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Fortsættes ...

DESCRIPTION

[0001] The present invention relates to synthetic routes for the preparation of 4-substituted analogs of cytisine.

BACKGROUND

[0002] Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels that are expressed in various parts of the brain and elsewhere in the central nervous system of humans. nAChRs are involved in a range of physiological functions, such as cognitive function, learning and memory, sleep, anxiety, arousal, reward, motor control and other neural functions. nAChRs have also been implicated in a number of pathological conditions such as Parkinson's disease, Alzheimer's disease, depression, epilepsy, autism and schizophrenia. nAChRs have also been implicated in addiction and dependence to a range of substances, for example nicotine addiction (Schalling and Waller, Acta Physiologica Scandinavica. Supplementum, 1980, volume 479, pages 53-56), alcohol addiction (Holgate et al., Brain Science, 2015, September 5(3), pages 258-274), drug dependence (Rahman et al., Frontiers in Neuroscience, 2014, volume 8, article 426).

[0003] Numerous subtypes of nAChRs are known to exist. Muscle-type nicotinic receptors (located in the neuromuscular junction) are known to be formed by five different substructures, named α, β, Y, δ, plus the recently discovered additional subunit ε.

[0004] Neuronal-type nAChRs (located in the CNS, the peripheral ganglia, and the adrenal medulla) display only two classes of subunits, named as α2-α9 and β2-β4, which can assemble into homomeric or heteromeric combinations. Although a large number of neuronal subtypes have been identified, the heteromeric combinations $(\alpha4)_3(\beta2)_2$, α3β4 and the homomeric α7 appear to play prominent roles in the brain. Among them, the heteromeric combination α4β2 is the predominant subtype in the CNS, accounting for approximately 90% of the receptors and binding ACh with high affinity. α7 homomeric combination is the other major subtype, binding ACh with low affinity.

[0005] The heteromeric combination α4β2 can be assembled into two different stoichiometries: $(\alpha4)_2(\beta2)_3$ and $(\alpha4)_3(\beta2)_2$, commonly referred as A2B3 and A3B2 respectively. The main α4β2 subtype is proposed to have a structure A2B3, being formed by two α4 and three β2 subunits; and it is the main subtype involved in addiction.

[0006] Nicotine is believed to activate this α4β2 receptor subtype, and thereby increasing the release of dopamine in the nucleus accumbens and prefrontal cortex, specific parts of the human brain which have been linked to drug-dependancy.

[0007] Additionally, the α4β2 receptor subtype has also been implicated in alcohol dependency (Mitchell et al., Pyschopharmacology, October 2012, 223, 3, pages 299 to 306) and drug addiction (Crunelle et al., European Neuropsychopharmacology, February 2010, 20, 2, pages 69 to 79).

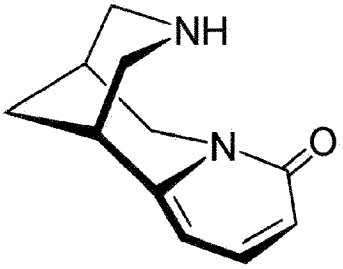
[0008] Compounds with the ability to modulate nAChRs have been found to be effective in treating conditions associated with those receptors. For example, studies suggest that transdermally administered nicotine may be able to improve cognitive function in people suffering from age associated memory impairment (see, for example, White et a/., Psychopharmacology, February 2004, 171, 4, pages 465 to 471). However, there are certain disadvantages to the use of nicotine, even when administered transdermally. For example, it is known to be addictive and, in the 2014 US Surgeon General's report, it was stated that nicotine negatively affects pregnancy outcomes and fetal brain development.

[0009] In the field of smoking cessation therapy, nicotine has been used to assist smokers give up smoking, and products to deliver nicotine via oral routes (e.g. tablets or chewing gum) or transdermally have been developed and are well known.

[0010] Alternative compounds which modulate nAChRs have also found use in the treatment of addictions. Varenicline has been commercialised under the brand name Chantix® in the US and Champix® in Europe by Pfizer and is approved for use in smoking cessation therapy. Additionally, the drug has been trialled in the treatment of alcohol and drug dependence (Mitchell et al., Pyschopharmacology, October 2012, 223, 3, pages 299 to 306, and Crunelle et al., European Neuropsychopharmacology, February 2010, 20, 2, pages 69 to 79).

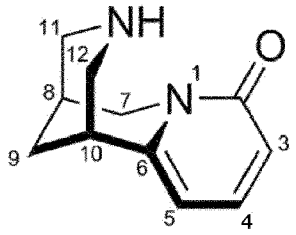
[0011] Mihalak et al. (Molecular Pharmacology, 2006, September, 70(3), pages 801 to 805) found that varenicline is a partial agonist at α4β2 receptors, is a low potency agonist at α 3β4 receptors, is a partial agonist at α3β2 and α6 receptors, and is a potent agonist at α 7 receptors.

[0012] A further drug used in smoking cessation therapy is cytisine. Cytisine is a naturally occurring, pyridone-containing alkaloid known to be a partial agonist of nAChRs. Pharmacologically, cytisine shows a high degree of similarity to nicotine and has already been used successfully as a smoking cessation aid for many years. The chemical structure of cytisine (or more specifically, the (-) enantiomer of cytisine) is shown below:



[0013] While cytisine is a safe and efficacious therapy for smoking cessation, there have been attempts to produce functionalised derivatives of that compound.

[0014] Conventionally, several different numbering systems for cytisine have been used. For the purposes of this discussion, and the disclosure of the present invention, the following numbering system will be used:

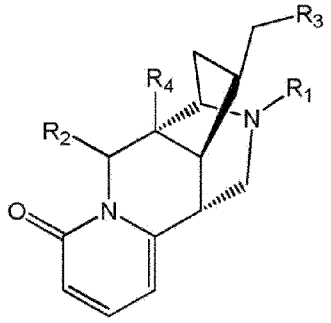


[0015] Kozikowski et al., in two papers (Journal of Medicinal Chemistry, 2006, 49, pages 2673 to 2676 and ChemMedChem, 2007, 2, pages 1157 to 1161) summarised work conducted previously on the introduction of substituents on the cytisine structure (principally at the 3- and 5- positions), as well as disclosing the synthesis of reportedly novel racemic analogues, including substituents at the 3-, 4- or 7- positions.

[0016] In the 2006 paper by Kozikowski *et al.,* racemic 4-substituted compounds were reported as not showing agonist activity at the α4β2 receptor subtype, despite high selectivity for this subtype. The results presented in the 2006 paper indicated that 4-substituted analogs of cytisine are weak antagonists of α4β2 receptor subtype.

[0017] Thus, the work done by Kozikowski *et al.* indicated that the activity of 4- substituted cytisine analogs was significantly different to the known addiction therapies cytisine and varenicline.

[0018] More recently, work by other teams has focussed on substitutions at other positions on the cytisine structure. For example, in International Patent Publication No. WO2014/001348, analogs of cytisine having the general structure shown below were synthesised:



[0019] Additionally, in Chinese Patent Publication No. 103509021, cytisine analogs including substituents at the 5- position and / or at the nitrogen atom on the piperidine ring.

[0020] Rouden et al., (Chemical Reviews, 2014, 114, pages 712 to 778) have prepared a comprehensive review of all of the different research into functionalised derivatives of cytisine.

[0021] Durkin et al., (Synlett 2010(18): 2789-2791; DOI: 10.1055/s-0030-1259006) disclose the application of a lactam enolate-pyrisone addition sequence for the generation of 4-halocytisines.

[0022] WO 2008/011484 describes compounds including a number of 4-substituted cytisine analogs as nicotinic desensitizers.

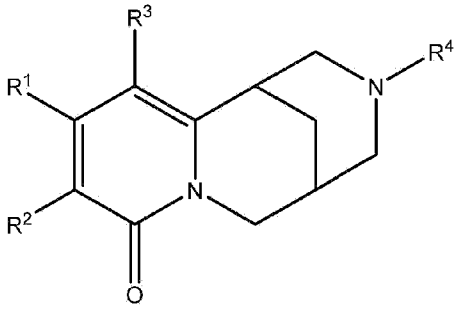
[0023] Chellappan et al., (Journal of Medicinal Chemistry, Americal Chemical Society, Vol. 49, no. 9, 6 April 2006, pp 2673-2676) discloses the synthesis and pharmacological properties of certain cytisine derivatives, including 4-substituted derivatives.

[0024] WO 2007/115092 relates to substituted cytsine compounds that are useful in treating diseases impacted by a nictotinic Ach receptor. The compounds include 4-substituted compounds.

[0025] US 2013/005689 discloses benzamide compounds for the treatment of addiction.

[0026] Despite the substantial investigations into cytisine analogs, and their potential to provide pharmaceutical agents with improved properties as compared to cytisine and / or other nAChR binding drugs, no such compound, to the inventors' knowledge, has been brought forward into clinical trials, let alone approved as pharmaceutical products. Thus, there remains a need for pharmaceutical agents having improved properties as compared to cytisine, for example improved safety and / or efficacy as medicinal agents, for example in the treatment of addiction.

[0027] According to the present invention, there is provided a synthetic process for conveniently preparing 4-substituted cytisine analogs of formula (I):



(I)

or a pharmaceutically acceptable salt, solvate and / or ester thereof, wherein R^1 to R^4 are as defined below.

[0028] The compounds prepared in accordance with the present invention ('the compounds') are useful in medicine. For example, they may be used to prevent, treat or ameliorate

symptoms of CNS disorders including addictive disorders such as nicotine, alcohol, drug addiction (eg opioid addiction).

[0029] The compounds of have been identified by the inventors as having use in therapeutic applications, particularly in the treatment of addiction and / or dependence on drugs, alcohol and / or tobacco. While a limited number of 4-substituted analogues of cytisine have previously been disclosed, the limited binding data relating to those compounds that was made available did not demonstrate their applicability for use in medicine and the authors of those disclosures concluded that those compounds exhibited weak potency as modulators of receptors associated with neurological conditions including dependency and addiction. For example, Rouden et al., in Chemical Reviews, 2014, 114, pages 712 to 778, concluded (on page 732 of that document) that the 4-cytisine analogues tested exhibited 'no agonist activity and exhibited very low potencies in inhibiting nicotine activated channel function at both the α4β2 and α3β4 receptors'.

[0030] Surprisingly and unexpectedly, however, the inventors have found that these compounds may exhibit advantages not previously realised, on the basis of newly generated data which is discussed below in greater detail.

[0031] Compounds having a wide range of substituents at the 4-position of cytisine have been identified as being of therapeutic benefit by the inventors.

[0032] As described herein, the compounds may be substituted with one or more substituents, as described herein, or as exemplified by particular compounds disclosed herein.

[0033] As used herein the term "aliphatic" encompasses the terms alkyl, alkenyl, alkynyl, each of which being optionally substituted as set forth below.

[0034] As used herein, an "alkyl" group refers to a saturated aliphatic hydrocarbon group containing 1-12 (e.g., 1-8, 1-6, or 1-4) carbon atoms. An alkyl group can be straight or branched. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-heptyl, or 2-ethylhexyl. An alkyl group can be substituted (i.e., optionally substituted) with one or more substituents such as halo, phospho, cycloaliphatic [e.g., cycloalkyl or cycloalkenyl], heterocycloaliphatic [e.g., heterocycloalkyl or heterocycloalkenyl], aryl, heteroaryl, alkoxy, aroyl, heteroaroyl, acyl [e.g., (aliphatic)carbonyl, (cycloaliphatic)carbonyl, or (heterocycloaliphatic)carbonyl], nitro, cyano, amido [e.g., (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalky^carbonylamino, (heterocycloalkylalky^carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino alkylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl], amino [e.g., aliphaticamino, cycloaliphaticamino, or heterocycloaliphaticarnino], sulfonyl [e.g., aliphatic-SO_2-], sulfinyl, sulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carboxy, carbamoyl, cycloaliphaticoxy, heterocycloaliphaticoxy, aryloxy, heteroaiyloxy, aralkyloxy, heteroarylalkoxy, alkoxycarbonyl,

alkylcarbonyloxy, or hydroxy.

[0035] As used herein, an "alkenyl" group refers to an aliphatic carbon group that contains 2-12 (e.g., 2-8, 2-6, or 2-4) carbon atoms and at least one double bond. Like an alkyl group, an alkenyl group can be straight or branched. Examples of an alkenyl group include, but are not limited to allyl, vinyl, isoprenyl 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 5-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl and 6-hexenyl. An alkenyl group can be optionally substituted with one or more substituents such as halo, phospho, cycloaliphatic [e.g., cycloalkyl or cycloalkenyl], heterocycloaliphatic [e.g., heterocycloalkyl or heterocycloalkenyl], aryl, heteroaryl, alkoxy, aroyl, heteroaroyl, acyl [e.g., (aliphatic)carbonyl, (cycloaliphatic)carbonyl, or (heterocycloaliphatic)carbonyl], nitro, cyano, amido [e.g., (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino alkylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl], amino [e.g., aliphaticamino, cycloaliphaticamino, heterocycloaliphaticamino, or aliphaticsulfonylamino], sulfonyl [e.g., alkyl-SO_2-, cycloaliphatic-SO_2-, or aryl-SO_2-], sulflnyl, sulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carboxy, carbamoyl, cycloaliphaticoxy, heterocycloaliphaticoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkoxy, alkoxycarbonyl, alkylcarbonyloxy, or hydroxy.

[0036] As used herein, an "alkynyl" group refers to an aliphatic carbon group that contains 2-12 (e.g., 2-8, 2-6, or 2-4) carbon atoms and has at least one triple bond. An alkynyl group can be straight or branched. Examples of an alkynyl group include, but are not limited to, propargyl, butynyl, acetylenyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 5-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and 6-hexynyl. An alkynyl group can be optionally substituted with one or more substituents such as aroyl, heteroaroyl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, nitro, carboxy, cyano, halo, hydroxy, sulfo, mercapto, sulfanyl [e.g., aliphaticsulfanyl or cycloaliphaticsulfanyl], sulfinyl [e.g., aliphaticsulfinyl or cycloaliphaticsulfinyl], sulfonyl [e.g., aliphatic-SO_2-, aliphaticamino-SO_2-, or cycloaliphatic-SO_2-], amido [e.g., aminocarbonyl, alkylaminocarbonyl, alkylcarbonylamino, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, cycloalkylcarbonylamino, arylaminocarbonyl, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (cycloalkylalkyl)carbonylamino, heteroaralkylcarbonylamino, heteroarylcarbonylamino or heteroarylaminocarbonyl], urea, thiourea, sulfamoyl, sulfamide, alkoxycarbonyl, alkylcarbonyloxy, cycloaliphatic, heterocycloaliphatic, aryl, heteroaryl, acyl [e.g., (cycloaliphatic)carbonyl or (heterocycloaliphatic)carbonyl], amino [e.g., aliphaticamino], sulfoxy, oxo, carboxy, carbamoyl, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, or (heteroaryl)alkoxy.

[0037] As used herein, an "aryl" group used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl" refers to monocyclic (e.g., phenyl); bicyclic (e.g., indenyl, naphthalenyl, tetrahydronaphthyl, tetrahydroindenyl); and tricyclic (e.g., fluorenyl tetrahydrofluorenyl, tetrahydroanthracenyl, anthracenyl) ring systems in which the monocyclic

ring system is aromatic or at least one of the rings in a bicyclic or tricyclic ring system is aromatic. The bicyclic and tricyclic groups include benzofused 2-3 membered carbocyclic rings. For example, a benzofused group includes phenyl fused with two or more C_{4-8} carbocyclic moieties. An aryl is optionally substituted with one or more substituents including aliphatic [e.g., alkyl, alkenyl, or alkynyl]; cycloaliphatic; (cycloaliphatic)aliphatic; heterocycloaliphatic; (heterocycloaliphatic)aliphatic; aryl; heteroaryl; alkoxy; (cycloaliphatic)oxy; (heterocycloaliphatic)oxy; aryloxy; heteroaryloxy; (araliphatic)oxy; (heteroaraliphatic)oxy; aroyl; heteroaroyl; amino; oxo (on a non-aromatic carbocyclic ring of a benzofused bicyclic or tricyclic aryl); nitro; carboxy; amido; acyl [e.g., (aliphatic)carbonyl; (cycloaliphatic)carbonyl; ((cycloaliphatic)aliphatic)carbonyl; (araliphatic)carbonyl; (heterocycloaliphatic)carbonyl; ((heterocycloaliphatic)aliphatic)carbonyl; or (heteroaraliphatic)carbonyl]; sulfonyl [e.g., aliphatic-SO_2- or amino-SO_2-]; sulfinyl [e.g., aliphatic-S(O)- or cycloaliphatic-S(O)-]; sulfanyl [e.g., aliphatic-S-]; cyano; halo; hydroxy; mercapto; sulfoxy; urea; thiourea; sulfamoyl; sulfamide; or carbamoyl. Alternatively, an aryl can be unsubstituted.

[0038] Non-limiting examples of substituted aryls include haloaryl [e.g., mono-, di (such as p,m-dihaloaryl), and (trihalo)aryl]; (carboxy)aryl [e.g., (alkoxycarbonyl)aryl, ((aralkyl)carbonyloxy)aryl, and (alkoxycarbonyl)aryl]; (amido)aryl [e.g., (aminocarbonyl)aryl, (((alkylamino)alkyl)aminocarbonyl)aryl, (alkylcarbonyl)aminoaryl, (arylaminocarbonyl)aryl, and (((heteroaryl)amino)carbonyl)aryl]; aminoaryl [e.g., ((alkylsulfonyl)amino)aryl or ((dialkyl)amino)aryl; (cyanoalkyl)aryl; (alkoxy)aryl; (sulfamoyl)aryl [e.g., (aminosulfonyl)aryl]; (alkylsulfonyl)aryl; (cyano)aryl; (hydroxy alkyl)aryl; ((alkoxy)alkyl)aryl; (hydroxy)aryl, ((carboxy)alkyl)aryl; (((dialkyl)amino)alkyl)aryl; (nitroalkyl)aryl; (((alkylsulfonyl)amino)alkyl)aryl; ((heterocycloaliphatic)carbonyl)aryl; ((alkylsulfonyl)alkyl)aryl; (cyanoalkyl)aryl; (hydroxyalkyl)aryl; (alkylcarbonyl)aryl; alkylaryl; (trihaloalkyl)aryl; p-amino-m-alkoxycarbonylaryl; p-amino-m-cyanoaryl; p-halo-m-aminoaryl; or (m-(heterocycloaliphatic)-o-(alkyl))aryl.

[0039] As used herein, an "araliphatic" such as an "aralkyl" group refers to an aliphatic group (e.g., a C_{1-4} alkyl group) that is substituted with an aryl group. "Aliphatic," "alkyl," and "aryl" are defined herein. An example of an araliphatic such as an aralkyl group is benzyl.

[0040] As used herein, an "aralkyl" group refers to an alkyl group (e.g., a C_{1-4} alkyl group) that is substituted with an aryl group. Both "alkyl" and "aryl" have been defined above. An example of an aralkyl group is benzyl. An aralkyl is optionally substituted with one or more substituents such as aliphatic [e.g., alkyl, alkenyl, or alkynyl, including carboxyalkyl, hydroxyalkyl, or haloalkyl such as trifluoromethyl], cycloaliphatic [e.g., cycloalkyl or cycloalkenyl], (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxy carbonyl, alkylcarbonyloxy, amido [e.g., aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, or

heteroaralkylcarbonylamino], cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0041] As used herein, a "bicyclic ring system" includes 8-12 (e.g., 9, 10, or 11) membered structures that form two rings, wherein the two rings have at least one atom in common (e.g., 2 atoms in common). Bicyclic ring systems include bicycloaliphatics (e.g., bicycloalkyl or bicycloalkenyl), bicycloheteroaliphatics, bicyclic aryls, and bicyclic heteroaryls.

[0042] As used herein, a "carbocycle" or "cycloaliphatic" group encompasses a "cycloalkyl" group and a "cycloalkenyl" group, each of which being optionally substituted as set forth below.

