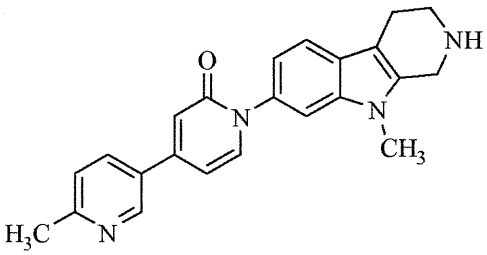
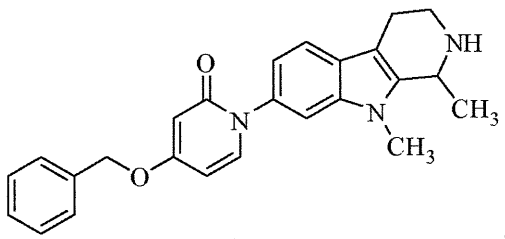
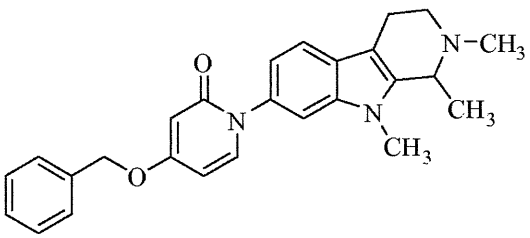
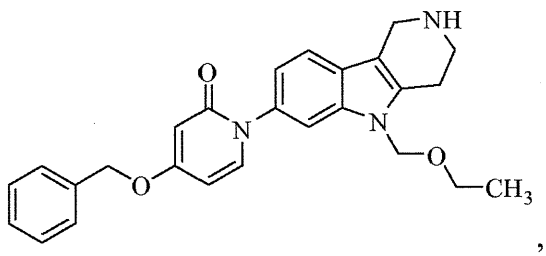
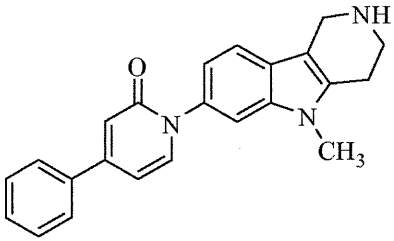
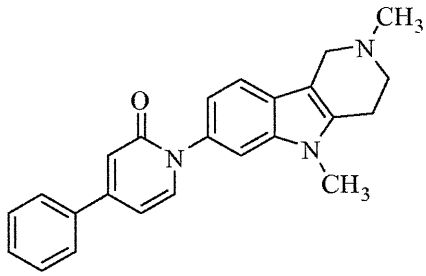