[0043] As used herein, a "cycloalkyl" group refers to a saturated carbocyclic mono- or bicyclic (fused or bridged) ring of 3-10 (e.g., 5-10) carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, norbornyl, cubyl, octahydro-indenyl, decahydro-naphthyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.2.]decyl, bicyclo[2.2.2]octyl, adamantyl, or ((aminocarbonyl)cycloalkyl)cycloalkyl.

[0044] A "cycloalkenyl" group, as used herein, refers to a non-aromatic carbocyclic ring of 3-10 (e.g., 4-8) carbon atoms having one or more double bonds. Examples of cycloalkenyl groups include cyclopentenyl, 1,4-cyclohexa-di-enyl, cycloheptenyl, cyclooctenyl, hexahydro-indenyl, octahydro-naphthyl, cyclohexenyl, cyclopentenyl, bicyclo[2.2.2]octenyl, or bicyclo[3.3.1]nonenyl.

[0045] A cycloalkyl or cycloalkenyl group can be optionally substituted with one or more substituents such as phosphor, aliphatic [e.g., alkyl, alkenyl, or alkynyl], cycloaliphatic, (cycloaliphatic) aliphatic, heterocycloaliphatic, (heterocycloaliphatic) aliphatic, aryl, heteroaryl, alkoxy, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, aryloxy, heteroaryloxy, (araliphatic)oxy, (heteroaraliphatic)oxy, aroyl, heteroaroyl, amino, amido [e.g., (aliphatic)carbonylamino, (cycloaliphatic)carbonylamino, ((cycloaliphatic)aliphatic)carbonylamino, (aryl)carbonylamino, (araliphatic)carbonylamino, (heterocycloaliphatic)carbonylamino, ((heterocycloaliphatic)aliphatic)carbonylamino, (heteroaryl)carbonylamino, or (heteroaraliphatic)carbonylamino], nitro, carboxy [e.g., HOOC-, alkoxycarbonyl, or alkylcarbonyloxy], acyl [e.g., (cycloaliphatic)carbonyl, ((cycloaliphatic) aliphatic)carbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, or (heteroaraliphatic)carbonyl], cyano, halo, hydroxy, mercapto, sulfonyl [e.g., alkyl-SO_2- and aryl-SO_2-], sulfinyl [e.g., alkyl-S(O)-], sulfanyl [e.g., alkyl-S-], sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0046] As used herein, the term "heterocycle" or "heterocycloaliphatic" encompasses a heterocycloalkyl group and a heterocycloalkenyl group, each of which being optionally substituted as set forth below.

[0047] As used herein, a "heterocycloalkyl" group refers to a 3-10 membered mono- or bicylic

(fused or bridged) (e.g., 5- to 10-membered mono- or bicyclic) saturated ring structure, in which one or more of the ring atoms is a heteroatom (e.g., N, O, S, or combinations thereof). Examples of a heterocycloalkyl group include aziridinyl, piperidyl, piperazyl, tetrahydropyranyl, tetrahydrofuryl, thietanyl, oxolanyl, dioxanyl, dioxolanyl, thianyl, dithianyl trithianyl, thiomorpholinyl, 1,3-dioxolanyl, imidazolidinyl, oxazolidyl, oxiranyl, oxetanyl, isoxazolidyl, morpholinyl, pyrrolidonyl, pyrazolidinyl, tetrahydrothiophenyl, oxathionlanyl, pyranyl, thiomorpholyl, octahydrobenzofuryl, octahydrochromenyl, octahydrothiochromenyl, octahydroindolyl, octahydropyrindinyl, decahydroquinolinyl, octahydrobenzo[b]thiopheneyl, 2-oxa-bicyclo[2.2.2]octyl, 1-aza-bicyclo[2.2.2]octyl, 3-aza-bicyclo[3.2.1]octyl, and 2,6-dioxa-tricyclo[3.3.1.$0^{3,7}$]nonyl. A monocyclic heterocycloalkyl group can be fused with a phenyl moiety to form structures, such as tetrahydroisoquinoline, which would be categorized as heteroaryls.

[0048] A "heterocycloalkenyl" group, as used herein, refers to a mono- or bicylic (e.g., 5- to 10-membered mono- or bicyclic) non-aromatic ring structure having one or more double bonds, and wherein one or more of the ring atoms is a heteroatom (e.g., N, O, or S). Monocyclic and bicyclic heterocycloaliphatics are numbered according to standard chemical nomenclature.

[0049] A heterocycloalkyl or heterocycloalkenyl group can be optionally substituted with one or more substituents such as phospho, aliphatic [e.g., alkyl, alkenyl, or alkynyl], cycloaliphatic, (cycloaliphatic)aliphatic, heterocycloaliphatic, (heterocycloaliphatic)aliphatic, aryl, heteroaryl, alkoxy, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, aryloxy, heteroaryloxy, (araliphatic)oxy, (heteroaraliphatic)oxy, aroyl, heteroaroyl, amino, amido [e.g., (aliphatic)carbonylamino, (cycloaliphatic)carbonylamino, ((cycloaliphatic) aliphatic)carbonylamino, (aryl)carbonylamino, (araliphatic)carbonylamino, (heterocycloaliphatic)carbonylamino, ((heterocycloaliphatic) aliphatic)carbonylamino, (heteroaryl)carbonylamino, or (heteroaraliphatic)carbonylamino], nitro, carboxy [e.g., HOOC-, alkoxycarbonyl, or alkylcarbonyloxy], acyl [e.g., (cycloaliphatic)carbonyl, ((cycloaliphatic) aliphatic) carbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, or (heteroaraliphatic)carbonyl], nitro, cyano, halo, hydroxy, mercapto, sulfonyl [e.g., alkylsulfonyl or arylsulfonyl], sulfinyl [e.g., alkylsulfinyl], sulfanyl [e.g., alkylsulfanyl], sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0050] A "heteroaryl" group, as used herein, refers to a monocyclic, bicyclic, or tricyclic ring system having 4 to 15 ring atoms wherein one or more of the ring atoms is a heteroatom (e.g., N, O, S, or combinations thereof) and in which the monocyclic ring system is aromatic or at least one of the rings in the bicyclic or tricyclic ring systems is aromatic. A heteroaryl group includes a benzofused ring system having 2 to 3 rings. For example, a benzofused group includes benzo fused with one or two 4 to 8 membered heterocycloaliphatic moieties (e.g., indolizyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furyl, benzo [b]thiophenyl, quinolinyl, or isoquinolinyl). Some examples of heteroaryl are azetidinyl, pyridyl (e.g. 2-pyridyl, 3-pyridyl, 4-pyridyl), pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, 1H-indazolyl, furyl, pyrrolyl, thienyl, thiazolyl, thiophenyl, oxazolyl, isoxazolyl, isothiazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, imidazolyl, diazolyl, triazolyl, tetrazolyl, benzofuryl, isoquinolinyl, benzthiazolyl, xanthene, thioxanthene, phenothiazine, dihydroindole, benzo[1,3]dioxole, benzo[b]furyl,

benzo[b]thiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, puryl, cinnolyl, quinolyl, quinazolyl, cinnolyl, phthalazyl, quinazolyl, quinoxalyl, isoquinolyl, 4H-quinolizyl, benzo-1,2,5-thiadiazolyl, or 1 ,8-naphthyridyl.

[0051] Without limitation, monocyclic heteroaryls include furyl, thiophenyl, 2H-pyrrolyl, pyrrolyl, oxazolyl, thazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4H-pyranyl, pyridyl, pyridazyl, pyrimidyl, pyrazolyl, pyrazyl, or 1,3,5-triazyl. Monocyclic heteroaryls are numbered according to standard chemical nomenclature.

[0052] Without limitation, bicyclic heteroaryls include indolizyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furyl. benzo[b]thiophenyl, quinolinyl, isoquinolinyl, indolizinyl, isoindolyl, indolyl, benzo[b]furyl, benzo[b]thiophenyl, indazolyl, benzimidazyl, benzthiazolyl, purinyl, 4H-quinolizyl, quinolyl, isoquinolyl, cinnolyl, phthalazyl, quinazolyl, quinoxalyl, 1,8-naphthyridyl, or pteridyl. Bicyclic heteroaryls are numbered according to standard chemical nomenclature.

[0053] A heteroaryl is optionally substituted with one or more substituents such as aliphatic [e.g., alkyl, alkenyl, or alkynyl]; cycloaliphatic; (cycloaliphatic) aliphatic; heterocycloaliphatic; (heterocycloaliphatic)aliphatic; aryl; heteroaryl; alkoxy; (cycloaliphatic)oxy; (heterocycloaliphatic)oxy; aryloxy; heteroaryloxy; (araliphatic)oxy; (heteroaraliphatic)oxy; aroyl; heteroaroyl; amino; oxo (on a non-aromatic carbocyclic or heterocyclic ring of a bicyclic or tricyclic heteroaryl); carboxy; amido; acyl [e.g., (aliphatic)carbonyl; (cycloaliphatic)carbonyl; ((cycloaliphatic)aliphatic)carbonyl; (araliphatic)carbonyl; (heterocycloaliphatic)carbonyl; ((heterocycloaliphatic)aliphatic)carbonyl; or (heteroaraliphatic)carbonyl]; sulfonyl [e.g., aliphaticsulfonyl or aminosulfonyl]; sulfinyl [e.g., aliphaticsulfinyl]; sulfanyl [e.g., aliphaticsulfanyl]; nitro; cyano; halo; hydroxy; mercapto; sulfoxy; urea; thiourea; sulfamoyl; sulfamide; or carbamoyl. Alternatively, a heteroaryl can be unsubstituted.

[0054] Non-limiting examples of substituted heteroaryls include (halo)heteroaryl [e.g., mono- and di-(halo)heteroaryl]; (carboxy)heteroaryl [e.g., (alkoxycarbonyl)heteroaryl]; cyanoheteroaryl; aminoheteroaryl [e.g., ((alkylsulfonyl)amino)heteroaryl and ((dialkyl)amino)heteroaryl]; (amido)heteroaryl [e.g., aminocarbonylheteroaryl, ((alkylcarbonyl)amino)heteroaryl, ((((alkyl)amino)alkyl)aminocarbonyl)heteroaryl, (((heteroaryl)amino)carbonyl)heteroaryl, ((heterocycloaliphatic)carbonyl)heteroaryl, and ((alkylcarbonyl)amino)heteroaryl]; (cyanoalkyl)heteroaryl; (alkoxy)heteroaryl; (sulfamoyl)heteroaryl [e.g., (aminosulfonyl)heteroaryl]; (sulfonyl)heteroaryl [e.g., (alkylsulfonyl)heteroaryl]; (hydroxyalkyl)heteroaryl; (alkoxyalkyl)heteroaryl; (hydroxy)heteroaryl; ((carboxy)alkyl)heteroaryl; (((dialkyl)amino)alkyl]heteroaryl; (heterocycloaliphatic)heteroaryl; (cycloaliphatic)heteroaryl; (nitroalkyl)heteroaryl; (((alkylsulfonyl)amino)alkyl)heteroaryl; ((alkylsulfonyl)alkyl)heteroaryl; (cyanoalkyl)heteroaryl; (acyl)heteroaryl [e.g., (alkylcarbonyl)heteroaryl]; (alkyl)heteroaryl, and (haloalkyl)heteroaryl [e.g., trihaloalkylheteroaryl].

[0055] A "heteroaraliphatic" (such as a heteroaralkyl group) as used herein, refers to an aliphatic group (e.g., a C_{1-4} alkyl group) that is substituted with a heteroaryl group. "Aliphatic,"

"alkyl," and "heteroaryl" have been defined above.

[0056] A "heteroaralkyl" group, as used herein, refers to an alkyl group (e.g., a C_{1-4} alkyl group) that is substituted with a heteroaryl group. Both "alkyl" and "heteroaryl" have been defined above. A heteroaralkyl is optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino. (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0057] As used herein, "cyclic moiety" and "cyclic group" refer to mono-, bi-, and tricyclic ring systems including cycloaliphatic, heterocycloaliphatic, aryl, or heteroaryl, each of which has been previously defined.

[0058] As used herein, a "bridged bicyclic ring system" refers to a bicyclic heterocyclicaliphatic ring system or bicyclic cycloaliphatic ring system in which the rings are bridged. Examples of bridged bicyclic ring systems include, but are not limited to, adamantanyl, norbornanyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.2.3]nonyl, 2-oxabicyclo[2.2.2]octyl, 1-azabicyclo[2.2.2]octyl, 3-azabicyclo[3.2.1]octyl, and 2,6-dioxa-tricyclo[3.3.1.$0^{3,7}$]nonyl. A bridged bicyclic ring system can be optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0059] As used herein, an "amido" encompasses both "aminocarbonyl" and "carbonylamino". These terms when used alone or in connection with another group refer to an amido group such as -N(R^X)-C(O)-R^Y or -C(O)-N(R^X)$_2$, when used terminally, and -C(O)-N(R^X)- or -N(R^X)-C(O)- when used internally, wherein R^X and R^Y are defined below. Examples of amido groups include alkylamido (such as alkylcarbonylamino or alkylaminocarbonyl), (heterocycloaliphatic)amido, (heteroaralkyl)amido, (heteroaryl)amido, (heterocycloalkyl)alkylamido, arylamido, aralkylamido, (cycloalkyl)alkylamido, or cyclo alkylamido.

[0060] As used herein, an "amino" group refers to $-NR^XR^Y$ wherein each of R^X and R^Y is independently hydrogen, aliphatic, cycloaliphatic, (cycloaliphatic)aliphatic, aryl, araliphatic, heterocycloaliphatic, (heterocycloaliphatic)aliphatic, heteroaryl, carboxy, sulfanyl, sulfinyl, sulfonyl, (aliphatic)carbonyl, (cycloaliphatic)carbonyl, ((cycloaliphatic)aliphatic)carbonyl, arylcarbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, (heteroaryl)carbonyl, or (heteroaraliphatic)carbonyl, each of which being defined herein and being optionally substituted. Examples of amino groups include alkylamino, dialkylamino, or arylamino. When the term "amino" is not the terminal group (e.g., alkylcarbonylamino), it is represented by $-NR^X-$. R^X has the same meaning as defined above.

[0061] As used herein, an "acyl" group refers to a formyl group or R^X-C(O)- (such as alkyl-C(O)-, also referred to as "alkylcarbonyl") where R^X and "alkyl" have been defined previously. Acetyl and pivaloyl are examples of acyl groups.

[0062] As used herein, an "aroyl" or "heteroaroyl" refers to an aryl-C(O)- or a heteroaryl-C(O)-. The aryl and heteroaryl portion of the aroyl or heteroaroyl is optionally substituted as previously defined.

[0063] As used herein, an "alkoxy" group refers to an alkyl-O- group where "alkyl" has been defined previously.

[0064] As used herein, a "carbamoyl" group refers to a group having the structure -O-CO-NR^XR^Y or $-NR^X$-CO-O-R^Z, wherein R^X and R^Y have been defined above and R^Z can be aliphatic, aryl, araliphatic, heterocycloaliphatic, heteroaryl, or heteroaraliphatic.

[0065] As used herein, a "carboxy" group refers to -COOH, $-COOR^X$, -OC(O)H, $-OC(O)R^X$, when used as a terminal group; or -OC(O)- or -C(O)O- when used as an internal group.

[0066] As used herein, a "haloaliphatic" group refers to an aliphatic group substituted with 1-3 halogen atoms. For instance, the term haloalkyl includes the group -CF3.

[0067] As used herein, a "mercapto" group refers to -SH.

[0068] As used herein, a "sulfo" group refers to $-SO_3H$ or $-SO_3R^X$ when used terminally or $-S(O)_3-$ when used internally.

[0069] As used herein, a "sulfamide" group refers to the structure $-NR^X-S(O)_2-NR^YR^Z$ when used terminally and $-NR^X-S(O)_2-NR^Y-$ when used internally, wherein R^X, R^Y, and R^Z have been defined above.

[0070] As used herein, a "sulfonamide" group refers to the structure $-S(O)_2-NR^XR^Y$ or $-NR^X-S(O)_2-R^Z$ when used terminally; or $-S(O)_2-NR^X-$ or $-NR^X-S(O)_2-$ when used internally, wherein R^X, R^Y, and R^Z are defined above.

[0071] As used herein a "sulfanyl" group refers to $-S-R^X$ when used terminally and -S- when used internally, wherein R^X has been defined above. Examples of sulfanyls include aliphatic-S-, cycloaliphatic-S-, aryl-S-, or the like.

[0072] As used herein a "sulfinyl" group refers to $-S(O)-R^X$ when used terminally and -S(O)- when used internally, wherein R^X has been defined above. Exemplary sulfinyl groups include aliphatic-S(O)-, aryl-S(O)-, (cycloaliphatic(aliphatic))-S(O)-, cycloalkyl-S(O)-, heterocycloaliphatic-S(O)-, heteroaryl-S(O)-, or the like.

[0073] As used herein, a "sulfonyl" group refers to-$S(O)_2-R^X$ when used terminally and $-S(O)_2-$ when used internally, wherein R^X has been defined above. Exemplary sulfonyl groups include aliphatic-$S(O)_2$-, aryl-$S(O)_2$-, (cycloaliphatic(aliphatic))-$S(O)_2$-, cycloaliphatic-$S(O)_2$-, heterocycloaliphatic-$S(O)_2$-, heteroaryl-$S(O)_2$-, (cycloaliphatic(amido(aliphatic)))-$S(O)_2$-or the like.

[0074] As used herein, a "sulfoxy" group refers to $-O-SO-R^X$ or $-SO-O-R^X$, when used terminally and -O-S(O)- or -S(O)-O- when used internally, where R^X has been defined above.

[0075] As used herein, a "halogen" or "halo" group refers to fluorine, chlorine, bromine or iodine.

[0076] As used herein, an "alkoxycarbonyl," which is encompassed by the term carboxy, used alone or in connection with another group refers to a group such as alkyl-O-C(O)-.

[0077] As used herein, an "alkoxyalkyl" refers to an alkyl group such as alkyl-O-alkyl-, wherein alkyl has been defined above.

[0078] As used herein, a "carbonyl" refers to -C(O)-.

[0079] As used herein, an "oxo" refers to =O.

[0080] As used herein, the term "phospho" refers to phosphinates and phosphonates. Examples of phosphinates and phosphonates include $-P(O)(R^P)_2$, wherein R^P is aliphatic, alkoxy, aryloxy, heteroaryloxy, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, aryl, heteroaryl, cycloaliphatic or amino.

[0081] As used herein, an "aminoalkyl" refers to the structure $(R^X)_2N$-alkyl-.

[0082] As used herein, a "cyanoalkyl" refers to the structure (NC)-alkyl-.

[0083] As used herein, a "urea" group refers to the structure $-NR^X-CO-NR^YR^Z$ and a "thiourea" group refers to the structure $-NR^X-CS-NR^YR^Z$ when used terminally and $-NR^X-$ CO-NR^Y- or -NR^X-CS-NR^Y- when used internally, wherein R^X, R^Y, and R^Z have been defined above.

[0084] As used herein, an "aliphatic chain" refers to a branched or straight aliphatic group (e.g., alkyl groups, alkenyl groups, or alkynyl groups). A straight aliphatic chain has the structure $-[CH_2]_V-$, where v is 1-12. A branched aliphatic chain is a straight aliphatic chain that is substituted with one or more aliphatic groups. A branched aliphatic chain has the structure -$[CQQ]_V$-. where each Q is independently a hydrogen or an aliphatic group; however, Q shall be an aliphatic group in at least one instance. The term aliphatic chain includes alkyl chains, alkenyl chains, and alkynyl chains, where alkyl, alkenyl, and alkynyl are defined above.

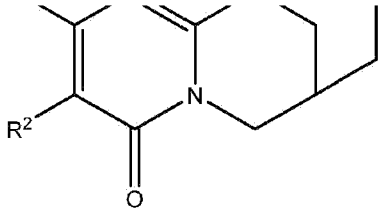
[0085] The phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." As described herein, compounds can optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species. As described herein, the variables R^1, R^2, R^3 and R^4, and other variables contained in formulae described herein encompass specific groups, such as alkyl and aryl. Unless otherwise noted, each of the specific groups for the variables R^1, R^2, R^3 and R^4 and other variables contained therein can be optionally substituted with one or more substituents described herein.