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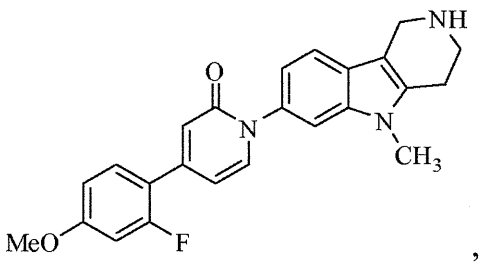
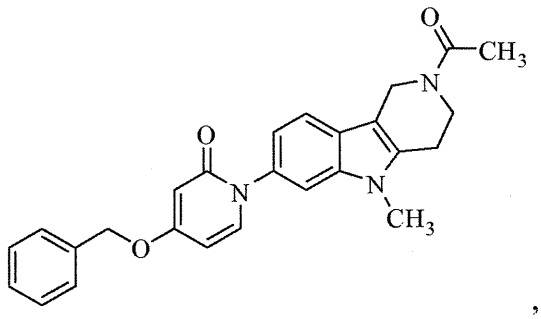
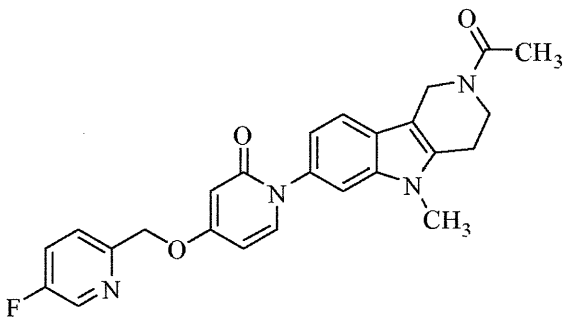
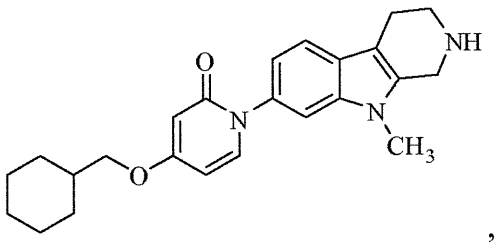
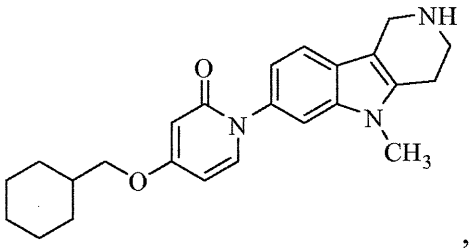
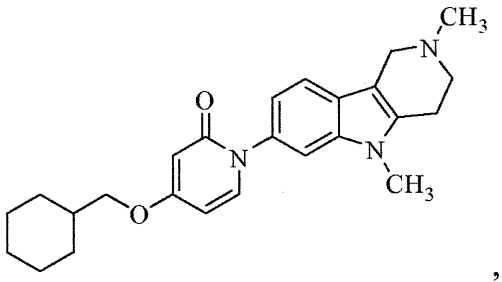
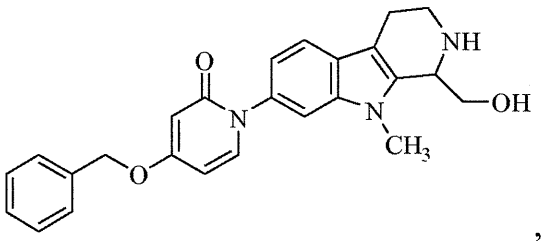
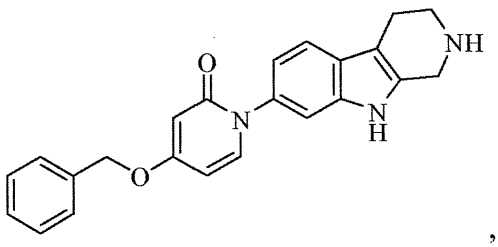
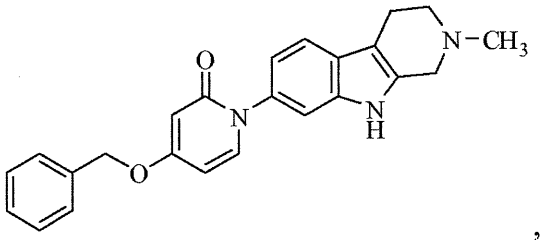
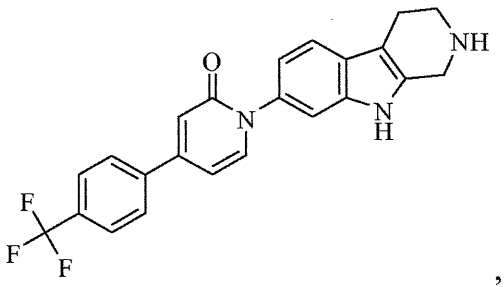