[0086] Each substituent of a specific group may be further optionally substituted with one to three of halo, cyano, oxo, alkoxy, hydroxy, amino, nitro, aryl, cycloaliphatic, heterocycloaliphatic, heteroaryl, haloalkyl, and alkyl. For instance, an alkyl group can be substituted with alkylsulfanyl and the alkylsulfanyl can be optionally substituted with one to three of halo, cyano, oxo, alkoxy, hydroxy, amino, nitro, aryl, haloalkyl, and alkyl. As an additional example, the cycloalkyl portion of a (cycloalkyl)carbonylamino can be optionally substituted with one to three of halo, cyano, alkoxy, hydroxy, nitro, haloalkyl, and alkyl. When two alkoxy groups are bound to the same atom or adjacent atoms, the two alkxoy groups can form a ring together with the atom(s) to which they are bound.

[0087] Compounds of the present invention are useful nAChRs and are useful in medicine, including for the treatment of CNS disorders such as addiction disorders.

[0088] According to the present invention, there is provided a process for preparing a compound of formula (I):





(I)

or a pharmaceutically acceptable salt, solvate and / or ester thereof, wherein:

R^1 is

- hydroxyl;
- halogen;
- optionally substituted aliphatic;
- optionally substituted cycloaliphatic;
- optionally substituted heterocycloaliphatic;
- optionally substituted aryl;
- optionally substituted heteroaryl;
- $-(CH_2)_m-NR^6R^7R^8$, wherein

  ◦ R^6 and R^7 are each independently selected from the group consisting of hydrogen, halo, hydroxy, oxo, amino, amido, nitro, cyano, alkoxy, N-alkyl amino, N,N-dialkyl amino, phospho, carbonyl, carboxy, sulfoxy, sulfinyl, sulfonyl, sulfanyl, sulfamide, sulfo, mercapto, carbamoyl, methyl pivalate, trimethylsilyl, urea, thiourea, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted cycloaliphatic, optionally substituted heterocycloaliphatic, optionally substituted heteroaryl, optionally substituted haloalkyl, optionally substituted aroyl, optionally substituted heteroaroyl, optionally substituted acyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycloalkyl or optionally substituted heterocycloalkenyl or

  ◦ one of R^6 or R^7 is $-CO-R^9$, and the other of R^6 or R^7 is as defined above,

  ◦ R^8 is selected from the group consisting of hydrogen, halo, hydroxy, oxo, amino, amido, nitro, cyano, alkoxy, N-alkyl amino, N,N-dialkyl amino, phospho, carbonyl, carboxy, sulfoxy, sulfinyl, sulfonyl, sulfanyl, sulfamide, sulfo, mercapto, carbamoyl, methyl pivalate, trimethylsilyl, urea, thiourea, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted cycloaliphatic, optionally substituted heterocycloaliphatic, optionally substituted heteroaryl, optionally substituted haloalkyl, optionally substituted aroyl, optionally substituted heteroaroyl, optionally substituted acyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycloalkyl or optionally substituted heterocycloalkenyl, or is absent,

◦ R^9 is selected from the group consisting of hydrogen, halo, hydroxy, oxo, amino, amido, nitro, cyano, alkoxy, N-alkyl amino, N,N-dialkyl amino, phospho, carbonyl, carboxy, sulfoxy, sulfinyl, sulfonyl, sulfanyl, sulfamide, sulfo, mercapto, carbamoyl, methyl pivalate, trimethylsilyl, urea, thiourea, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted cycloaliphatic, optionally substituted heterocycloaliphatic, optionally substituted heteroaryl, optionally substituted haloalkyl, optionally substituted aroyl, optionally substituted heteroaroyl, optionally substituted acyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycloalkyl or optionally substituted heterocycloalkenyl,

◦ and m is 0, 1, 2, 3, 4 or 5,

- $-(CH_2)_m-O-(CH_2)_n-R^{10}$, wherein

◦ R^{10} is selected from the group consisting of hydrogen, halo, hydroxy, oxo, amino, amido, nitro, cyano, alkoxy, N-alkyl amino, N,N-dialkyl amino, phospho, carbonyl, carboxy, sulfoxy, sulfinyl, sulfonyl, sulfanyl, sulfamide, sulfo, mercapto, carbamoyl, methyl pivalate, trimethylsilyl, urea, thiourea, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted cycloaliphatic, optionally substituted heterocycloaliphatic, optionally substituted heteroaryl, optionally substituted haloalkyl, optionally substituted aroyl, optionally substituted heteroaroyl, optionally substituted acyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycloalkyl or optionally substituted heterocycloalkenyl, and

◦ m and n are each independently 0, 1, 2, 3, 4 or 5,

- -CN
- $-COOR^{12}$, wherein

◦ R^{12} is selected from the group consisting of hydrogen, halo, hydroxy, oxo, amino, amido, nitro, cyano, alkoxy, N-alkyl amino, N,N-dialkyl amino, phospho, carbonyl, carboxy, sulfoxy, sulfinyl, sulfonyl, sulfanyl, sulfamide, sulfo, mercapto, carbamoyl, methyl pivalate, trimethylsilyl, urea, thiourea, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted cycloaliphatic, optionally substituted heterocycloaliphatic, optionally substituted heteroaryl, optionally substituted haloalkyl, optionally substituted aroyl, optionally substituted heteroaroyl, optionally substituted acyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycloalkyl or optionally substituted heterocycloalkenyl,

- $-(CH_2)_o-CO-(CH_2)_p-R^{13}$, wherein

  - R^{13} is selected from the group consisting of hydrogen, halo, hydroxy, oxo, amino, amido, nitro, cyano, alkoxy, N-alkyl amino, N,N-dialkyl amino, phospho, carbonyl, carboxy, sulfoxy, sulfinyl, sulfonyl, sulfanyl, sulfamide, sulfo, mercapto, carbamoyl, methyl pivalate, trimethylsilyl, urea, thiourea, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted cycloaliphatic, optionally substituted heterocycloaliphatic, optionally substituted heteroaryl, optionally substituted haloalkyl, optionally substituted aroyl, optionally substituted heteroaroyl, optionally substituted acyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycloalkyl or optionally substituted heterocycloalkenyl, and

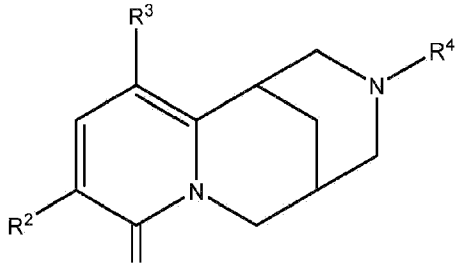
  - o and p are each independently 0, 1, 2, 3, 4 or 5,

- an amino acid or ester thereof,
- acyl chloride,
- a protecting group, or
- cytisine,

R^2, R^3 and R^4 are each independently selected from the group consisting hydrogen, halo, hydroxy, oxo, amino, amido, nitro, cyano, alkoxy, N-alkyl amino, N,N-dialkyl amino, phospho, carbonyl, carboxy, sulfoxy, sulfinyl, sulfonyl, sulfanyl, sulfamide, sulfo, mercapto, carbamoyl, methyl pivalate, trimethylsilyl, urea, thiourea, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted cycloaliphatic, optionally substituted heterocycloaliphatic, optionally substituted heteroaryl, optionally substituted haloalkyl, optionally substituted aroyl, optionally substituted heteroaroyl, optionally substituted acyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycloalkyl or optionally substituted heterocycloalkenyl, amino acid or cytisine, or R^4 may be a protecting group, or a group having the structure $-(CH_2)v$-FORMULA 1, wherein v is 0, 1, 2, 3, 4, 5 or 6 and FORMULA 1 is a compound of Formula (I) as described herein.

[0089] The process comprises:

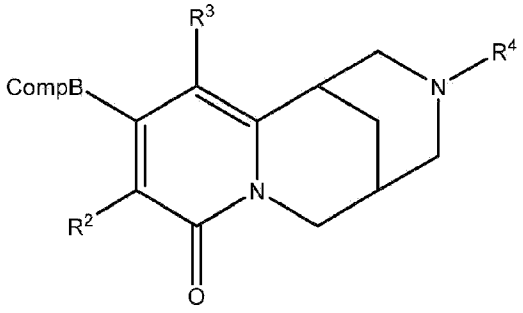
1. i) providing a compound of Formula IIa





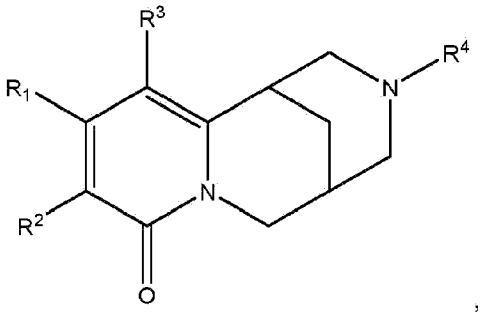
wherein R^2, R^3 and R^4 are as defined above;

2. ii) producing a compound of Formula IIb



wherein R^2, R^3 and R^4 are as defined above, and BComp is a borylated complex, by contacting the compound of Formula IIa with a borylating agent; and

3. iii) replacing BComp with R^1 to produce a compound of Formula I:



,

wherein R^1 is as defined above.

[0090] As explained above, the substituent at the R^1 position may be an optionally substituted aliphatic; optionally substituted cycloaliphatic; optionally substituted hetercycloaliphatic; optionally substituted aryl; optionally heteroaryl.

[0091] In embodiments of the invention, the substituent at the R^1 position may be a C_{1-8}, a C_{1-4} or C_{3-8} alkyl group, which may or may not be substituted, for example, propyl, isopropyl, butyl or tert-butyl. In certain embodiments of the invention, the substituent at the R^1 position may be a substituted C_{1-2} alkyl group or a C_{3-8} optionally substituted alkyl group. In such embodiments, the C_{1-2} alkyl group may be a substituent other than hydroxymethyl or fluoromethyl.

[0092] Examples of substituted alkyl groups that are envisaged as being employed at substituents at the R^1 position in the compounds of the present invention include substituted methyl groups, for example aminomethyl, halogenated methyl e.g. chloromethyl, dichloromethyl, trichloromethyl, difluoromethyl, trifluoromethyl bromomethyl, dibromomethyl or tribromomethyl; substituted ethyl groups, for example 1- or 2-aminoethyl, hydroxyethyl, halogenated ethyl e.g. 2,2,2-trichloroethyl, 2,2,2-tribromoethyl or 2,2,2-trifluoroethyl;

substituted propyl groups, for example 1-, 2- or 3-aminomethyl; hydroxypropyl; or halogenated propyl.

[0093] In embodiments of the invention, the substituent at the R^1 position may be unsubstituted or substituted aryl. For example, the substitutent may be a phenyl group, or may be a substituted phenyl group, for example a halogenated phenyl group, such as chlorophenyl, bromophenyl, fluorophenyl, perchlorophenyl, perbromophenyl, perfluorophenyl; or tolyl, aniline, phenol, styrene, benzonitrile, anisole, acetophenone, benzaldehyde or benzoic acid groups.

[0094] In alternative embodiments, the substituent at the R^1 position may be an optionally substituted heteroaryl, such as benzyloxy pyridine, pyridone (e.g. 2-pyridone), pyridine (e.g. 2-pyridine, 3-pyridine or 4 pyridine), phenyltriazole, optionally substituted triazole, and triazole methylpivalate groups.

[0095] The R^1 substituent may alternatively be an optionally substituted cycloalkyl or heterocycloalkyl, such as cyclopentyl, cyclohexyl, morpholinyl, piperidyl, piperazyl, tetrahydrofuryl, oxolanyl or dioxanyl.

[0096] Examples of optionally substituted alkenyl groups that may be included at the R^1 position include C_{2-8} alkenyl, such as vinyl, acrylate or $-C=C-C_6H_5$ groups.

[0097] Optionally substituted alkynyl groups that may be present at the R^1 position include C_{2-8} alkynyl, $-C\equiv C-C_6H_5$ or $-C\equiv C$-trimethylsilyl groups.

[0098] Additionally, other groups that may be employed as R^1 substituents in the compounds of the present invention include the following groups:

- $(CH_2)_m$-$NR^6R^7R^8$, where R^6, R^7 and R^8 are as defined above. In such embodiments, the compounds may include amine, N-alkyl amine, N,N-dialkyl amine and amide groups as substituents at the R^1 position. Examples of such groups that are envisaged for inclusion at that position include amine, methylamine, ethylamine, propylamine, isopropylamine, benzylamine, dimethylamine, trimethylammonium methyl, dimethylamino methyl, benzamido and acetamido groups. In embodiments of the invention, where m is zero and R^8 is absent, R^6 and R^7 may not both be hydrogen and / or neither of R^6 or R^7 may be an oxo.
- $(CH_2)_n$-O-$(CH_2)_o$-R^{10}, wherein R^{10} is as defined above. In such embodiments, the compounds may include groups including ether linkages at the R^1 position. Examples of such groups that are envisaged for inclusion at that position include methoxy, ethoxy, propoxy, benzyloxy or trifluoromethylbenzyloxy groups. In embodiments of the invention, the proviso applies that the substituent at R^1 is not a propoxymethyl group (i.e. $-CH_2$-O-CH_2-CH_2CH_3), an alkoxymethyl group, or a group having the following structure: $-CH_2$-

$O\text{-}CH_2\text{-}C_6H_4\text{-}R^{12}$ or $\text{-}CH_2\text{-}O\text{-}CH_2\text{-}C_6H_{10}\text{-}R^{12}$, wherein R^{12} is hydrogen, trifluoromethyl, substituted phenyl, halo or fluorine.

- CN
- $COOR^{12}$, wherein R^{12} is as defined above. In such embodiments, the compounds may include carboxylic acid groups or esters at the R^1 position, for example ethyl ester, propyl ester, isopropyl ester, butyl ester or phenyl ester. In embodiments of the invention, the the substituent at R^1 may be a substituent other than a $C_{1\text{-}3}$ alkyl ester group, or a methyl ester group.
- $(CH_2)_p\text{-}CO\text{-}(CH_2)_q\text{-}R^{13}$, wherein R^{13} is as defined above. In such embodiments, the compounds may include ketone or aldehyde groups at the R^1 position, for example acetophenone. In certain embodiments, the substituent at R^1 is a substituent other than $\text{-}CO\text{-}NH_2$.
- an amino acid, for example a naturally occuring amino acid or ester thereof, e.g. alanine, arginine, asparagine, aspartate, cysteine, glutamine, glutamate, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, or methyl, ethyl, propyl or isopropyl esters thereof.

[0099] In embodiments of the invention in which the compounds include an amino acid or ester thereof at the R^1 position, the amino acid (or ester) may be bonded to the pyridine ring on the cytisine basic structure via any atom (e.g. via an oxygen, carbon, sulphur or nitrogen atom), for example, via the oxygen atom in the acid unit thus forming an amide of an amino cytisine, or via the nitrogen atom in the amine unit.

- acyl chloride.
- a protecting group, e.g. a tert-Butyloxycarbonyl (Boc), formyl, acetyl (Ac), succinyl (Suc), methoxysuccinyl (MeOSuc), benzyloxycarbonyl (Cbz), or fluorenylmethoxycarbonyl (Fmoc) or a protected boryl protecting group, optionally having the structure $(RO)_2B\text{-}$ such as (pinacolato)borane (BPin) and (catecholato)borane (BCat). In embodiments of the invention, any protecting group commonly employed in organic synthesis, may be employed, for example those outlined in Gross and Mienhoffer, eds., The Peptides, Vol. 3, Academic Press, New York, 1981, pp. 3-88 ; Green and Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley and Sons, Inc., New York, 1999, the contents of which are incorporated by reference.
- cytisinyl. In embodiments, the compound may be a cytisine-cytisine dimer. The cytisine compounds may be coupled directly to each other, e.g. via the carbon atoms at the 3-, 4- or 5- position of each respective compound. Alternatively, the two cytisine structures may be coupled via a linker, for example via a carbon, oxygen, or nitrogen atom. Where a linker is employed, this may itself bear a functionalising group, e.g. $C_{1\text{-}6}$ alkyl.

[0100] The substituents at positions R^2 to R^4 are as defined above. In embodiments of the invention, R^2 and R^3 or each of R^2, R^3 and R^4 may be hydrogen. Alternatively, R^2 may be halogen while R^3 and R^4 are hydrogen. In some embodiments of the invention, the substituent at R^4 may be a substituent other than C_{2-6} alkyl.

[0101] In embodiments of the invention, the substituent at position R^4 may be a protecting group, e.g. tert-Butyloxycarbonyl (Boc) formyl, acetyl (Ac), succinyl (Suc), methoxysuccinyl (MeOSuc), benzyloxycarbonyl (Cbz), or fluorenylmethoxycarbonyl (Fmoc). or a borylated protecting group, optionally having the structure $B(OR)_2$ such as (pinacolato)borane (BPin) and (catecholato)borane (BCat). In embodiments of the invention, any protecting group commonly employed in organic synthesis, may be employed, for example those outlined in Gross and Mienhoffer, eds., The Peptides, Vol. 3, Academic Press, New York, 1981, pp. 3-88; Green and Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley and Sons, Inc., New York, 1999, the contents of which are incorporated by reference.

[0102] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the compounds. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the compounds. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a 13C- or 14C-enriched carbon are within the scope of the compounds.