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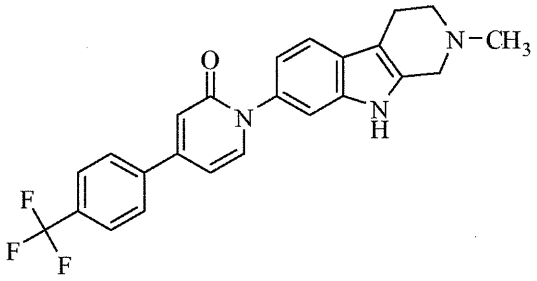
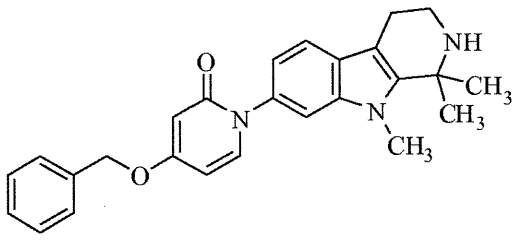
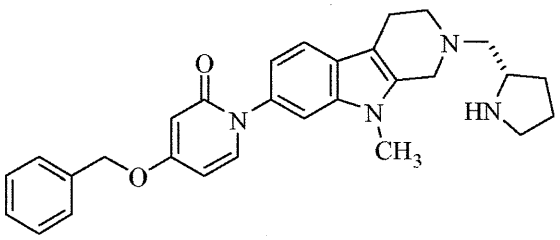
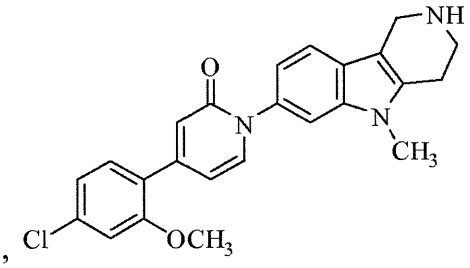
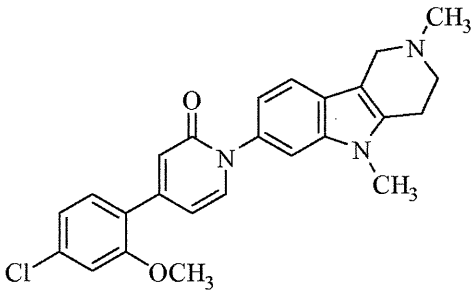
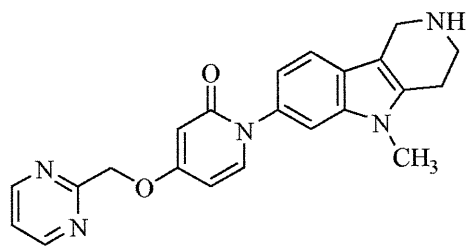
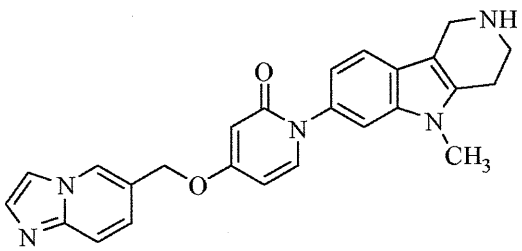
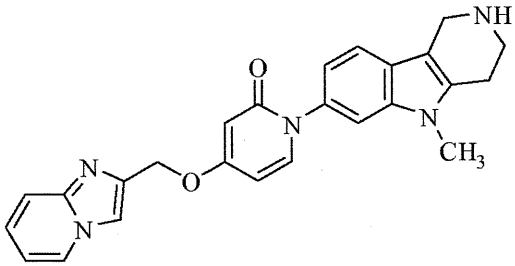
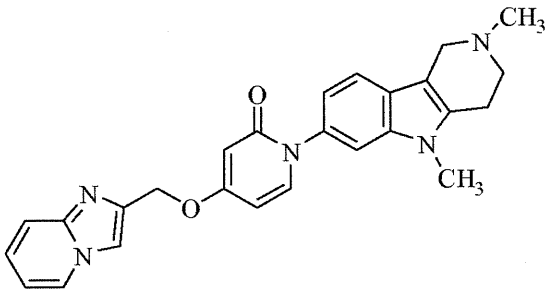
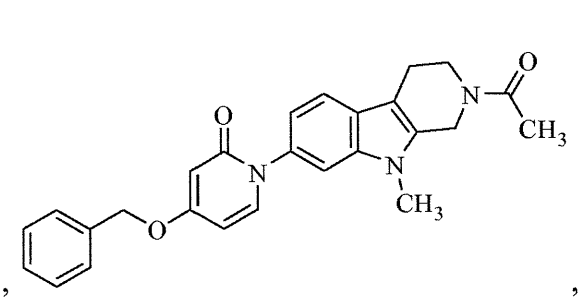