[0103] Exemplary compounds include, but are not limited to the following compounds:

4-Bpincytisine

4-Hydroxycytisine

(+)4-Hydroxycytisine

(-)4-Methoxycytisine

4-Methoxycytisine

4-(N-Benzylamino)cytisine

(+)4-(N-Benzylamino)cytisine

(-)4-(2,2,2-Trifluoroethyl)cytisine

4-(2,2,2-Trifluoroethyl)cytisine

(-)4-(Perfluorophenyl)cytisine

4-(Perfluorophenyl)cytisine

(-)4-(2-Pyridinyl)cytisine

4-(2-Pyridinyl)cytisine

(-)4-(3-Pyridinyl)cytisine

4-(3-Pyridinyl)cytisine

(-)4-(4-Pyridinyl)cytisine

4-(4-Pyridinyl)cytisine

4-(4-(2-Benzyloxy)pyridine)cytisine

4-(4-(2-Pyridone))cytisine

(+)4-(4-(2-Pyridone))cytisine

(-)4-Chlorocytisine

(-)4-Iodocytisine

(+)4-Iodocytisine

(-)4-Trifluoromethylcytisine

4-Trifluoromethylcytisine

(-)4-Bromocytisine

(+)4-Aminocytisine

(-)4-Fluorocytisine

4-(N-Methylamino)cytisine

(+)4-(N-Methylamino)cytisine

4-(N, *N*'-dimethylamino)cytisine

(+)4-(N, *N*'-dimethylamino)cytisine

4-(*N*-Benzoylamino)cytisine

(+)4-(N-Benzoylamino)cytisine

(+)4-(*N*-Acetylamino)cytisine

4-(*N*-morpholine)cytisine

(+)4-(*N*-morpholine)cytisine

4-(*N*-(L-proline methyl ester)cytisine

(+)4-(*N*(L-proline methyl ester)cytisine

(-)4-(*N*-(L-proline)cytisine

4-(*N*-(L-proline)cytisine

(-)4-(Carboxymethyl)cytisine

(-)4-Carboxylic acid cytisine

4-Carboxylic acid cytisine

(-)4-(Hydroxymethyl)cytisine

(-)4-((Trifluoromethyl)benzyl)oxycytisine

(-)4-Methylcytisine

()4-Vinylcytisine

(+)4-Vinylcytisine

(-)4-Ethylcytisine

(+)4-p-Tolylcytisine

(-)4-(*N*-2-pyridone)cytisine

4-(*N*-2-pyridone)cytisine

4-(Trimethylsilylacetylene)cytisine

(-)4-(Acetylenyl)cytisine

4-(Acetylenyl)cytisine

4-(Phenylacetylene)cytisine

(+)4-(Phenylacetylene)cytisine

4-(E-2-Propenoate methyl ester)cytisine

(+)4-(E-2-Propenoate methyl ester)cytisine

4-(E-(2-phenylethenyl))cytisine

(+)4-(E-(2-phenylethenyl))cytisine

4-(1-(4-phenyl)-NH-1, 2, 3, triazolyl)cytisine

(+)4-(1-(4-phenyl)-NH-1, 2, 3, triazolyl)cytisine

(-)4-(1,2,3-Triazol-1-yl)methylpivalate)cytisine

(+)4-(1,2,3-Triazol-1-yl)methylpivalate)cytisine

4-(NH-1, 2, 3-triazolyl)cytisine

(+)4-(NH-1, 2, 3-triazolyl)cytisine

4-(N-Ethylamino)cytisine

(+)4-(*N*-Ethylamino)cytisine

4-(*N*-Isopropylamino)cytisine

(+)4-(*N*-Isopropylamino)cytisine

(-)4-Cyanocytisine

4-Cyanocytisine

(-)4-(Carboxyamido)cytisine

(-)4-Aminomethylcytisine

4-Aminomethylcytisine

(-)4-(*N*-methyl-aminomethyl)cytisine

4-(N-methyl-aminomethyl)cytisine

(1*R*, 5S, 10S, 11a*R*)-10-(aminomethyl)decahydro-8H-1,5-methanopyrido[1,2-a][1,5]diazocine-8-one

Amino Bis(cytisine) derivative

Methylamino Bis(cytisine) derivative

(-)4-Tetrazoylcytisine

4-Tetrazoylcytisine

(-)4-(Trimethylammonium)methylcytisine

4-(Trimethylammonium)methylcytisine

(-)4-(N-acetyl)aminomethylcytisine

4-(N-acetyl)aminomethylcytisine

4-(*N*-Piperazine)cytisine

(+)4-(*N*-Piperazine)cytisine

(-)3-(Trifluoromethyl)-4-bromocytisine

3-(Trifluoromethyl)-4-bromocytisine

3-Bromo-4-iodocytisine

(+)3-Bromo-4-iodocytisine

3-Bromo-4-N-methylaminocytisine

(+)3-Bromo-4-N-methylaminocytisine

[0104] While there have been limited disclosures in the prior art of 4-substituted cytisine compounds, no convenient synthesis of such compounds has been proposed previously. To the inventors' knowledge, no synthetic route for obtaining 4-substituted analogs of cytisine which starts from cytisine has been previously disclosed. Instead, such compounds had to be produced from a total synthesis starting from monocyclic materials. See for example, Scheme 1 of Kozikowski et al., ChemMedChem, 2007, 2, pages 1157 to 1161 and Gallagher et al., Synlett, 2010, pages 2798-2791.

[0105] The starting material may be any compound encompassed within Formula IIa as outlined above. However, one advantage of the present invention is that the process can advantageously be operated using cytisine as a starting material. Thus, in embodiments, all of R^2, R^3 and R^4 may be hydrogen. Alternatively, the substituent at position R^4 may be a protecting group, or a group having the structure -(CH_2)v-FORMULA 1, wherein v is 0, 1, 2, 3, 4, 5 or 6 and FORMULA 1 is a compound of Formula (I) as described herein.

[0106] Thus, in embodiments, the compound of Formula IIa may comprise a protecting group at R^4 and the process of the invention may comprise the step of adding the protecting group to a compound of Formula IIa (which encompasses cytisine). Those skilled in the art will be familiar with techniques for adding protecting groups to secondary amines and any process step for doing so is encompassed within the scope of the invention. For example, in embodiments where the protecting group to be added at the R^4 position is Boc (tert-butoxyl carbonyl), the process involves the step of providing a Boc containing reagent (e.g. $(Boc)_2O$) and contacting it with cytisine in an appropriate solvent (e.g. one containing tetrahydrofuran and sodium tricarbonate).

[0107] Thus, in embodiments of the invention, the protecting group present at the R^4 position may be Boc. Alternative protecting groups that may be used include formyl, acetyl (Ac), succinyl (Suc), methoxysuccinyl (MeOSuc), benzyloxycarbonyl (Cbz), or fluorenylmethoxycarbonyl (Fmoc), or a borylated protecting group, optionally having the structure $(RO)_2B\text{-}B(OR)_2$ such as bis(pinacolato)diborane (B_2Pin_2) and bis(catecholato)diborane (B_2Cat_2). In embodiments of the invention, any protecting group commonly employed in organic synthesis, may be employed, for example those outlined in Gross and Mienhoffer, eds., The Peptides, Vol. 3, Academic Press, New York, 1981, pp. 3-88 ; Green and Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley and Sons, Inc., New York, 1999, the contents of which are incorporated by reference.

[0108] The borylated agent employed in step ii) of the process of the present invention may be any borylating agent known to one skilled in the art of borylation chemistry. For example, the borylating agent may be a dialkyloxyborane or an alkylborane. Examples of dialkyloxyboranes include bis(pinacolato)diborane (B_2Pin_2) and bis(catecholato)diborane (B_2Cat_2) as well as any other borylating agent having the general formula $(RO)_2\text{-}B\text{-}B\text{-}(OR)_2$ or $HB(OR)_2$, for example those disclosed in Hartwig et al, Chemical Reviews, 2010, 110, pages 890-931, the contents of which are incorporated by reference. Examples of alkylborane borylating agents include 9-borabicyclo(3.3.1)nonane (9-BBN), B-alkyl-9-oxa-10-borabicyclo[3.3.2]decane (OBBD), disiamylborane, thexylborane and $HB(cHex)_2$.

[0109] In embodiments of the invention, the molar ratio of borylating agent : starting material of Formula IIa may range from about 10 or less : about 1, about 7 or less : about 1, or about 5 or less : about 1. Additionally or alternatively, the molar ratio of borylating agent : starting material of formula IIa may range from about 0.1 or more : about 1, about 0.2 or more : about 1, about 0.3 or more : about 1, about 0.4 or more : about 1, or about 0.5 or more : about 1.

[0110] In certain embodiments of the invention, the borylating agent may be in molar excess as compared to the starting material of Formula IIa. This may be preferable in certain embodiments in which cytisine is employed as the starting material of formula IIa.

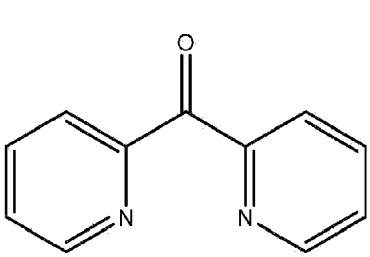
[0111] In alternative embodiments of the invention, the starting material of Formula IIa may be in molar excess as compared to the borylating agent. This may be preferable in certain embodiments in which certain analogs of cytisine (e.g. N-boc cytisine) are employed as the starting material of formula IIa.

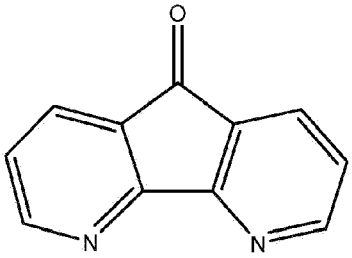
[0112] The reaction in in step ii) of the process of the present invention may be catalysed using catalysts known to those skilled in the art. In embodiments of the invention, step ii) is catalysed, for example using a transition metal catalyst. In preferred embodiments, the catalyst used contains iridium, palladium, zinc, nickel and / or rhodium atoms, which may be provided in the form of an organic co-ordination complex. Specific examples of catalysts that may be used in the process of the present invention include $Ir[(COD)(OMe)]_2$, $PdCl_2$, $Pd/P(t\text{-}bu)_3$, $Pd(dba)_2$, $NiCl_2$, $[RhCl(cod)]_2$, or Et_2Zn. Iodine may also or alternatively be used as a catalyst.

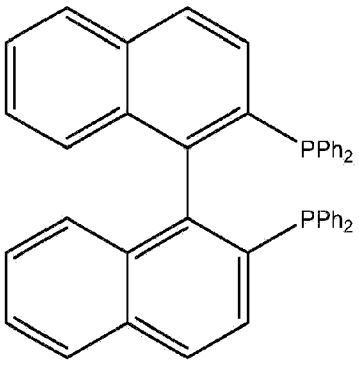
[0113] Step ii) of the process of the present invention may be carried out in a solvent. Any solvent which is capable of permitting the borylation process to proceed may be employed in the process of the present invention. Examples of solvents that may be employed include esters (e.g. ethyl acetate), ethers (e.g. dioxane, tetrahydrofuran), ketones (e.g. 2-butanone), sulfoxides (e.g. DMSO) aromatics (e.g. toluene), fluorinated aromatics (e.g. trifluorotoluene) and alkanes (e.g. cyclohexane, n-pentane, n-hexane).

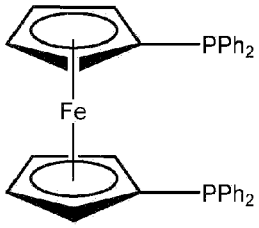
[0114] In the process of the present invention, a ligand may be employed in step ii).

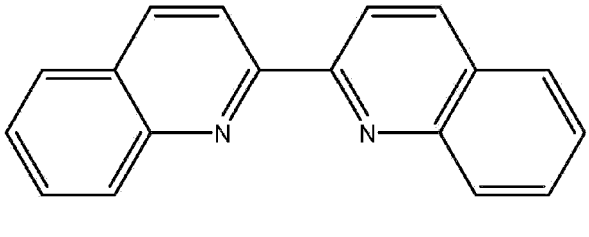
[0115] Examples of ligands that may be employed include aromatic or heteroaromatic compounds which may be monocyclic or multicyclic, for example phenanthroline compounds including, but not limited to, phenanthroline (phen), dimethylphenanthroline (me2phen) tetramethyl-1,10-phenanthroline (me4phen) and / or bathophenanthroline (bathophen); bipyridyl compounds such as bipyridyl (bpy), di-tert-butyl-2,2'-bipyridyl (dtbpy), 2,2'-bipyridine (bpy), dimethoxy-2,2'-bipyridyl (MeO-bpy); and / or other compounds such as 1,1'-bis(diphenylphosphino)ferrocene (dppf), bis(2-di-tert-butylphosphinophenyl)ether, 1,3-bis(diphenylphosphino)propane (dppp), 1,2-bis(diphenylphosphino)ethane (dppe), hexamethylbenzene (C6Me6), neocuproine, and xantphos. Other examples include 1,2-bis(dimethylphosphino)ethane (dmpe) and those disclosed in Hartwig et al, Chemical Reviews, 2010, 110, pages 890-931, the contents of which are incorporated by reference, and also the compounds illustrated below:

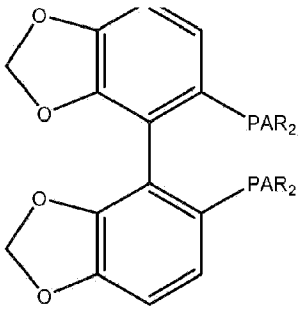


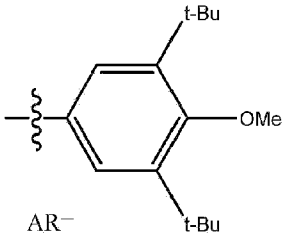












[0116] Alernatively, examples of ligands that may be employed include aromatic or heretoraromatic compounds which may be multicylic, for example tetramethyl-1,10-phenanthroline (Me4phen), di-tert-butyl-2,2'-bipyridyl (dtbpy), 2,2'-bipyridine (bpy), 1,1-bis(diphenylphosphino)ferrocene (dppf), bis(2-di-tert-butylphosphonophenyl)ether, 1,3-bis(diphenylphosphino)propane (dppp), 1,2- bis(diphenylphosphino)ethane (dppe), hexamethylbenzene (C6Me6) and xantphos. Other examples include 1,2-bis(diphenylphosphino)ethane (dmpe) and those disclosed in Hartwig et al, Chemical Reviews, 2010, 110, pages 890-931, the contents of which are incorporated by reference.

[0117] The inventors of the process of the invention have found that the molar ratio of ligand (where used) to starting material of formula IIa can impact on the rate of conversion to the borylated compound of formula IIb. In embodiments of the invention, the molar ratio of ligand : starting material of Formula IIa is less than about 2 : 1, less than about 1.5 : 1, less than about 1 : 1, less than about 0.75 : 1, less than about 0.5 : 1, less than about 0.1 : 1, less than about 0.05 : 1 to at least about 0.001 : 1.

[0118] Borylation step ii) may be conducted at any temperature provided that the borylation proceeds at an acceptable rate. In embodiments of the invention, the reaction may be carried out at a temperature of about 0°C, about 10°C, about 20°C, about 30°C, about 40°C or about 50°C to about 100°C, about 120°C or about 150°C.

[0119] The inventors of the process of the invention have found that the molar ratio of borylating agent to starting material of formula IIa can impact on the rate of conversion to the borylated compound of formula IIb. In embodiments of the invention, the molar ratio of borylating agent : starting material of Formula IIa is at least about 0.5 : 1, at least about 0.75 : 1, at least about 1 : 1, at least about 1.5 : 1, at least about 2 : 1, at least 2.5 : 1 or at least 3 : 1 optionally to about 5:1, or about 10:1.

[0120] The selective and efficient synthesis of 4-substituted analogues of cytisine has been achieved regardless of the order in which the starting material, solvent, catalyst, ligand and / or borylating agent are added.

[0121] In certain embodiments of the invention, the borylating agent and the starting material of Formula IIa are added simultaneously or substantially simultaneously into a reaction zone. In such embodiments, the reaction zone may or may not have been pre-loaded with solvent,

catalyst and / or ligand.

[0122] In alternative embodiments of the invention, the borylating agent may be added to the reaction zone (optionally pre-loaded with solvent, catalyst and / or ligand) prior to the starting material of Formula IIa being added. In such embodiments, the borylating agent may be present in the reaction zone (optionally with solvent, catalyst and / or ligand) for a period of time, e.g. about 1 or more, about 2 or more, or about 5 or more minutes, prior to the addition of the starting material of Formula IIa.

[0123] One advantage of the process of the present invention is that the crude product obtained in step ii) does not require purification prior to step iii) being commenced. Thus, in embodiments of the invention, no purification step is carried out between steps ii) and iii).

[0124] This advantage of the process of the present invention enables step ii) and at least the commencement of step iii) to be performed in the same reaction zone, i.e. as a 'one-pot' synthesis. Thus, in such embodiments, step iii) may be commenced in the same reaction zone in which the borylated compound of Formula IIb was prepared.

[0125] In step iii) BComp is removed from the 4-position on the cytisine ring and replaced with substituent R^1, defined as discussed above. For the avoidance of doubt, the replacement of BComp with R^1 does not have to take place in a single substitution step, although this may be desirable and, as is demonstrated in the examples that follow, can be achieved.

[0126] In embodiments of the invention, in step iii) BComp may firstly be replaced with one or more intermediate R^1 substituents before the final R^1 substituent is located at the 4-position on the cytisine ring. In embodiments of the invention, the intermediate R^1 substituent may be a halo (e.g. bromo, chloro or iodo), benzyloxypyridine, alkyl ester (e.g. methyl ester), alkenyl (e.g. vinyl), alkynyl (acetylene), trimethylsilylacetylene, 1, 2, 3-triazol-1-yl)methyl pivalate, cyano, aminomethyl, N-Boc-aminomethyl or (benzyloxy)carbonyl)piperazin-1-yl.

[0127] For brevity, full details of how the borylated compound of Formula IIb to each of the compounds of Formula I optionally via one or more intermediate R^1 substituents are not provided here, as those skilled in the art will recognise and appreciate how such substitutions may be carried out. The examples which follow provide further details of reaction conditions which can be employed in this regard.

[0128] In embodiments, the process of the present invention may comprise an additional step of conducting a substitution at the R^2, R^3 and / or R^4 positions on the cytisine ring. For example, where substitutions at the 3- or 5- positions on the cytisine ring are required, this can be carried out. Such a step can be achieved using any techniques and reagents known to those skilled in the art. In the event that guidance is needed regarding how such substitutions can be carried out, reference is made to the examples which follow in which such steps are exemplified. Additionally or alternatively, reference can be made to Rouden et al., (Chemical

Reviews, 2014, 114, pages 712 to 778) including to the articles referred to therein, which provide additional guidance in this regard.

[0129] Additionally or alternatively, in embodiments where a protecting group is located at the R^4 position, the process of the present invention may include the step of deprotecting the nitrogen atom at position 13- of the cytisine ring. This deprotection step may be conducted after the completion of step ii), before the commencement of step iii), during step iii) or after the completion of step iii). The skilled person will be familiar with deprotection techniques. However, in the event that any guidance in this connection is required, reference may be made to the examples which follow.

[0130] As can be seen from the foregoing, the process of the present invention advantageously, and for the first time, permits the convenient preparation of 4-substituted cytisine analogs from cytisine itself, rather than requiring a lengthy total synthesis of such compounds.

[0131] A further advantage of the present invention is that steps ii) and step iii) do not involve any chiral rearrangement of the molecule and thus, the process is stereoselective. This provides a further advantage over the art, which resulted in the formation of racemic analogs of cytisine.

[0132] Certain of the compounds can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative or a prodrug thereof. In the present context, a pharmaceutically acceptable derivative or a prodrug includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[0133] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any salt or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof.

[0134] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other

methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

Preparations and Examples

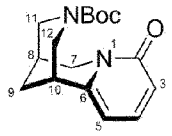
Extraction of (-)-Cytisine from Laburnum anagyroides seeds

[0135] As explained above, the process of the present invention advantageously commences from cytisine, a naturally occurring compounds which can be isolated from laburnum trees. While cytisine is commercially available, and those skilled in the art will be familiar with processes for extracting cytisine from natural sources, the following process is provided for completeness.

[0136] Powdered *Laburnum anagyroides* seeds (332 g), DCM (465 mL), MeOH (135 mL) and NH_4OH (50 mL, 35% aq. sol.) were stirred vigorously for 3 days at r.t. with a mechanic stirrer (400 rpm). The mixture was filtered and the solids were washed with DCM (4 × 200 mL) until the filtrate was colourless. The filtrate was acidified with 3M HCl (330 mL) to pH 1 and the mixture was stirred for 2 h (350 rpm). The two layers were separated and the aqueous layer was slowly basified to pH 9-10 with NH_4OH (70 mL, 35% aq.sol.). The mixture was stirred for 2 h, and extracted with DCM (10 × 70 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* yielding cytisine (4.76 g) as brown-yellow solid. Recrystallisation from toluene (5 mL) yielded (-)-cytisine (4.27 g, 1.3%) as a solid.

Addition of Protecting Group - *N*-Boc cytisine (56)

[0137]



56

[0138] To a solution of (-)-cytisine (6.41 g, 33.7 mmol) and $(Boc)_2O$ (9.3 mL, 40.4 mmol) in THF (135 mL) and water (70 mL) was added an aqueous solution of Na_2CO_3 (4.28 g, 40.4 mmol, 1 M). The mixture was stirred for 3 days, and then diluted with EtOAc (200 mL) and brine (70 mL). The aqueous layer was extracted with EtOAc (3 × 150 mL) and the combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude reaction mixture was purified by flash column chromatography on silica gel [DCM/MeOH (3% MeOH)] to give 56 (9.10 g, 93%) as a colourless solid.

[0139] **R_f:**0.28 [DCM/MeOH (5% MeOH)]; **mp:** 154-155 °C (lit: 156-157 °C); **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 7.26 (dd, 1H, J = 9.0, 7.0 Hz, C4-H), 6.41 (d, 1H, J = 9.0 Hz, C3-H), 6.04 (br s, 1H, C5-H), 4.40-4.08 (m, 3H, C7-H_a, C11-H, C12-H), 3.81 (dd, 1H, J= 15.5, 6.5 Hz, C7-H_b), 3.12-2.91 (m, 3H, C11-H, C12-H, C10-H), 2.40 (br s, 1H, C8-H), 2.00-1.90 (m, 2H, C9-H), 1.31-1.20 (m, 9H, Boc); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 163.3 (CO), 154.4/154.3 (C6, rotamers), 149.3/148.7 (CO Boc, rotamers), 138.9/138.4 (C4, rotamers), 117.0 (C3), 105.6/104.9 (C5, rotamers), 80.2/79.6 (q Boc, rotamers), 51.5/50.5/49.2 (C11, C12, rotamers), 48.8 (C7), 34.8 (C10), 28.0 (3C, Boc), 27.5 (C8), 26.1 (C9). The spectroscopic properties of this compound were consistent with the data available in literature.