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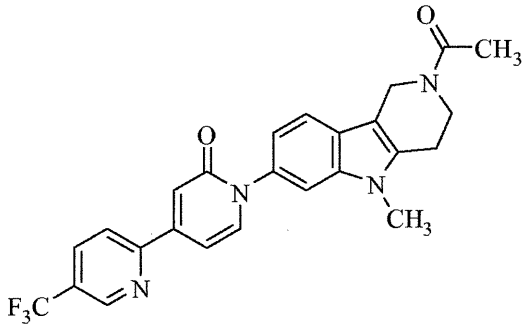
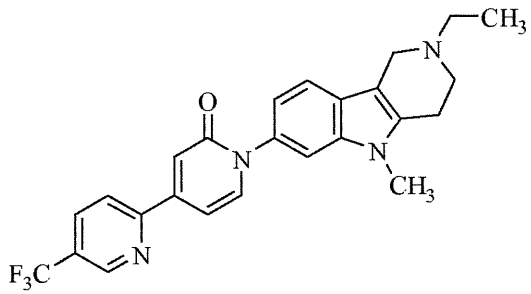
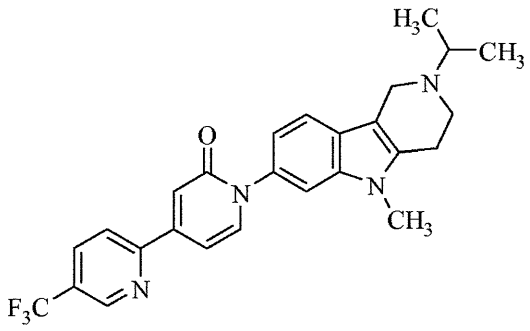
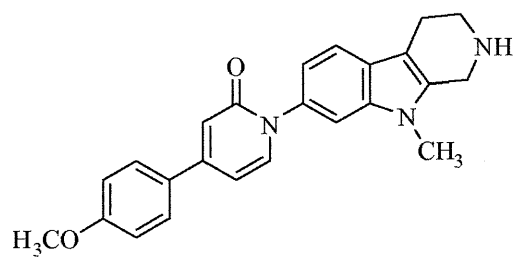
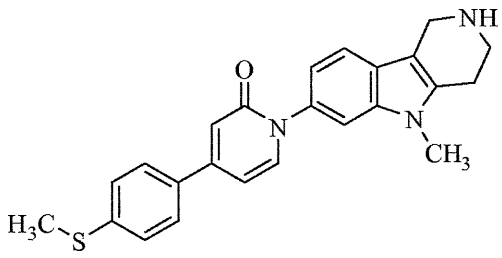
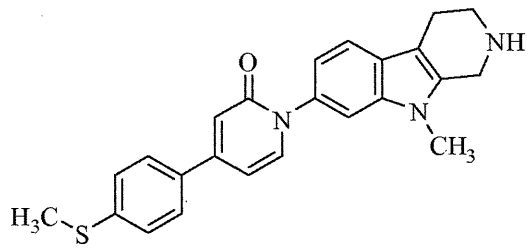
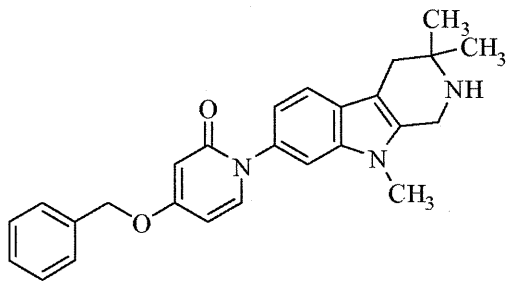
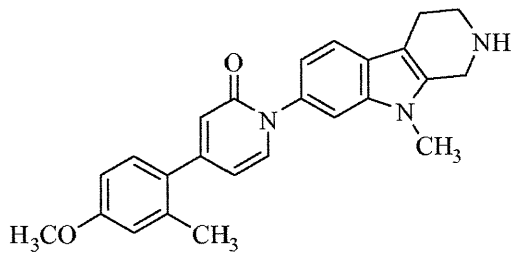
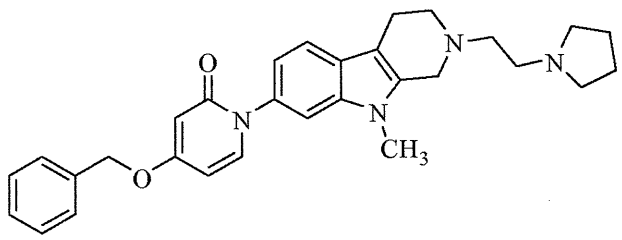
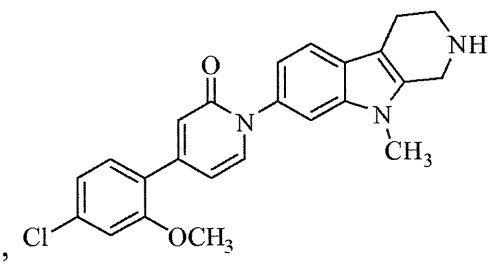

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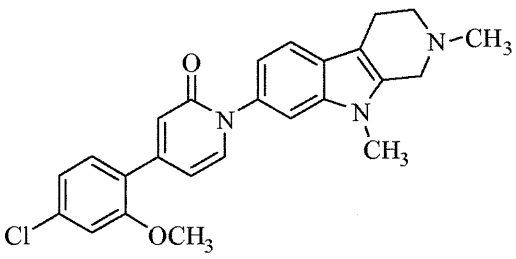
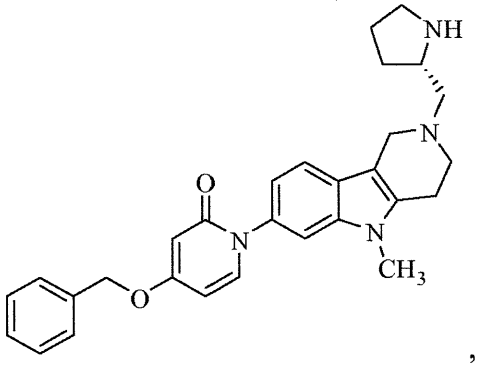
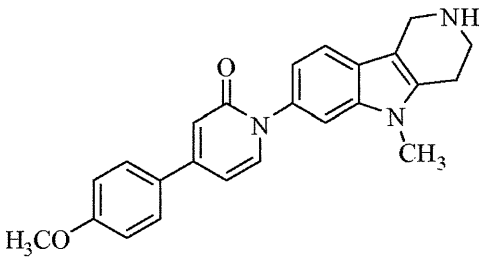
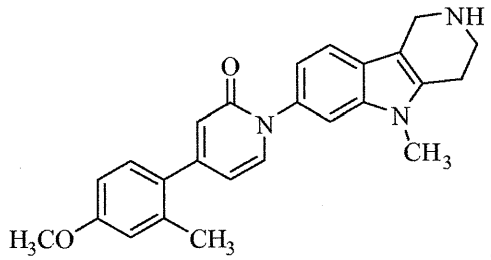
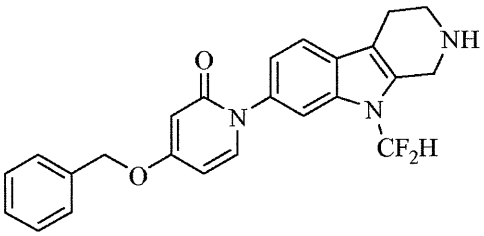
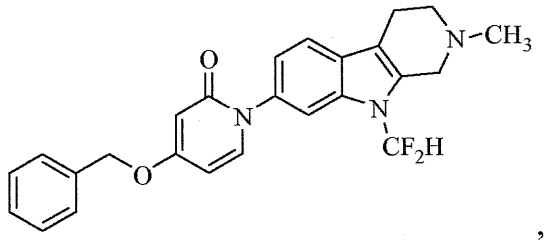
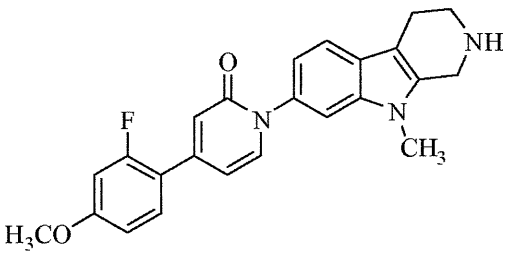
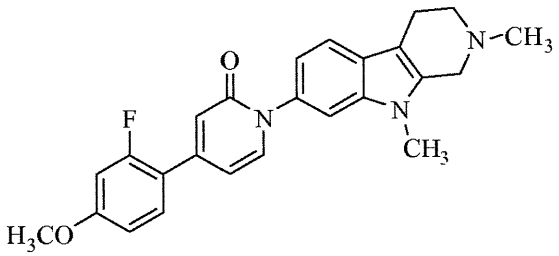
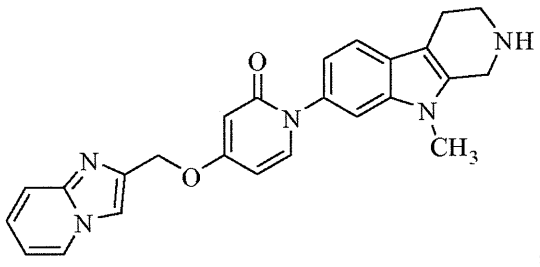
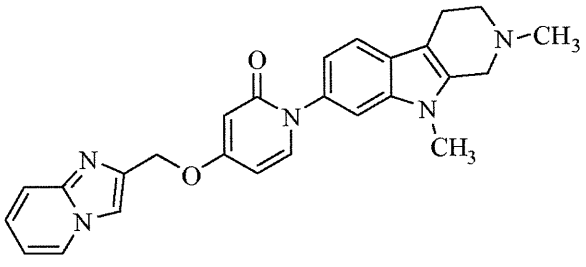