Removal of Protecting Group

[0140] As will be exemplified below, a wide range of 4-substituted cytisine derivatives can be prepared according to the process of the present invention. For such compounds, it may be desirable to remove the Boc protecting group. In the examples below, the Boc protecting group where present on the 4-substituted cytisine analogs was removed by one of the two following processes

General Procedure A

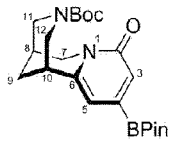
[0141] The cytisine derivative was dissolved in a solution 0.5 M HCl in MeOH (concentration of the substrate 0.1 M) and the reaction mixture was stirred for 72 h at r.t. Then, the solvent was removed *in vacuo.* The residue was dissolved in the minimum amount of MeOH and 10 times the MeOH volume of acetone was added slowly. The solution was stirred for 2 h. After, the precipitate was collected by filtration and washed with cold acetone.

General Procedure B

[0142] The cytisine derivative was dissolved in a solution 4.0 M HCl in dioxane (concentration of the substrate 0.1 M) and the reaction mixture was stirred for 72 h at r.t. Then, the solvent was removed *in vacuo.* The residue was dissolved in the minimum amount of MeOH and 10 times the MeOH volume of acetone was added slowly. The solution was stirred for 2 h. After, the precipitate was collected by filtration and washed with cold acetone.

Example 1 - *N*-Boc 4-Bpincytisine (58)

[0143]



58

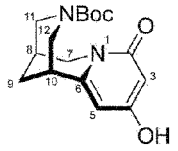
[0144] A Schlenk tube was charged with N-Boc-cytisine, **56** (290 mg, 1.00 mmol), bis-(iridium-cycloctadienyl-methoxide) (6.6 mg, 0.01 eq.), 4,4'-2,2'-di-tert-butylbispyridine (5.4 mg, 0.02 eq.) and bis (pinacolato)-diborane (177 mg, 0.7 eq.). The Schlenk tube was placed under vacuum and backfilled with nitrogen for three times, THF (1.4 mL) was added and the mixture was heated at 80 °C for 24 h. The mixture was cooled to r.t. and concentrated *in vacuo.* Although purification (see below) is possible, this was not essential; the crude reaction mixture was used in a number of subsequent conversion steps without further purification.

[0145] The crude reaction mixture was purified by flash column chromatography on silica gel [DCM/MeOH (5% MeOH)] to give **58** (180 mg, 43%; unstable compound on silica, only pure fractions collected; full conversion by ^{1}H-NMR) as a pale orange foam.

[0146] **R_f:** 0.23 [DCM/MeOH (5% MeOH)]; **FTIR ν_{max} / cm^{-1} (neat):** 3433, 2977, 1688, 1657, 1563, 1423; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 6.85 (s, 1H, C3-H), 6.31 (s, 1H, C5-H), 4.34-4.10 (m, 3H, C7-H_a, C12-H, C11-H), 3.80 (dd, 1H, J = 15.5, 6.5 Hz, C7-H_b), 3.07-2.91 (m, 3H, C10-H, C11-H, C12-H), 2.41 (s, 1H, C10-H), 1.95-1.88 (m, 2H, C9-H), 1.41-1.09 (m, 23H, 12 × Bpin-H, 9 × Boc); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 162.9 (CO), 154.6/154.3 (C6, rotamers), 147.9/147.5 (CO Boc, rotamers), 124.4 (C3), 109.3/108.8 (C5, rotamers), 84.4 (q Boc), 82.6/80.3, 79.7/75.0 (2C, q Bpin, rotamers), 51.7/50.6/50.3/49.2 (C11, C12, rotamers), 48.9 (C7), 34.7 (C10), 28.0 (4C, Bpin), 27.5 (C8), 26.1 (C9), 24.8/24.6 (3C, Boc, rotamers), C4 non-detected; **^{11}B NMR (96.4 MHz, $CDCl_3$, δ_B):** 28.94 (br s); **HRMS (ESI^{+}):** calculated for $C_{22}H_{33}BN_2NaO_5$ $[M+Na]^+$: 439.2379, found: 439.2373.

Example 2a - *N*-Boc4-Hydroxycytisine (66)

[0147]



66

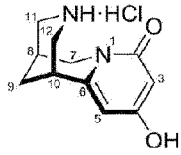
[0148] *N*-Boc-4-(4,4,5,5-tetramethyl-1,3,2,-dioxaborolan-2-yl)-cytisine 58 was made following the general procedure for the borylation of cytisine discussed above in Example 1 in a 1.0 mmol scale.

[0149] The borylation reaction mixture was cooled to 0 °C and dissolved in THF (8.6 mL). NaOH 3 M (1.0 mL, 3.0 mmol) was added followed by a slow addition of 30% aqueous H_2O_2 (1.0 mL) over 5 min. The mixture was stirred at 0 °C for 30 min and then stirred under air at r.t. overnight. The mixture was diluted with water (3 mL) and the aqueous layer was washed with DCM (3 × 5 mL). The aqueous layer was acidified with 3 M HCl to pH 4-5 and extracted with DCM (5 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude reaction mixture was purified by flash column chromatography on silica gel [DCM/MeOH (5% MeOH)] to give **66** (240 mg, 79%) as an off-white solid.

[0150] **R_f:** 0.13 [DCM/MeOH (5% MeOH)]; **mp:** >200 °C, colourless powder; **FTIR ν_{max} / cm^{-1} (neat):** 2864, 1673, 1652, 1535, 1423; **^{1}H NMR (400 MHz, DMSO-d_6, δ_H):** 10.27 (s, 1H, OH), 5.76 (s, 1H, C3-H), 5.45 (s, 1H, C5-H), 4.12-3.78 (m, 3H, C7-H_a, C11-H, C12-H), 3.51 (dd, 1H, J= 15.0, 6.5 Hz, C7-H), 3.16-2.93 (m, 3H, C10-H, C11-H, C12-H), 2.29 (br s, 1H, C8-H), 1.84 (s, 2H, C9-H), 1.23-1.14 (m, 9H, Boc); **^{13}C NMR (100 MHz, DMSO-d_6, δ_C):** 166.0 (C4), 164.2 (CO), 154.1 (C6), 150.4 (CO Boc), 98.8/98.7 (C3, rotamers), 96.3 (C5), 79.3/78.8 (q Boc, rotamers), 51.7/50.6/50.3/49.3 (C11, C12, rotamers), 48.3 (C7), 34.5 (C10), 28.1 (3C, Boc), 27.4 (C8), 25.9 (C9); **HRMS (ESI$^+$):** calculated for $C_{16}H_{23}N_2O_4$: 307.1652, found $[M+H]^+$: 307.1650, $C_{16}H_{22}N_2NaO_4$: 329.1472, found $[M+Na]^+$: 329.1469.

Example 2b - (+)4-Hydroxycytisine hydrochloride salt (67)

[0151]



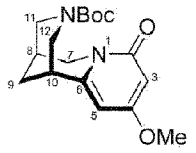
67

[0152] Following the general procedure A, alcohol **66** (0.79 mmol) gave alcohol **67** (184 mg, 96%) as an off-white solid.

[0153] mp: >200 °C, colourless powder; **$[\alpha]_D^{25}$** = +3.0 [c 1.0, MeOH]; **FTIR ν_{max} / cm^{-1} (neat):** 3444, 2934, 2597, 1641, 1589; **^{1}H NMR (400 MHz, D_2O, δ_H):** 6.33 (d, 1H, C3-H, *J* = 2.0 Hz), 6.02 (d, 1H, C5-H, J = 2.0 Hz), 4.07 (d, 1H, C7-H_a, J = 15.5 Hz), 3.93 (dd, 1H, J = 15.5, 6.5 Hz, C7-H_b), 3.40-3.24 (m, 5H, C10-H, C11-H, C12-H), 2.69 (br s, 1H, C8-H), 2.03-1.93 (m, 2H, C9-H); **^{13}C NMR (100 MHz, D_2O, δ_C):** 168.4 (CO), 164.2 (C6), 149.3 (C4),105.3 (C3), 97.2 (C5), 49.1 (C11 or C12), 49.0 (C7), 48.1 (C11 or C12), 31.5 (C10), 24.6 (C8), 22.4 (C9); **HRMS (ESI$^+$):** calculated for $C_{11}H_{15}N_2O_2$: 207.1128, found $[M+H-HCl]^+$: 207.1136.

Example 3a - *N*-Boc4-Methoxycytisine (68)

[0154]



68

[0155] N-Boc-4-(4,4,5,5-Tetramethyl-1,3,2,-dioxaborolan-2-yl)-cytisine **58** was made following the general procedure for the borylation of cytisine discussed above in Example 1 in a 0.50 mmol.

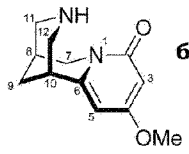
[0156] A freshly prepared solution of $CuSO_4 \cdot 5H_2O$ (37 mg, 0.15 mmol), KOH (84 mg, 1.50 mmol) and molecular sieves 4Å (300 mg) in methanol (5 mL) was stirred for 5 h under nitrogen atmosphere, and then transferred over the crude of the borylation reaction using a syringe. The reaction mixture was stirred at reflux for 18 h under an oxygen atmosphere. The reaction was diluted with 10 mL of methanol, filtered through a Celite® pad and the solvent was removed under vacuum. The crude was distributed between ammonia solution (15 mL, 15% aq. sol.) and DCM (15 mL), and the aqueous phase was extracted with DCM (4 × 15 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. Purification of the crude reaction mixture by flash column chromatography [DCM/MeOH, (2% MeOH)] afforded **69** (130 mg, 81%) as a colourless solid.

[0157] mp: 170-171 °C, colourless needles (toluene); **R_f:** 0.41 [DCM/MeOH (6% MeOH)]; **FTIR ν_{max} / cm^{-1} (neat):** 2971, 1673, 1646, 1427; **^{1}H NMR (500 MHz, $CDCl_3$, δ_H, 52.0 °C):** 5.85 (s, 1H, C3-H), 5.79 (s, 1H, C5-H), 4.39-4.07 (m, 3H, C11-H, C12-H, C7-H), 3.82-3.74 (m,

1H, C7-H), 3.73 (s, 3H, OMe), 3.13-2.85 (m, 3H, C11-H, C12-H, C10-H), 2.38 (s, 1H, C8-H), 1.93 (m, 2H, C9-H), 1.41-1.18 (s, 9H, Boc); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C, 52.0 °C):** 167.4 (C4), 164.9 (CO), 154.4 (C6), 148.7 (CO Boc), 99.5 (C5), 94.8 (C3), 80.1 (q Boc), 55.1 (OMe), 50.6 (C11, C12), 48.4 (C7), 34.9 (C10), 28.1 (3C, Boc), 27.6 (C8), 26.4 (C9); **HRMS (ESI^+):** calculated for $C_{17}H_{25}N_2O_4$: 321.1809, found $[M+H]^+$: 321.1800; **Anal. Calc.** for $C_{17}H_{25}N_2O_4$: C 63.73, H 7.55, N 8.74. Found C 64.15, H 7.49, N 8.77.

Example 3b - (-)4-Methoxycytisine (69)

[0158]



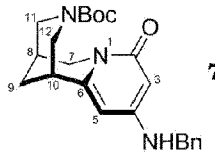
69

[0159] To a solution of ether **68** (130 mg, 0.42 mmol) in DCM (4 mL, 0.1 M) was added TFA (0.3 mL, 10 eq.) at once, and the reaction mixture was stirred at r.t. for 18 h. Water (10 mL) was added and the aqueous phase was washed with DCM (3 × 10 mL). The aqueous phase was basified with ammonia (10 mL, 15% aq. sol.) and extracted with DCM (3 × 10 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated, yielding **69** (76 mg, 85%) as a colourless solid.

[0160] mp: > 200°C, colourless powder; **$[\alpha]_D^{24}$** = -42 [c 1.0, EtOH]; **FTIR ν_{max} / cm^{-1} (neat):** 2889, 1645, 1580, 1557, 1158; **^{1}H NMR (500 MHz, $CDCl_3$, δ_H):** 5.87 (d, *J* = 3.0 Hz, 1H, C3-H), 5.74 (d, J = 3.0 Hz, 1H, C5-H), 4.10 (d, J = 15.0 Hz, 1H, C7-H), 3.85 (dd, J = 15.0, 6.5 Hz, 1H, C7-H), 3.77 (s, 3H, OMe), 3.14-2.98 (m, 4H, C11-H, C12-H), 2.84 (s, 1H, C10-H), 2.30 (s, 1H, C8-H), 1.96 (s, 2H, C9-H), 1.55 (s, 1H, NH); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C):** 167.4 (CO), 165.1 (C6), 150.6 (C4), 98.6 (C5), 94.5 (C3), 55.2 (OMe), 53.4, 53.0 (C11, C12), 49.2 (C7), 35.7 (C10), 27.7 (C8), 26.4 (C9); **HRMS (ESI^+):** calculated for $C_{12}H_{17}N_2O_2$: 221.1285, found $[M+H]^+$: 221.1283.

Example 4a - *N*-Boc4-(N-Benzylamino)cytisine (70)

[0161]



70

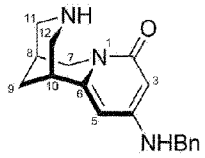
[0162] N-Boc-4-(4,4,5,5-Tetramethyl-1,3,2,-dioxaborolan-2-yl)-cytisine **58** was made following the genenal procedure for the borylation of cytisine as detailed in Example 1 above in a 5.00 mmol scale.

[0163] In a separate vessel, $Cu(OAc)\cdot H_2O$ (300 mg, 1.5 mmol), KF (320 mg, 5.5 mmol), and molecular sieves 4Å (4 g) were stirred in MeCN (20 mL) for 15-20 min. The crude of the borylation reaction was solubilised in MeCN (5 mL) and the copper solution was added via syringe to the crude reaction, stirring for 10 min. Freshly distilled $BnNH_2$ (1.1 mL, 10.0 mmol) was added and the reaction mixture was heated at reflux for 18 h under an oxygen atmosphere. The reaction mixture was cooled, filtered through Celite® and concentrated. The crude of the reaction was distributed between ammonia (25 mL, 15% aq. sol.) and DCM (25 mL) and the aqueous phase was extracted with DCM (4 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude reaction mixture was purified by flash column chromatography [DCM/MeOH (2% MeOH)] affording **70** (1.70 g, 72%), together with an inseparable impurity, as a colourless solid.

[0164] **^{1}H NMR (500 MHz, $CDCl_3$, δ_H):** 7.35-7.19 (m, 5H, Ar), 5.52 (s, 1H, C3-H), 5.46 (s, 1H, C5-H), 4.66 (s, 1H, NH), 4.38-4.11 (m, 3H, C13-H, C11-H or C12-H); 4.05 (d, J = 15.5 Hz, 1H, C7-H), 3.71 (m, 1H, C7-H), 3.17-2.78 (m, 3H, 2x C11-H or C12-H, 1H × C11-H or C12-H), 2.74 (s, 1H, C10-H), 2.31 (s, 1H, C8-H), 1.96-1.80 (m, 2H, C9-H), 1.28 (s, 9H, Boc).

Example 4b - (+)4-(N-Benzylamino)cytisine (71)

[0165]



71

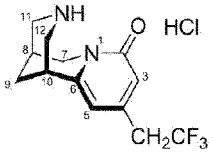
[0166] To a solution of the secondary amine **70** (1.70 g, 4.30 mmol) in DCM (43 mL, 0.1 M) was added TFA (0.4 mL, 10 eq.) and the solution was stirred at r.t. for 16 h. Water was added (20 mL) and the aqueous phase was washed with DCM (3 × 30 mL). Then, the aqueous phase was basified with ammonia (15 mL, 15% aq. sol.) and extracted with DCM (4 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated, yielding **71** (970 mg, 76 %) as a colourless solid.

[0167] **R_f:** 0.39 [DCM/MeOH (8% MeOH)]; **mp:** 208-211 °C, (toluene); **$[\alpha]_D^{25}$=** +58 [c 0.5, EtOH]; **FTIR ν_{max}/cm^{-1} (neat):** 3266, 2919, 1637, 1559, 1533; **^{1}H NMR (500 MHz, $CDCl_3$, δ_H):** 7.35-7.23 (m, 5H, Ar), 5.52 (s, 1H, C3-H), 5.48 (s, 1H, C5-H), 4.58 (s, 1H, NHPh), 4.26 (s, 1H,

CH_2Ph), 4.25 (s, 1H, CH_2Ph), 4.03 (d, J = 14.5 Hz, 1H, C7-H), 3.77 (dd, J = 6.5, 14.5 Hz, 1H, C7-H), 3.09-2.93 (m, 4H, C11-H C12-H), 2.71 (s, 1H, C10-H), 2.21 (s, 1H, C8-H), 1.90 (s, 2H, C9-H), 2.07-1.71 (s, 1H, NH); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C):** 164.6 (CO), 154.9 (C4), 149.7 (C6), 137.8 (Ar), 128.7 (Ar, 2C), 127.5 (Ar), 127.4 (Ar, 2C), 97.2 (C5), 91.2 (C3), 53.8 (C11), 52.8 (C12), 48.7 (C7), 47.0 (CH_2-Ph), 35.5 (C10), 27.7 (C8), 26.5 (C9); **HRMS (ESI^+):** calculated for $C_{18}H_{22}N_3O$: 296.1757, found $[M+H]^+$: 296.1766; **Anal. Calc.** for $C_{18}H_{21}N_3O$: C: 73.19, H: 7.17, N: 14.23; found C: 73.24, H: 7.18, N: 14.35

Example 5 - (-)4-(2,2,2-Trifluoroethyl)cytisine hydrochloride salt (79)

[0168]



79

[0169] N-Boc-4-(4,4,5,5-Tetramethyl-1,3,2,-dioxaborolan-2-yl)-cytisine **58** was made following the genenal procedure for the borylation of cytisine as detailed in Example 1 above in a 1.00 mmol scale.

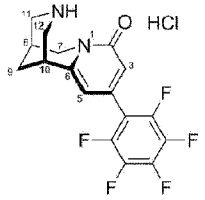
[0170] To the crude borylation reaction mixture, $[Pd_2(dba)_3]$ (23 mg, 1 mmol%), Xphos (47 mg, 2.5 mmol%), caesium fluoride (450 mg, 3.0 eq.) and copper (I) chloride anhydrous (99 mg, 1.0 eq.) were added, and the Schlenk tube was placed under vacuum and backfilled with nitrogen for three times. The reaction mixture was dissolved in DMF (4.0 mL, 0.25 M) and 2-iodo-1,1,1-trifluoroethane (0.19 mL, 2.0 eq.) and water (0.14 mL, 8.0 eq.) were added. The reaction mixture was stirred at 65 °C for 18 h. The solvent was removed *in vacuo* and the reaction crude distributed between EtOAc (15 mL) and water (15 mL). The aqueous phase was extracted with EtOAc (3 × 15 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. Purification of the crude reaction mixture by flash column chromatography [DCM/MeOH (2% MeOH)] afforded N-Boc-4-(2,2,2-trifluoroethyl)-cytisine (190 mg, 50%) as a colourless solid. The resulting trifluoro-cytisine derivative was deprotected and converted into its HCl salt following the general procedure A yielded ligand **79** (93 mg, 34%) as a colourless solid.