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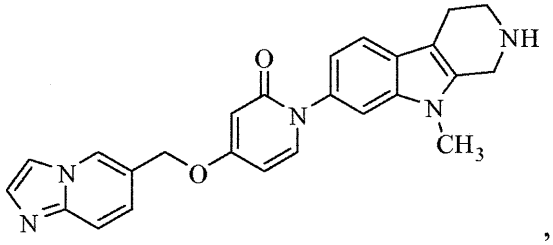
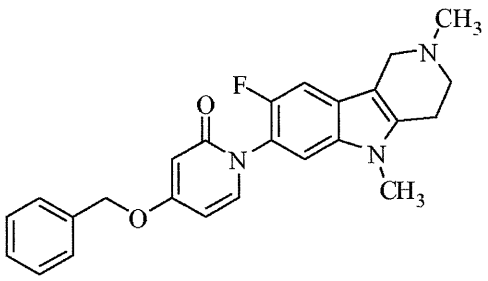
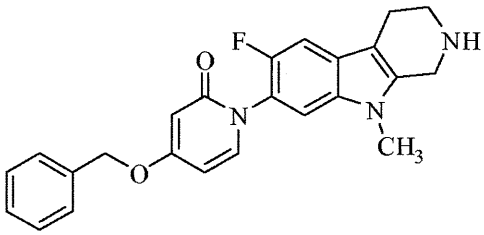
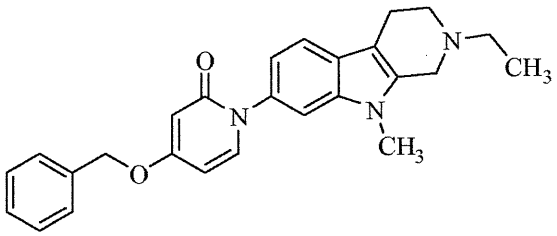
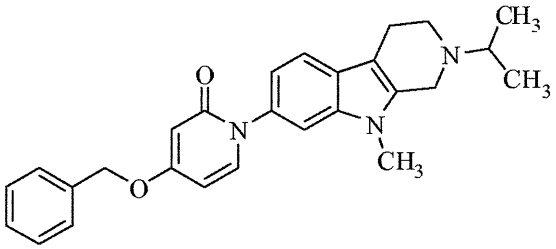
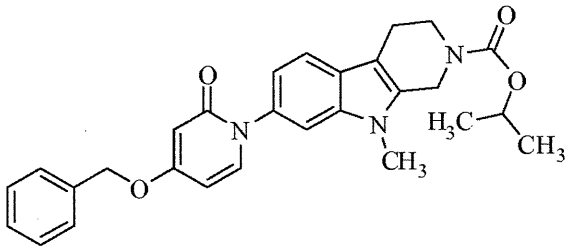
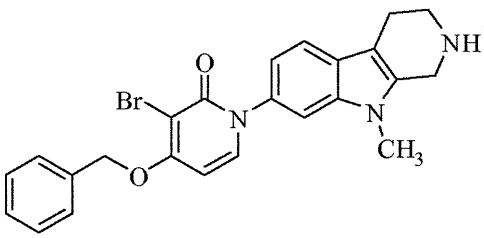
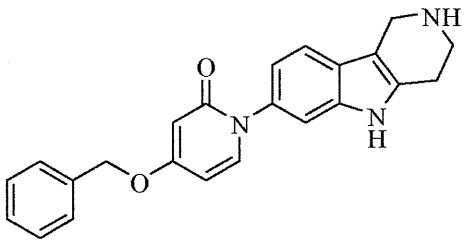
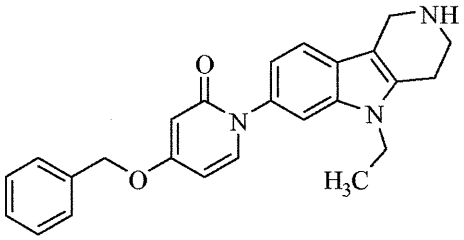