[0171] mp: >200 °C, colourless powder; **$[\alpha]_D^{26}$** = -42 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1} (neat):** 2723, 1640, 1563, 1467, 1458; **^{1}H NMR (500 MHz, D_2O, δ_H):** 6.61-6.55 (m, 2H, C3-H, C5-H), 4.14-3.88 (m, 2H, C7-H), 3.5-3.26 (m, 7H, C10-H, C11-H, C12-H, CH_2-CF_3), 2.75 (s, 1H, C8-H), 2.15-1.95 (m, 2H, C9-H); **^{13}C NMR (125 MHz, D_2O, δ_C):** 164.5 (CO), 147.0 (C6), 145.3 (C4), 125.0 (d, J = 276 Hz, CF_3), 118.4, 111.4 (C3, C5), 49.4, 48.2 (C11, C12), 48.6 (C7), 38.3

(q, J = 30.0 Hz, C14), 31.4 (C10), 24.7 (C8), 22.5 (C9); **^{19}F NMR (376 MHz, D_2O, δ_F):** -64.5 (t, 11.0 Hz); **HRMS (ESI^+):** calculated for $C_{13}H_{16}F_3N_2O$: 273.1209, found $[M+H-HCl]^+$: 273.1220.

Example 6 - (-)4-(Perfluorophenyl)cytisine hydrochloride salt (75)

[0172]



75

[0173] N-Boc-4-(4,4,5,5-Tetramethyl-1,3,2,-dioxaborolan-2-yl)-cytisine **58** was made following the genenal procedure for the borylation of cytisine detailed in Example 1 above in a 1.00 mmol scale.

[0174] Bromopentafluorobenzene (0.15 mL, 1.2 eq.), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 eq.) and Cs_2CO_3 (410 mg, 2.5 eq.) were added over the crude of the borylation reaction and the reaction mixture was dissolved in THF (5 mL, 0.2 M) and stirred at 80 °C for 18 h. The reaction mixture was diluted with ammonia (25 mL, 15 % aq. sol.), and the aqueous phase was extracted with EtOAc (4 × 25 mL). The combined organic phases were dried over $MgSO_4$, the solids were filtered off and the solvent was evaporated *in vacuo.* Purification of the crude reaction mixture by flash column chromatography [DCM/MeOH (1.5% MeOH)] yielded **74** (509 mg, 99%) as a colourless solid. (Contaminated with $[PdCl_2(PPh_3)_2]$).

[0175] ^{1}H NMR (500 MHz, $CDCl_3$, δ_H): 6.53 (s, 1H, C3-H), 6.09 (s, 1H, C5-H), 4.49-4.12 (m, 3H, C11-H C12-H C7-H), 3.88 (dd, J = 16.5, 6.5 Hz, 1H, C7-H), 3.18-2.96 (m, 3H, C11-H C12-H C8-H), 2.47 (s, 1H, C10-H), 2.02 (m, 2H, C9-H), 1.29 (s, 9H, Boc).

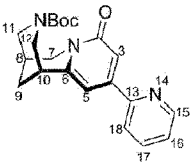
[0176] Following the general procedure A, ***N*-Boc** protected cytisine derivative **74** (1.1 mmol) gave 4-(perfluorophenyl)-cytisine hydrochloride salt **75** (160 g, 43%) as a colourless solid.

[0177] mp: >200°C, colourless powder; **$[\alpha]_D^{26}$** = -16 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1}(neat):** 2977, 2869, 1658, 1536; **^{1}H NMR (500 MHz, MeOH,** δ_H): 6.58 (s, 1H, C3-H), 6.43 (s, 1H, C5-H), 4.13 (d, J = 15.5 Hz, 1H, C7-H), 4.00 (dd, J = 6.0, 15.0 Hz, 1H, C7-H), 3.14-2.99 (m, 5H, C11-H C12-H C10-H), 2.43 (s, 1H, C8-H), 2.07 (m, 2H, C9-H); **^{13}C NMR (125 MHz, MeOH, δ_C):** 163.7 (CO), 152.4 (C4), 144.9 (m), 143.1 (m), 142.2 (m), 140.2 (m), 138.8 (m), 136.7 (m) (6C, Ar), 138.5 (C6), 117.0 (C3), 107.4 (C5), 52.6, 51.6 (C11, C12), 49.8 (C7), 35.2 (C10), 27.4 (C8), 25.2 (C9); **^{19}F NMR (376 MHz, D_2O, δ_F):** -140.7, -141.3, -152.9, -160.8, -161.1; **HRMS**

(ESI$^+$): calculated for $C_{17}H_{14}F_5N_2O$: 357.1021, found $[M+H^+-HCl]^+$: 357.1017.

Example 7a - *N*-Boc4-(2-Pyridinyl)cytisine (100)

[0178]



100

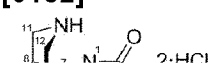
[0179] N-Boc-4-(4,4,5,5-Tetramethyl-1,3,2,-dioxaborolan-2-yl)-cytisine **58** was made following the genenal procedure for the borylation of cytisine as detailed above in Example 1 in a 1.00 mmol scale.

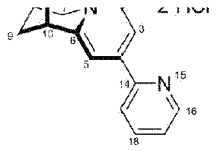
[0180] Anhydrous Cs_2CO_3 (814 mg, 2.5 mmol) and $PdCl_2(PPh_3)_2$ (35 mg, 5 mol %) were added over the borylation reaction crude mixture. Dry THF (10 mL) was added followed by 2-bromopyridine (115 µL, 1.2 mmol). The mixture was stirred at 80 °C for 48 h. The reaction was cooled to r.t., diluted with EtOAc (50 mL) and filtered through Celite®. The organic layer was washed with water (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [DCM/MeOH (4% MeOH)+ 0.1% ammonia (15% aq. sol.)] to give **100** (205 mg, 56%) as a yellow oil. The product was used in the next step without any further purification.

[0181] R_f: 0.17 [DCM/MeOH (5% MeOH)]; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 8.65 (d, 1H, J = 2.0 Hz, C15-H), 7.75-7.68 (m, 2H, C17-H, C18-H), 7.29-7.26 (m, 1H, C16-H), 6.92 (s, 1H, C3-H), 6.86 (s, 1H, C5-H), 4.37-4.17 (m, 3H, C7-H_a, C11-H, C12-H), 3.84 (dd, 1H, J = 6.5, 15.5 Hz, C7-H_b), 3.11-2.96 (m, 3H, C10-H, C11-H, C12-H), 2.42 (s, 1H, C8-H), 2.01-1.92 (m, 2H, C9-H), 1.30-1.13 (m, 9H, Boc); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 163.7 (CO), 154.5 (CO Boc), 154.2 (C6), 149.6 (C4), 148.8 (C13), 145.4 (C16), 136.9 (C17), 123.8 (C16), 121.1 (C18), 113.8 (C3), 104.4/103.9 (C5, rotamers), 80.3/79.8 (q Boc, rotamers), 51.6/50.6/50.3/49.3 (C11, C12, rotamers), 48.9 (C7), 35.1 (C10), 27.5 (C8), 26.2 (C9), 24.8 (3C, Boc); **HRMS (ESI$^+$):** calculated for $C_{21}H_{26}N_3O_3$ $[M+H]^+$: 368.1969, found: 368.1965; calculated for $C_{21}H_{25}N_3NaO_3$: 390.1788, found $[M+Na]^+$: 390.1784.

Example 7b - (-)4-(2-Pyridinyl)cytisine dihydrochloride salt (101)

[0182]





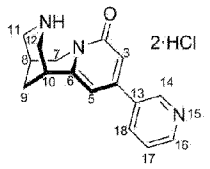
101

[0183] Following the general procedure A for the deprotection of cytisine, N-Boc-4-(2-Pyridinyl)-cytisine **100** (0.55 mmol) gave **101** (99.2 mg, 63%) as a colourless solid.

[0184] mp: >200°C, colourless powder; **$[\alpha]_D^{24}$** = -12 [c 1.0, MeOH]; **FTIR ν_{max} / cm^{-1} (neat):** 3471, 2750, 1658, 1572; **^{1}H NMR (400 MHz, D_2O, δ_H):** 8.71-8.70 (m, 1H, C16-H), 8.53-8.49 (m, 1H, C18-H), 8.16 (d, 1H, *J* = 8.0 Hz, C19-H), 7.97-7.94 (m, 1H, C17-H), 6.89 (d, 1H, J = 2.0 Hz, C3-H), 6.84 (s, 1H, J = 2.0 Hz, C5-H), 4.11 (d, 1H, J = 16.0 Hz, C7-H_a), 3.98 (dd, 1H, *J* = 6.5, 16.0 Hz, C7-H_b), 3.52 (br s, 1H, C10-H), 3.45-3.30 (m, 4H, C11-H, C12-H), 2.77 (br s, 1H, C10-H), 2.10-2.00 (m, 2H, C9-H); **^{13}C NMR (100 MHz, D_2O, δ_C):** 164.3 (CO), 149.3 (C6), 148.7 (C4), 146.9 (Ar py), 143.3 (Ar py), 142.7 (Ar py), 127.3 (Ar py), 126.2 (Ar py), 116.4 (C3), 107.0 (C5), 49.3, 49.0 (C11, C12), 48.2 (C7), 31.8 (C8), 24.7 (C10), 22.4 (C9); **HRMS (ESI^+):** calculated for $C_{16}H_{18}N_3O$: 268.1444, found $[M+H^+-2HCl]^+$: 268.1444.

Example 8 - (-)4-(3-Pyridinyl)cytisine dihydrochloride salt (104)

[0185]



104

[0186] A Schlenk tube was charged with N-Boc-4-bromo-cytisine **61** (370 mg, 1.0 mmol), $[Pd_2(dba)_3]$ (9.0 mg, 1 mmol%), tricyclohexylphosphine (7.0 mg, 2.4 mmol%) and 3-pyridinylboronic acid (140 mg, 1.1 eq.), and placed under vacuum and backfilled with nitrogen three times. The mixture was dissolved in dioxane (2.6 mL, 0.4 M) and a solution of tripotassium phosphate in water (360 g, 1.7 eq., 1.3 M) was added dropwise with a syringe over 10 min. The reaction mixture was heated at 100 °C for 18 h. The solution was filtered through Celite® and the solvent was removed *in vacuo.* Ammonia solution (5 mL, 15% aq. sol.) was added and the aqueous phase was extracted with DCM (4 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The resulting N-Boc-4-(3-pyridinyl)-cytisine derivative was deprotected and converted into the HCl salt following the general procedure A yielding **104** (210 mg, 78%) as a colourless solid.

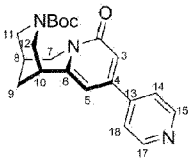
[0187] mp: >200 °C, colourless powder; **$[\alpha]_D^{24}$** = -11 [c 1.0, MeOH]; **FTIR ν_{max} / cm^{-1}(neat):**

2926, 2528, 2072, 1650, 1539; **^{1}H NMR (500 MHz, MeOD, δ_H):** 9.39 (s, 1H, Ar Py), 9.07 (s, 1H, Ar Py), 9.01 (s, 1H, Ar Py), 8.27 (s, 1H, Ar Py), 7.10 (s, 1H, C3-H), 7.06 (s, 1H, C5-H), 4.35 (d, 1H, *J* = 15.5 Hz, C7-H), 4.14 (dd, 1H, J = 15.5, 6.0 Hz, C7-H), 3.69-3.53 (m, 5H, C11-H C12-H C10-H), 2.89 (s, 1H, C8-H), 2.28 (d, J = 13.5 Hz, 1H, C9-H), 2.17 (d, 1H, J = 13.5 Hz, C9-H); **^{13}C NMR (125 MHz, MeOD,** δ_C): 163.6 (CO), 148.9 (C6), 145.3 (q Py), 144.9 (Py), 141.7 (Py), 140.2 (Py), 136.7 (C4), 127.7 (Py), 115.0 (C5), 107.1 (C3), 49.1, 48.5 (C11, C12), 48.9 (C7), 32.0 (C10), 25.2 (C8), 22.7 (C9); **HRMS (ESI$^+$):** calculated for $C_{16}H_{18}N_3O$: 268.1444, found $[M+H-2HCl]^+$: 268.1444.

Example 9a - (-)N-Boc4-(4-Pyridinyl)cytisine (102)

N-Boc-4-(4,4,5,5-Tetramethyl-1,3,2,-dioxaborolan-2-yl)-cytisine 58 was made following

[0188]



102

the general procedure for the borylation of cytisine detailed in Example 1 above in a 1.00 mmol scale.

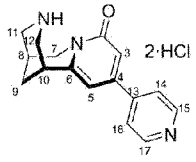
[0189] Anhydrous Cs_2CO_3 (814 mg, 2.5 mmol) and $PdCl_2(PPh_3)_2$ (35 mg, 5 mol%) were added over the crude borylation reaction mixture. Dry THF (10 mL) was added followed by 4-iodopyridine (246 mg, 1.2 mmol). The mixture was stirred at 80 °C for 48 h. The mixture was cooled to r.t., diluted with EtOAC (50 mL) and filtered through Celite®. The organic layer was washed with brine (10 mL), dried on Na_2SO_4, filtered and concentrated *in vacuo.* The crude mixture was purified by flash column chromatography on silica gel [DCM/MeOH (5% MeOH)+ 0.1% ammonia (15% aq. sol.) to give **102** (312 mg, 85%) as an orange oil. The product was used in the next step without any further purification.

[0190] R_f: 0.39 [DCM/MeOH (10% MeOH)]; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 8.63 (d, 2H, J = 6.0 Hz, C15-H, C17-H), 7.41 (d, 2H, J = 6.0 Hz, C14-H, C18-H), 6.66 (s, 1H, C3-H), 6.28 (s, 1H, C5-H), 4.38-4.15 (m, 3H, C7-H_a, C11-H, C12-H), 3.82 (dd, 1H, J = 6.5, 15.5 Hz, C7-H_b), 3.06 (br s, 3H, C10-H, C11-H, C12-H), 2.42 (br s, 1H, C8-H), 2.02-1.93 (m, 2H, C9-H), 1.30-1.13 (m, 9H, Boc); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 163.3 (CO), 154.5/154.2 (CO Boc, rotamers), 150.4 (C15, C17), 149.6 (C6), 148.0/147.8 (C4, rotamers), 145.2 (C13), 121.1 (C14, C18), 114.4 (C3), 104.3/103.5 (C5, rotamers), 80.5/79.8 (q Boc, rotamers), 51.7/50.6/50.3/49.3 (C11, C12, rotamers), 49.0 (C7), 35.1 (C10), 27.4 (C8), 26.1 (C9), 24.8

(3C, Boc); **HRMS (ESI$^+$):** calculated for $C_{21}H_{26}N_3O_3$: 368.1969, found $[M+H]^+$: 368.1970, calculated for $C_{21}H_{25}N_3NaO_3$: 390.1788, found $[M+Na]^+$: 390.1791.

Example 9b - (-)4-(4-Pyridinyl)cytisine dihydrochloride salt (103)

[0191]



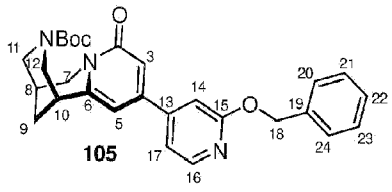
103

[0192] Following the general procedure A, N-Boc4-(4-pyridinyl)cytisine **102** (0.85 mmol) gave **103** (122 mg, 48%) as a pale-orange solid.

[0193] mp: >200°C, colourless powder; **$[\alpha]_D^{24}$=** -12 [c 0.5, water]; **FTIR ν_{max} / cm^{-1} (neat):** 2590, 1653 (w), 1631, 1579, 1545; **^{1}H NMR (400 MHz, D_2O, δ_H):** 8.75 (d, 2H, *J* = 6.5 Hz, C14-H, C18-H), 8.20 (d, 2H, J = 6.5 Hz, C15-H, C17-H), 6.90 (d, 1H, J = 2.0 Hz, C3-H), 6.86 (s, 1H, J = 2.0 Hz, C5-H), 4.10 (d, 1H, J = 16.0 Hz, C7-H_a), 3.97 (dd, 1H, *J* = 6.5, 16.0 Hz, C7-H_b), 3.51 (s, 1H, C10-H), 3.45-3.28 (m, 4H, C11-H, C12-H), 2.76 (br s, 1H, C8-H), 2.09-1.99 (m, 2H, C9-H); **^{13}C NMR (100 MHz, D_2O, δ_C):** 164.5 (CO), 154.3 (C4), 148.7 (C6), 146.7 (C13), 141.6 (2C, C15, C17), 125.2 (2C, C14, C17), 116.3 (C3), 107.4 (C5), 49.4 (C11 or C12), 48.9 (C7), 48.2 (C11 or C12), 31.8 (C10), 24.7 (C8), 22.5 (C9); **HRMS (ESI$^+$):** calculated for $C_{16}H_{18}N_3O$: 268.1444, found $[M+H]^+$: 268.1453.

Example 10a - *N*-Boc4-(4-(2-Benzyloxy)pyridine)cytisine 105

[0194]



105

[0195] N-Boc-4-(4,4,5,5-Tetramethyl-1,3,2,-dioxaborolan-2-yl)-cytisine **58** was made following the genenal procedure for the borylation of cytisine detailed above in Example 1 in a 1.00 mmol scale.

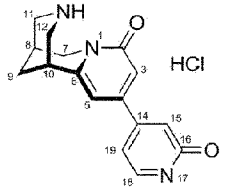
[0196] Anhydrous Cs_2CO_3 (814 mg, 2.5 mmol) and $PdCl_2(PPh_3)_2$ (35 mg, 5 mol%) were added

over the crude borylation reaction mixture. Dry THF (5.0 mL) was added followed by a solution of 4-bromo-2-benzyloxypyridine (316 mg, 1.2 mmol) in dry THF (5.0 mL). The mixture was stirred at 80 °C for 48 h. The solution was cooled to r.t., diluted with EtOAc (50 mL) and filtered through Celite®. The organic layer was washed with water (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude reaction mixture was purified by flash column chromatography on silica gel [DCM/MeOH (4% MeOH)+ 0.1% ammonia (15% aq. sol.)] to give **105** (485 mg, 99%) with few impurities as a pale yellow oil. The product was used in the next step without any further purification.

[0197] R_f: 0.23 [DCM/MeOH (5% MeOH)]; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 8.22 (d, 1H, J = 5.0 Hz, C16-H), 7.46 (d, 2H, J = 7.0 Hz, C20-H, C24-H), 7.39-7.29 (m, 3H, C21-H, C22-H, C23-H), 7.04 (d, 1H, J = 5.0 Hz, C17-H), 6.96 (s, 1H, C14-H), 6.67 (s, 1H, C3-H), 6.27 (s, 1H, C5-H), 5.41 (s, 2H, C18-H), 4.40-4.18 (m, 3H, C7-H_a, C11-H, C12-H), 3.84 (dd, 1H, J = 6.5, 15.5 Hz, C7-H_b), 3.05 (s, 3H, C10-H, C11-H, C12-H), 2.44 (s, 1H, C8-H), 2.03-1.94 (m, 2H, C9-H), 1.33-1.17 (m, 9H, Boc); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 164.4 (C15), 163.4 (CO), 154.7/154.4 (CO Boc, rotamers), 150.0, 149.5 (C6, C4), 148.3, 147.7 (C13, C16), 137.2 (C19), 128.6, 128.1, 128.0 (5C, C20, C21, C22, C23, C24), 114.9, 114.5 (C3, C17), 108.9/108.7 (C14, rotamers), 104.4/103.7 (C5, rotamers), 80.5/79.9 (q Boc, rotamers), 68.0 (C18), 51.8/50.7/50.5/49.4 (C11, C12, rotamers), 49.0 (C7), 35.3 (C10), 28.2 (3C, Boc), 27.6 (C8), 26.3 (C9); **HRMS (ESI$^+$):** calculated for $C_{28}H_{32}N_3O_4$: 474.2387, found $[M+H]^+$: 474.2383, calculated for $C_{28}H_{31}N_3NaO_4$: 496.2207, found $[M+Na]^+$: 496.2198.

Example 10b - (+)4-(4-(2-Pyridone))cytisine hydrochloride salt (106)

[0198]



106

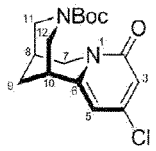
[0199] To a solution of ***N*-Boc** 4-(4-(2-benzyloxy)pyridine)cytisine **105** (448 mg, 0.95 mmol) in MeOH (5.7 mL) was added HCl (2.9 mL, conc. aq. sol.). The mixture was heated at reflux for 24 h. After cooling to r.t., the solvent was removed *in vacuo.* The crude was solubilized in MeOH (55 mL) and acetone (550 mL) was added. The mixture was stirred for 2 h. The solids were filtered, washed with acetone and dried to give **106** (254 mg, 84%) as a pale yellow solid.

[0200] mp: >200 °C, colourless powder; **$[\alpha]_D^{23}$** = +26 [c 0.5, water]; **FTIR ν_{max} / cm^{-1} (neat):** 2946, 2732, 2582, 1638, 1567; **^{1}H NMR (400 MHz, D_2O, δ_H):** 7.56 (d, 1H, J = 6.5 Hz, C18-H),

6.77-6.64 (m, 4H, C3-H, C5-H, C15-H, C19-H), 4.19 (d, 1H, J= 15.5 Hz, C7-H_a), 4.00 (dd, 1H, *J* = 5.5, 15.5 Hz, C7-H_b), 3.56-3.34 (m, 5H, C10-H, C11-H, C12-H), 2.89 (s, 1H, C8-H), 2.23-2.09 (m, 2H, C9-H); **^{13}C NMR (100 MHz, D_2O, δ_C):** 164.3 (C16), 164.0 (CO), 150.4 (C14), 148.4 (C4), 147.8 (C6), 135.4 (C18), 116.3, 114.3 (C15, C19), 107.2 (C3), 106.9 (C5), 49.3 (C11 or C12), 48.7 (C7), 48.2 (C11 or C12), 31.6 (C10), 24.7 (C8), 22.5 (C9); **HRMS (ESI^+):** calculated for $C_{16}H_{17}N_3O_2$: 284.1394, found $[M+H-HCl]^+$: 284.1386.

Example 11 - (-)*N*-Boc 4-Chlorocytisine (59)

[0201]



59

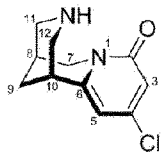
[0202] *N*-Boc-4-(4,4,5,5-Tetramethyl-1,3,2,-dioxaborolan-2-yl)-cytisine **58** was made following the genenal procedure for the borylation of cytisine outlined in Example 1 above in a 1.00 mmol scale.

[0203] The borylation reaction crude mixture was solubilized in MeOH (2.5 mL). A solution of $CuCl_2$ (470 mg, 3.5 mmol) in H_2O (2.5 mL) was added and the mixture was stirred at r.t. for 4 days under air. The mixture was diluted with NH_4OH (10 mL, 15 % aq.sol.) and the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [EtOAc] to give **59** (247 mg, 76%) as an off-white solid.

[0204] **R_f:** 0.21 [EtOAc]; mp: 148-149 °C (toluene); **FTIR ν_{max} / cm^{-1} (neat):** 2976, 2925, 1678, 1639, 1539; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 6.43 (s, 1H, C3-H), 6.08 (s, 1H, C5-H), 4.34-4.07 (m, 3H, C7-H_a, C11-H, C12-H), 3.74 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.12-2.94 (m, 3H, C10-H, C11-H, C12-H), 2.40 (s, 1H, C8-H), 1.90 (s, 2H, C9-H), 1.31-1.22 (m, 9H, Boc); **^{13}C NMR (100 Hz, $CDCl_3$, δ_C):** 162.5 (CO), 154.5/154.2 (CO Boc, rotamers), 149.9/149.4 (C4, rotamers), 146.1/145.8 (C6, rotamers), 115.7 (C3), 107.1/106.4 (C5, rotamers), 80.5/80.0 (q Boc, rotamers), 51.5/50.5/50.1/49.2 (C11, C12, rotamers), 48.9 (C7), 34.8 (C10), 28.0 (3C, Boc), 27.4 (C8), 26.0 (C9); **HRMS (ESI^+):** calculated for $C_{16}H_{22}ClN_2O_3$: 325.1313, found [M+H]+: 325.1301, calculated for $C_{16}H_{21}ClN_2NaO_3$: 347.1133, found [M+Na]+: 347.1121.

Example 12 - (-)4-Chlorocytisine (60)

[0205]



60

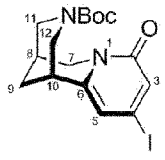
[0206] *N*-Boc-4-(4,4,5,5-Tetramethyl-1,3,2,-dioxaborolan-2-yl)-cytisine **58** was made following the genenal procedure for the borylation of cytisine as outlined above in Example 1 in a 1.00 mmol scale.

[0207] In a sealed tube, the borylation reaction crude mixture was solubilized in MeOH (2.5 mL) and an aqueous solution of $CuCl_2$ (470 mg, 3.5 mmol, 1.4 M) was added. The reaction was stirred at 90 °C for 18 h. The reaction was cooled, diluted with NH_4OH (5 mL, 15% aq.sol.) and the aqueous phase was extracted with DCM (5 × 5 mL). The combined organic layers were concentrated *in vacuo.* The residue was partitioned between 3M HCl (5 mL) and DCM (5 mL). The aqueous layer was washed with DCM (2 × 5 mL), basified with concentrated NH_4OH to pH 10 and extracted with DCM (5 × 5 mL). The combined organic layers were dried on Na_2SO_4, filtered and concentrated in vacuo. The crude reaction mixture was purified by flash column chromatography on silica gel [DCM/MeOH/ammonia (89:10:1)] to give **60** (179 mg, 80%) as an off-white solid. A high purity sample sample was obtained by recrystallization in toluene.

[0208] **R_f:** 0.22 [DCM/MeOH (10% MeOH)]; **mp:** 167-168 °C, colourless solid (toluene); **$[\alpha]_D^{25}$** = -32 [c 1.0, EtOH]; **FTIR ν_{max} / cm^{-1} (neat):** 3330, 3064, 2930, 2793, 1634, 1538; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 6.45 (d, 1H, *J* = 2.0 Hz, C3-H), 6.02 (d, 1H, *J* = 2.0 Hz, C5-H), 4.03 (d, 1H, *J* = 15.5 Hz, C7-H_a), 3.82 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.07-2.85 (m, 4H, C11-H, C12-H), 2.85 (s, 1H, C10-H), 2.31 (s, 1H, C8-H), 1.92 (s, 2H, C9-H), 1.36 (s, 1H, NH); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 162.7 (CO), 151.8 (C4), 146.0 (C6), 115.2 (C3), 106.3 (C5), 53.7, 52.9 (C11, C12), 49.8 (C7), 35.6 (C10), 27.5 (C8), 26.2 (C9); **HRMS (ESI^+):** calculated for $C_{11}H_{14}ClN_2O$: 225.0789, found $[M+H]^+$: 225.0791. **Anal. Calc.** for $C_{11}H_{13}ClN_2O$: theor. C = 58.80, H = 5.83, N = 12.47, found C = 58.40, H = 5.86, N = 12.32.

Example 13a - (-)*N*-Boc 4-Iodocytisine (64)

[0209]



64

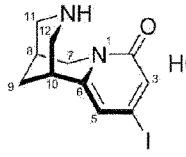
[0210] *N*-Boc-4-(4,4,5,5-Tetramethyl-1,3,2,-dioxaborolan-2-yl)-cytisine **58** was made following the genenal procedure for the borylation of cytisine as detailed in Example 1 above in a 5.00 mmol scale.

[0211] $Cu(NO_3)_2 \cdot 3H_2O$ (2.42 g, 10.0 mmol), NH_4I (1.45 g, 10.0 mmol) and sieves molecules 4 Å (500 mg) were added over the crude borylation reaction mixture, and the Schlenk flask was placed under nitrogen and backfilled with oxygen for three times. The reaction mixture was dissolved in DMF (25 mL) and heated at 80 °C for 24 h. The solvent was removed *in vacuo* and the residue was dissolved in DCM. The mixture was poored over ammonia (30 mL, 15% aq. sol.) and the aqueous phase was extracted with DCM (4 × 25 mL). The combined organic lawyers were dried on $MgSO_4$, filtered and concentrated, and the crude was purified by flash column chromatography [DCM/MeOH (2% MeOH)]) yielding iodide **64** (1.99 g, 95 %) as an off-yellow solid.

[0212] **R_f:** 0.21 [DCM:MeOH (3% MeOH)]; **mp:** 139 - 140 °C, needles (toluene); **FTIR ν_{max} / cm^{-1} (neat):** 2920, 1679, 1632, 1523; **^{1}H NMR (500 MHz, $CDCl_3$, δ_H, 52.0 °C):** 6.90 (d, *J* = 2.0 Hz, 1H, C3-H), 6.37 (d, *J* = 2.0 Hz, 1H, C5-H), 4.39-4.04 (m, 3H, C11-H, C12-H, C7-H), 3.72 (dd, *J* = 16.0, 7.0 Hz, 1H, C7-H), 3.09-2.93 (m, 2H, C11-H, C12-H), 2.89 (s, 1H, C10-H), 2.39 (s, 1H, C8-H), 1.99-1.87 (m, 2H, C9-H), 1.26 (s, 9H, Boc) ; **^{13}C NMR (125 MHz, $CDCl_3$, δ_C, 52.0 °C):** 161.6 (CO), 154.3 (CO Boc), 148.8 (C6), 126.3 (C3), 114.3 (C5), 108.2 (C4), 80.1 (q Boc), 50.4, 49.3 (C11, C12), 48.8 (C7), 34.5 (C10), 28.1 (3C, Boc), 27.5 (C8), 26.1 (C9) ; **HRMS (ESI$^+$):** calculated for $C_{16}H_{22}IN_2O_3$: 417.0670, found $[M+H]^+$: 417.0672,; calculated for $C_{16}H_{21}IN_2NaO_3$: 439.0489, found $[M+Na]^+$: 439.0491.

Example 13b - (+)4-Iodocytisine hydrochloride salt (65)

[0213]



65

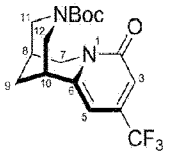
[0214] Following the general procedure A, *N*-Boc 4-Iodocytisine **64** (0.68 mmol) gave **65** (0.18 g, 86 %) as a colourless solid.

[0215] **mp:** >200°C, colourless powder; **$[\alpha]_D^{21}$** = +12 [c 1.0, water]; **FTIR ν_{max} / cm^{-1} (neat):** 2714, 1615, 1551, 1455; **^{1}H NMR (500 MHz, D_2O, δ_H):** 7.07 (s, 1H, C3-H), 6.89 (s, 1H, C5-H), 4.03 (d, *J* = 15.5 Hz, 1H, C7-H), 3.88 (dd, *J* = 15.5, 6.0 Hz, 1H, C7-H), 3.44 (s, 1H, C10-H),

3.41-3.29 (m, 4H, C11-H C12-H), 2.76 (s, 1H, C8-H), 2.08-1.98 (m, 2H, C9-H); **^{13}C NMR (125 MHz, D_2O, δ_C):** 163.3 (CO), 146.8 (C6), 126.4 (C3), 118.9 (C5), 110.7 (C4), 49.3, 48.2 (C11, C12), 48.7 (C7), 31.0 (C10), 24.7 (C8), 22.4 (C9); **HRMS (ESI$^+$):** calculated for $C_{11}H_{14}IN_2O$: 317.0145, found $[M+H^+-HCl]^+$: 317.0141.

Example 14a - (-)*N*-Boc 4-Trifluoromethylcytisine (76)

[0216]



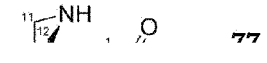
76

[0217] A Schlenk flask was charged with *N*-Boc 4-iodocytisine **64** (2.08 g, 5 mmol), copper iodide (4.52 g, 23.7 mmol), potassium fluoride anhydrous (1.38 g, 23.7 mmol) and trimethyl (trifluoromethyl)silane (3.5 mL, 23.7 mmol) and the reaction mixture was placed under nitrogen. DMF (24 mL, 0.2 M) was added and the reaction mixture was stirred at 50 °C for 16 h. The solvent was removed *in vacuo* and the residue distributed between DCM (20 mL) and ammonia (20 mL, 15% aq.sol.). The aqueous phase was extracted with DCM (3 × 20 mL) and the combined organic phases were dried over $MgSO_4$, the solids were filtered off and the solvent was evaporated *in vacuo.* Purification of the crude of the reaction by flash column chromatography [EtOAc/*n*-Hexane (4:1)] yielded **76** (1.52 g, 85%) as a colourless solid.

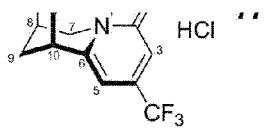
[0218] mp: 150-151 °C, colourless solid (toluene); **FTIR ν_{max} / cm^{-1} (neat):** 2981, 1680, 1664, 1547; **^{1}H NMR (500 MHz, $CDCl_3$, δ_H):** 6.73 (s, 1H, C3-H), 6.22 (s, 1H, C3-H), 4.48-4.15 (m, 3H, C11-H C12-H C7-H), 3.85 (dd, 1H, *J* = 16.0, 6.5 Hz, C7-H), 3.22-2.95 (m, 3H, C11-H, C12-H, C8-H), 2.49 (s, 1H, C10-H), 2.02 (m, 2H, C7-H), 1.43-1.15 (m, 9H, Boc); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C):** 162.2 (CO), 153.6 (d, *J* = 43.0 Hz, CO Boc), 151.0 (d, J= 53.0 Hz, C6), 140.5 (C4), 122.3 (d, *J* = 273 Hz, C13), 114.1 (C3), 100.1 (d, *J* = 83.0 Hz, C5), 80.0 (d, *J* = 62.0 Hz, q Boc), 51.1, 50.3 (C11, C12), 49.3 (C7), 35.3 (C10), 28.0 (3C, Boc), 27.4 (C8), 26.0 (C9); **^{19} F NMR (470 MHz, $CDCl_3$, δ_F):** -66.5 (d, *J* = 102 Hz); **HRMS (ESI$^+$):** calculated for $C_{17}H_{22}F_3N_2O_3$: 359.1577, found $[M+H]^+$: 359.1584, calculated for $C_{17}H_{21}F_3N_2NaO_3$: 381.1396, found $[M+Na]^+$: 381.1406; Anal. Calc: calculated: C 56.9 H 5.91 N 7.82, found: C 56.6, H 5.5 N 8.1.

Example 14b - (-)4-Trifluoromethylcytisine hydrochloride salt (77)

[0219]



77

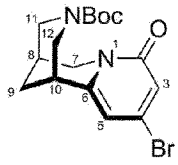


[0220] Following the general procedure A, *N*-Boc 4-trifluoromethylcytisine **76** (0.28 mmol) gave **77** (55 mg, 77 %) as a colourless solid.

[0221] mp: >200 °C; colourless powder; **$[\alpha]_D^{26}$** = -66 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1}(neat):** 1658, 1551, 1278, 1166, 857; **^{1}H NMR (500 MHz, D_2O, δ_H):** 6.82 (s, 1H, C3-H), 6.70 (s, 1H, C5-H), 4.11 (d, 1H, *J* = 15.5 Hz, C7-H), 3.97 (d, 1H, *J* = 15.5, 6.5 Hz, C7-H), 3.53-3.30 (m, 5H, C11-H C12-H C10-H), 2.78 (s, 1H, C8-H), 2.05 (m, 2H, C9-H); **^{13}C NMR (125 MHz, D_2O, δ_C):** 164.3 (CO), 149.3 (C6), 141.5 (q, J= 34.0 Hz, C4), 122.2 (q, J= 273.0 Hz, CF_3), 114.5 (C3), 104.4 (C5), 49.2, 48.9 (C11, C12), 48.2 (C7), 31.8 (C10), 24.7 (C8), 22.3 (C9); **^{19}F NMR (376 MHz, D_2O, δC, ppm):** -66.2 (s); **HRMS (ESI^+):** calculated for $C_{12}H_{14}F_3N_2O$; 259.1053, found $[M+H-HCl]^+$: 259.1060.

Example 15a - *N*-Boc4-Bromocytisine (61)

[0222]



61

[0223] *N*-Boc-4-(4,4,5,5-Tetramethyl-1,3,2,-dioxaborolan-2-yl)-cytisine **58** was made following the genenal procedure for the borylation of cytisine detailed in Example 1 above in a 5.00 mmol scale.

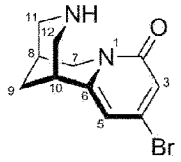
[0224] The borylation reaction crude mixture was solubilized in MeOH (12.5 mL) and cooled to 0 °C. A solution of $CuBr_2$ (3.35 g, 15.0 mmol) in H_2O (12.5 mL) was added over 5 min. The ice bath was removed after 30 min and the reaction mixture was stirred at r.t. for two days in an open-air flask. The mixture was diluted with NH_4OH (25 mL, 15% aq.sol.) and the aqueous phase extracted with DCM (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [EtOAc] to give **61** (1.54 g, 83%) as an off-white solid.

[0225] **R_f:** 0.25 [EtOAc]; **mp:** 163-164 °C, off-white solid (toluene); **FTIR ν_{max} / cm^{-1}(neat):** 2976, 2924, 1679, 1635, 1531; **^{1}H NMR (500 MHz, D_2O, δ_H):** 6.66 (s, 1H, C3-H), 6.21 (s, 1H,

C5-H), 4.35-4.06 (m, 3H, C7-H_a, C11-H, C12-H), 3.73 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.10-2.93 (m, 3H, C10-H, C11-H, C12-H), 2.40 (s, 1H, C8-H), 1.94 (s, 2H, C9-H), 1.31-1.23 (m, 9H, Boc); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 162.2 (CO), 154.4/154.2 (CO Boc, rotamers),149.6/149.1 (C6, rotamers) 135.1/134.6 (C4, rotamers), 119.2 (C3), 109.6/109.0 (C5, rotamers), 80.5/80.0 (q Boc, rotamers), 51.5/50.5/50.1/49.2 (C11, C12, rotamers), 48.9 (C7), 34.7 (C10), 28.0 (3C, Boc), 27.3 (C8), 26.0 (C9); **HRMS (ESI$^+$):** calculated for $C_{16}H_{22}BrN_2O_3$: 369.0808, found $[M+H]^+$: 369.0797, calculated for $C_{16}H_{21}BrN_2NaO_3$: 391.0628, found $[M+Na]^+$: 391.0620.

Example 15b - (-)4-Bromocytisine (62)

[0226]



62

[0227] *N*-Boc-4-(4,4,5,5-Tetramethyl-1,3,2,-dioxaborolan-2-yl)-cytisine **58** was made following the genenal procedure for the borylation of cytisine as detailed above in Example 1 in a 1.00 mmol scale.

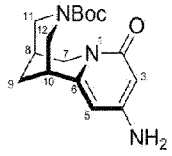
[0228] The borylation reaction crude mixture was solubilized in MeOH (2.5 mL) in a sealed tube, and a solution of $CuBr_2$ (670 mg, 3.0 mmol) in H_2O (2.5 mL) was added. The mixture was heated at 80 °C overnight. The mixture was cooled, diluted with NH_4OH (5 mL, 15% aq.sol.) and extracted with DCM (5 × 5 mL). The combined organic layers were concentrated *in vacuo.* The crude was partitioned between 3M HCl (5 mL) and DCM (5 mL). The aqueous layer was washed with DCM (2 × 5 mL), basified with concentrated NH_4OH to pH 10 and extracted with DCM (5 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [DCM/MeOH/NH_4OH: (89:10:1)] to give bromide **62** (228 mg, 85%) as an off-white solid. A high purity sample sample was obtained by recrystallization in toluene.