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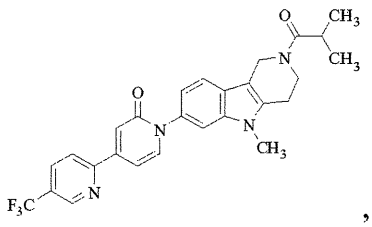
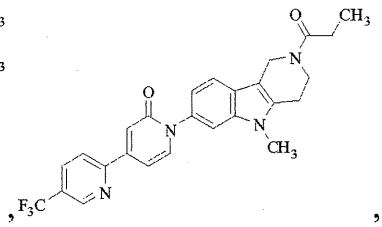
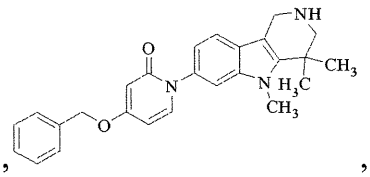
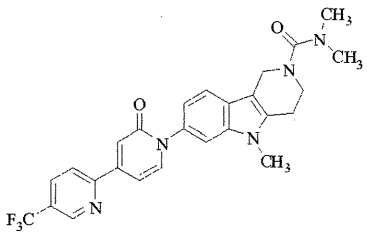
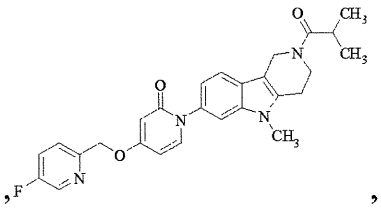
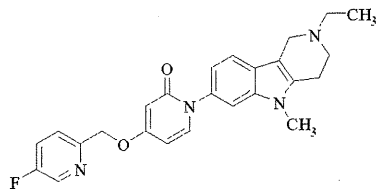
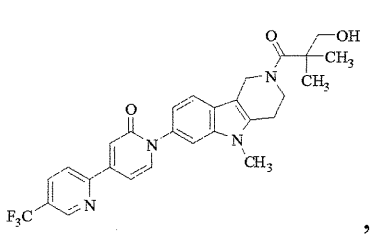
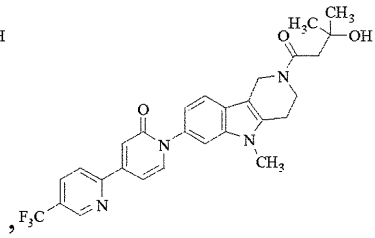
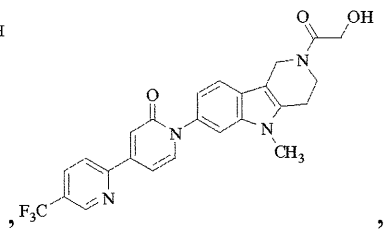
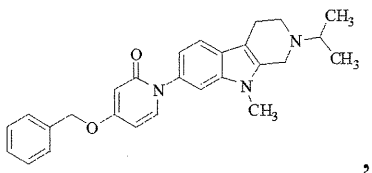
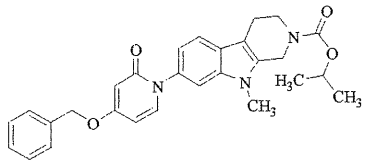

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44. A compound according to claim 1 wherein the compound is selected from


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45. A compound according to any of claims 1 to 36 wherein R^1 is substituted alkyl.

46. A compound according to claim 45 wherein R^1 is selected from difluoromethyl and ethoxymethyl.

47. A compound according to any of claims 1 to 36 wherein at least one of R^8 and R^9 is H.

48. A compound according to any of claims 1 to 36 wherein at least one of R^8 and R^9 is alkyl.

49. A compound according to claim 48 wherein at least one of R^8 and R^9 is methyl.

50. A compound according to any of claims 1 to 36 wherein R^{10} is alkyl.

51. A compound according to claim 50 wherein R^{10} is methyl.

52. A compound according to any of claims 1 to 36 wherein R^{10} is substituted alkyl.

53. A compound according to claim 52 wherein R^{10} is hydroxymethyl.

54. A compound according to any of claims 1 to 36 wherein R^{11} is alkyl.

55. A compound according to claim 54 wherein R^{11} is methyl.

56. A compound according to any of claims 1 to 36 wherein R^{12} is alkyl.

57. A compound according to claim 56 wherein R^{12} is methyl.

58. A compound according to any of claims 1 to 36 wherein R^{13} is alkyl.

59. A compound according to claim 58 wherein R^{13} is methyl.

60. A compound according to any of claims 1 to 36 wherein R^{10}, R^{11}, R^{12} and R^{13} are each methyl.

61. A compound according to any of claims 1 to 36 wherein R^{14} is H.

62. A compound according to any of claims 1 to 36 wherein R^{14} is halogen.

63. A compound according to claim 1 wherein

G is $-CH_2-NR^5-$ or $-NR^5-CH_2-$;

R^1 and R^5 are each independently H or methyl;

R^{14} is H;

R^{15} is H or halogen;

B is phenyl or heteroaryl; and

(a) when L is $-CH_2-O-$, $-CH_2CH_2-$, or $-CH=CH-$; then

R^2, R^3, R^4 are each independently selected from H, -O-alkyl, -S-alkyl, alkyl, halo, $-CF_3$, and –CN; or

(b) when L is a direct bond, R^2 is selected from -O-alkyl, -S-alkyl, alkyl, Cl, Br, $-CF_3$ and –CN, and R^3 and R^4 are each independently selected from H, -O-alkyl, -S-alkyl, alkyl, halo, $-CF_3$ and –CN.

64. A compound according to any of claims 1 to 63 wherein the compound is in a pharmaceutically acceptable salt form.

65. A compound according to claim 64 wherein the salt is an HCl salt.

66. A pharmaceutical composition comprising a compound according to any of claims 1 to 65 and a pharmaceutically acceptable carrier, excipient or diluent therefore.

67. A method of treating obesity, comprising administering to a patient in need of obesity reduction an obesity-reducing effective amount of a compound according to any of claims 1 to 65.

68. A method of treating anxiety, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound according to any of claims 1 to 65.

69. A method of treating depression, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound according to any of claims 1 to 65.

70. A method of treating non-alcoholic fatty liver disease, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound according to any of claims 1 to 65.

71. A method of treating a disease or condition which is susceptible to treatment with an MCH_1 receptor modulator, comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 65.

72. A compound according to claim 1 wherein R^5 is $-C(=O)-NR^{19}R^{20}$.