[0229] **R_f:** 0.21 [DCM/MeOH (10% MeOH)]; **mp:** 169-170 °C, off-white solid (toluene); **$[\alpha]_D^{25}$** = -32 [c 1.0, EtOH]; **FTIR ν_{max} / cm^{-1}(neat):** 3335, 3061, 2934, 2791, 2741, 1622, 1531; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 6.67 (d, 1H, *J* = 2.0 Hz, C3-H), 6.17 (d, 1H, *J* = 2.0 Hz, C5-H), 4.04 (d, 1H, *J* = 15.5 Hz, C7-H_a), 3.83 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.10-2.97 (m, 4H, C11-H, C12-H), 2.87-2.86 (m, 1H, C10-H), 2.35-2.32 (m, 1H, C8-H), 1.94 (s, 2H, C9-H), 1.46 (s, 1H, NH); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 162.5 (CO), 151.6 (C4), 135.0 (C6), 118.7 (C3),

108.8 (C5), 53.7, 52.9 (C11, C12), 49.8 (C7), 35.5 (C10), 27.6 (C8), 26.2 (C19); **HRMS (ESI$^+$):** calculated for $C_{11}H_{14}BrN_2O$: 269.0284, found $[M+H]^+$: 269.0289.

Example 16a - *N*-Boc 4-aminocytisine (80)

[0230]



80

Method A:

[0231] In a Schlenk tube, a mixture of *N*-Boc-4-bromo-cytisine **61** (184 mg, 0.5 mmol), NaN_3 (65 mg, 1.0 mmol), CuI (9 mg, 10 mol%), *L*-proline (17 mg, 30 mol%), NaOH (6 mg, 30 mol%) in EtOH/H_2O (7:3) (5 mL) was heated at 95 °C overnight. The mixture was cooled and partitioned between H_2O and DCM. The aqueous layer was extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [DCM/MeOH/NH_4OH (89:10:1)] to give amine **80** (116 mg, 76%) as an off-white solid.

Method B:

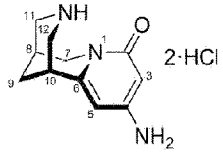
[0232] A mixture of *N*-Boc-4-bromo-cytisine **61** (92 mg, 0.25 mmol) and copper (2 mg, 10 mol%) in NH_4OH (0.5 mL, conc. aq. sol.) was stirred at 100 °C for 24 h in a sealed tube. The mixture was cooled and extracted with DCM (5 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [DCM/MeOH/NH_4OH: (89:10:1)] to give **80** (64 mg, 85%) as an off-white solid.

[0233] **R_f:** 0.28 [DCM/MeOH (10% MeOH)]; **mp:** >200 °C; **FTIR ν_{max} / cm^{-1} (neat):** 3414, 3302, 3211, 2905, 1679, 1642, 1551; **^{1}H NMR (400 MHz, MeOD, δ_H):** 5.83 (s, 1H, C3-H), 5.51 (s, 1H, C5-H), 4.29-4.02 (m, 3H, C7-H_a, C11-H, C12-H), 3.68 (dd, 1H, J = 6.5, 14.5 Hz, C7-H_b), 3.34-2.93 (m, 3H, C10-H, C11-H, C12-H), 2.36 (s, 1H, C8-H), 1.98 (s, 2H, C9-H), 1.34-1.24 (m, 9H, Boc); **^{13}C NMR (100 MHz, MeOD, δ_C):** 165.2 (CO), 157.7 (CO Boc), 154.7 (C6), 149.0/148.8 (C4, rotamers), 99.6/99.3 (C3, rotamers), 91.9 (C5), 80.1/79.6 (q Boc, rotamers), 51.4/50.2/50.1 (C11, C12, rotamers), 49.0 (C7), 34.9 (C10), 27.9/27.7 (C8, rotamers), 27.0

(3C, Boc), 25.7 (C9); **HRMS (ESI$^+$):** calculated for $C_{16}H_{24}N_3O_3$: 306.1812, found $[M+H]^+$: 306.1809.

Example 16b - (+)4-aminocytisine dihydrochloride salt (81)

[0234]



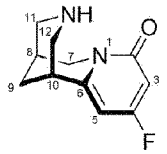
81

[0235] Following the general procedure A, *N*-Boc 4-amino-cytisine **80** (1.0 mmol) gave amine **81** (273 mg, 98%) as an off-white solid.

[0236] mp: >200 °C; **$[\alpha]_D^{25}$** = +77 [c 1.0, MeOH]; **FTIR ν_{max} / cm^{-1} (neat):** 2929, 2790, 1649, 1533; **^{1}H NMR (400 MHz, D_2O, δ_H):** 6.26 (s, 1H, C3-H), 4.09 (d, 1H, J= 15.0 Hz, C7-H_a), 3.95 (dd, 1H, *J* = 6.5, 15.0 Hz, C7-H_b), 3.41-3.26 (m, 5H, C10-H, C11-H, C12-H), 2.68 (s, 1H, C8-H), 2.07-1.94 (m, 2H, C9-H), C5-H not detected due to deuterium exchange; **^{13}C NMR (100 MHz, D_2O, δ_C):**160.9 (CO), 159.1 (C4), 148.1 (C6),104.5 (d, J= 7.2 Hz, C3), 91.5-91.0 (m, C5), 49.2 (C11 or C12), 48.8 (C7), 48.1 (C11 or C12), 31.2 (C10), 24.5 (C8), 22.5 (C9); **HRMS (ESI$^+$):** calculated for $C_{11}H_{16}N_3O$: 206.1288, found $[M+H^+-2HCl]^+$: 206.1292.

Example 17 - (-)4-Fluorocytisine (82)

[0237]



82

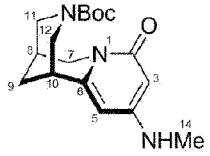
[0238] To a solution of *N*-Boc-4-amino-cytisine **80** (305 mg, 1.0 mmol) in HF-pyridine complex (70%, 2.0 mL) at -20 °C was slowly added tBuONO (0.18 mL, 1.5 mmol) over 1 min. The reaction was stirred at -20 °C for 30 min, then allowed to warm to r.t. for 2 h and finally heated at 60 °C overnight. The mixture was cooled to 0 °C and quenched to pH 10 with conc. aq. NH_4OH. The mixture is diluted with EtOAC (10 mL) and filtered to remove the insoluble salts. The aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layers were concentrated *in vacuo.* The crude was partitioned between 3M HCl (5 mL) and DCM (5 mL). The aqueous layer was washed with DCM (2 × 5 mL), basified with concentrated NH_4OH to pH

10 and extracted with DCM (5 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [DCM/MeOH/NH_4OH (89:10:1)] to give **82** (140 mg, 67%) as a pale yellow solid. An analytic pure sample was obtained by recrystallization in toluene.

[0239] R_f: 0.25 [DCM/MeOH (20% MeOH)]; **mp:** 143-145 °C (toluene); **$[\alpha]_D^{25}$=** -92 [c 1.0, EtOH]; **FTIR ν_{max} / cm^{-1} (neat):** 3391, 3289, 3069, 2948, 2898, 2852, 1644, 1552; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 6.06 (dd, 1H, *J* = 2.5, 11.0 Hz, C3-H), 5.87 (dd, 1H, *J* = 2.5, 7.0 Hz, C5-H), 4.04 (d, 1H, *J* = 15.5 Hz, C7-H_a), 3.83 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.08-2.95 (m, 4H, C11-H, C12-H), 2.89-2.86 (m, 1H, C10-H), 2.34-2.29 (m, 1H, C8-H), 1.93 (t, 2H, *J* = 3.0 Hz, C9-H), 1.56 (br s, 1H, NH); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 169.9 (d, *J* = 264.0 Hz, C4), 164.8 (d, *J* = 19.0 Hz, CO), 153.5 (d, *J* = 13.5 Hz, C6), 99.6 (d, *J* = 16.5 Hz, C3), 96.5 (d, *J* = 26.0 Hz, C5), 53.7, 52.9 (C11, C12), 49.8 (C7), 36.0 (d, *J* = 2.0 Hz, C10), 27.5 (C8), 26.2 (C9); **^{19}F NMR (376 MHz, $CDCl_3$, δ_F):** -99.6 (m); **HRMS (ESI^+):** calculated for $C_{11}H_{14}FN_2O$: 209.1090, found $[M+H]^+$: 209.1095. **Anal. Calc.** for $C_{11}H_{13}FN_2O$: theor. C = 63.45, H = 6.29, N = 13.45, found C = 63.05, H = 6.33, N = 13.20.

Example 18a - *N*-Boc 4-(*N*-Methylamino)cytisine (83)

[0240]



83

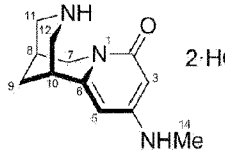
[0241] A mixture of *N*-Boc-4-bromo-cytisine **61** (369 mg, 1.0 mmol) and copper (7 mg, 10 mol%) in 40% aq. $MeNH_2$ (2.0 mL) was stirred at 100 °C for 24 h in a sealed tube. The mixture was cooled to r.t. and extracted with DCM (5 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude was purified by flash chromatography on silica gel (DCM/MeOH (94:6)] to give **83** (274 mg, 86%) as an off-white solid.

[0242] R_f: 0.58 [DCM/MeOH (10% MeOH)]; **mp:** 198-200 °C (toluene); **FTIR ν_{max} / cm^{-1} (neat):** 3266, 2928, 1684, 1641, 1571; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 5.49 (s, 1H, C3-H), 5.37 (s, 1H, C5-H), 4.53 (s, 1H, NH), 4.28-4.03 (m, 3H, C7-H_a, C10-H, C12-H), 3.72 (dd, 1H, *J* = 6.5, 15.0 Hz, C7-H_b), 3.02-2.70 (m, 6H, C10-H, C11-H, C12-H, C14-H), 2.31 (s, 1H, C8-H), 1.93-1.81 (m, 2H, C9-H), 1.32-1.22 (m, 9H, Boc); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 164.7 (CO), 156.0 (CO Boc), 154.8/154.5 (C6, rotamers), 147.9/147.3 (C4, rotamers), 98.0/97.2 (C3,

rotamers), 90.4/90.1 (C5, rotamers), 80.2/79.6 (q Boc, rotamers), 51.7/50.7/50.4/49.4 (C11, C12, rotamers), 47.9 (C7), 34.8 (C10), 29.4 (C14), 28.1 (3C, Boc), 27.6 (C8), 26.4 (C9); **HRMS (ESI$^+$):** calculated for $C_{17}H_{26}N_3O_3$: 320.1969, found $[M+H]^+$: 320.1974.

Example 18b - (+)4-(*N*-Methylamino)cytisine dihydrochloride salt (84)

[0243]



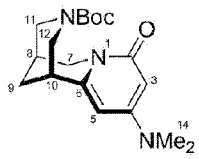
84

[0244] Following the general procedure A, 4-*N*-methylamino-*N*-Boc-cytisine **83** (0.77 mmol) gave amine **84** (190 mg, 85%) as a colourless solid.

[0245] mp: >200 °C, colourless powder; **$[\alpha]_D^{25}$ =** +66 [c 1.0, MeOH]; **FTIR ν_{max} / cm^{-1} (neat):** 3240, 2939, 2714, 2583, 1644, 1557; **^{1}H NMR (400 MHz, D_2O, δ_H):** 6.25 (s, 1H, C3-H), 4.09 (d, 1H, *J* = 15.0 Hz, C7-H_a,), 3.95 (dd, 1H, *J* = 6.5, 15.0 Hz, C7-H_b), 3.42-3.26 (m, 5H, C10-H, C11-H, C12-H), 2.71 (s, 4H, C8-H, C14-H), 2.05-1.94 (m, 2H, H9), C5-H not detected due to deuterium exchange; **^{13}C NMR (100 MHz, D_2O, δ_C):** 160.7 (CO), 158.7 (C4), 147.1 (C6),103.6 (C3), 88.4-87.9 (C5), 49.3 (C11 or C12), 48.7 (C7), 48.1 (C11 or C12), 31.3 (C10), 28.5 (C14), 24.5 (C8), 22.6 (C9); **HRMS (ESI$^+$):** calculated for $C_{12}H_{18}N_3O$: 220.1444, found $[M+H-2HCl]^+$: 220.1441.

Example 19a - *N*-Boc 4-(*N, N'*-Dimethylamino)cytisine (85)

[0246]



85

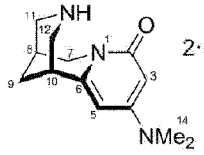
[0247] A mixture of *N*-Boc-4-bromo-cytisine **61** (369 mg, 1.0 mmol) and copper (6 mg, 10 mol %) in 40% aq. Me_2NH (2.0 mL) was stirred at 100 °C for 24 h in a sealed tube. The mixture was cooled, diluted with 35% ammonia (2 mL) and the aqueous phase was extracted with DCM (5 × 10 mL). The combined organic layers were dried on Na_2SO_4, filtered and concentrated *in vacuo.* The crude reaction mixture was purified by flash column chromatography on silica gel [DCM/MeOH/NH_4OH (94.5:5:0.5)] to give **85** (212 mg, 64%) as a

white foam.

[0248] **R_f:** 0.19 [DCM/MeOH (10% MeOH)]; **FTIR ν_{max} / cm^{-1} (neat):** 2972, 2928, 2863, 1687, 1645, 1578; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 5.64 (d, 1H, *J* = 2.5 Hz, C3-H), 5.42 (s, 1H, C5-H), 4.31-4.04 (m, 3H, C7-H_a, C11-H, C12-H), 3.73 (dd, 1H, *J* = 6.5, 15.0 Hz, C7-H_b), 3.04-2.81 (m, 9H, C10-H, C11-H, C12-H, 2 x C14-H), 2.31 (s, 1H, C8-H), 1.94-1.83 (m, 2H, C9-H), 1.32-1.19 (m, 9H, Boc); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 164.2 (CO), 156.0 (CO Boc), 154.8/154.4 (C4, rotamers), 147.9/147.5 (C6, rotamers), 95.6/95.1 (C3, rotamers), 91.9/91.5 (C5, rotamers), 80.2/79.5 (q Boc, rotamers), 51.8/50.7/50.4/49.3 (C11, C12, rotamers), 47.8 (C7), 39.3 (2C, C14), 35.2 (C10), 28.1 (3C, Boc), 27.5 (C8), 26.5 (C9); **HRMS (ESI^+):** calculated for $C_{18}H_{28}N_3O_3$: 334.2125, found $[M+H]^+$: 334.2113.

Example 19b - (+)4-(*N, N'*-dimethylamino)cytisine dihydrochloride salt (86)

[0249]



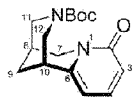
2·H **86**

[0250] Following the general procedure A, N-Boc-4-N, N'-dimethylamino-cytisine **85** (202 mg, 0.61 mmol) gave amino **86** (174 mg, 93%) as a colourless solid.

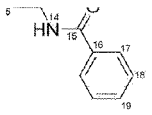
[0251] **mp:** >200 °C, colourless powder; **$[\alpha]_D^{25}$** = +84 [c 1.0, MeOH]; **FTIR ν_{max} / cm^{-1} (neat):** 3202, 2960, 2753, 1644, 1551; **^{1}H NMR** (400 **MHz, D_2O, δ_H):** 6.41 (s, 1H, C3-H), 4.12 (d, 1H, *J* = 15.0 Hz, C7-H_a), 3.98 (dd, 1H, *J* = 6.5, 15.0 Hz, C7-H_b), 3.42-3.27 (m, 5H, C10-H, C11-H, C12-H), 2.96 (s, 6H, C14-H), 2.68 (s, 1H, C8-H), 2.07-1.96 (m, 2H, C9 H), H5 not detected due to deuterium exchange; **^{13}C NMR (100 MHz, D_2O, δ_C):** 159.8 (CO), 157.4 (C4), 147.1 (C6),102.5 (d, *J* = 5.0 Hz, C3), 89.0-88.5 (m, C5), 49.3 (C11 or C12), 48.7 (C7), 48.1 (C11 or C12), 39.1 (2C, C14), 31.5 (C10), 24.5 (C8), 22.6 (C9); **HRMS (ESI^+):** calculated for $C_{13}H_{20}N_{3O}[M+H-2HCl]^+$: 234.1601, found: 234.1606.

Example 20a - *N*-Boc 4-(*N*-benzoylamino)cytisine (95)

[0252]



95

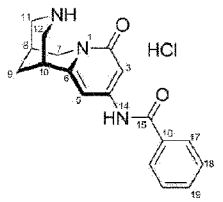


[0253] To a mixture of *N*-Boc-4-bromo-cytisine **61** (369 mg, 1.0 mmol), CuI (19 mg, 10 mol %), benzamide (145 mg, 1.2 mmol) and K_2CO_3 (276 mg, 2.0 mmol) in dry toluene (5.0 mL) was added *N*,*N*'-dimethylethylenediamine (11 µL, 10 mol%). The mixture was heated at 110 °C for three days. After cooling, the mixture was diluted with H_2O (10 mL) and the aqueous phase was extracted with DCM (5 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude reaction mixture was purified by flash column chromatography on silica gel [DCM/MeOH/NH_4OH (95:5:0.1)] to give the **95** (425 mg) as a yellow solid. The resultant solid was washed in boiling toluene (10 mL) overnight to give **95** (372 mg, 91%) as a colourless solid.

[0254] **R_f:** 0.49 [DCM/MeOH (10% MeOH)]; **mp:** >200 °C, colourless powder; **FTIR ν_{max} / cm^{-1} (neat):** 3067, 2972, 2864, 1648, 1626, 1548, 1483; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 7.74-7.72 (m, 2H, C17-H), 7.40-7.28 (m, 3H, C18-H, C19-H), 7.06/6.75 (2 br s, 2 × 0.5H, C3-H, rotamers), 6.62/6.33 (2 br s, 2 × 0.5H, C5-H, rotamers), 4.08-3.94 (m, 4H, NH, C7-H_a, C11-H, C12-H), 3.61 (dd, 1H, J = 6.5, 15.5 Hz, C7-H_b), 3.16-2.91 (m, 3H, C10-H, C11-H, C12-H), 2.27 (s, 1H, C8-H), 1.83 (s, 2H, C9-H), 1.16-1.05 (m, 9H, Boc); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 167.5 (C14), 164.5 (CO), 154.5 (CO Boc), 149.5, 148.8 (C6, C4), 133.9 (C16), 131.9 (C19), 128.2 (C17, C21), 127.4 (C18, C20), 102.2/101.9 (C3, rotamers), 101.2 (C5), 80.5/79.9 (q Boc, rotamers), 51.3/50.3/50.1/49.1/48.9/48.7/48.5/48.4/48.2/48.0/47.8 (C7, C11, C12, rotamers), 34.8 (C10), 27.5 (3C, Boc), 27.2 (C8), 25.7 (C9); **HRMS (ESI$^+$):** calculated for $C_{23}H_{28}N_3O_4$: 410.2074, found $[M+H]^+$: 410.2064, calculated for $C_{23}H_{27}N_3$ NaO_4: 432.1894, found $[M+Na]^+$: 432.1884.

Example 20b - (+)4-(*N*-Benzoylamino)cytisine hydrochloride salt (96)

[0255]



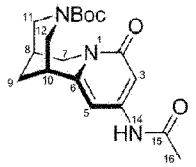
96

[0256] Following the general procedure B, *N*-Boc-4-(*N*-benzamide)-cytisine **95** (363 mg, 0.89 mmol) gave benzamide **96** (290 mg, 80%) as a colourless solid.

[0257] mp: >200 °C, colourless powder; **$[\alpha]_D^{26}$** = +30 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1} (neat):** 2937, 2798, 1677, 1633, 1599; **^{1}H NMR (400 MHz, D_2O, δ_H):** 7.55 (d, 2H, *J* = 7.5 Hz, C17-H, C21-H), 7.45-7.42 (m, 1H, C19-H), 7.32-7.28 (m, 2H, C18-H, C20-H), 6.76 (d, 1H, *J* = 2.0 Hz, C3-H), 6.62 (d, 1H, *J* = 2.0 Hz, C5-H), 3.96 (d, 1H, *J* = 15.5 Hz, C7-H_a), 3.70 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.39-3.23 (m, 5H, C10-H, C11-H, C12-H), 2.64 (s, 1H, C8-H), 1.96 (d, 1H, *J* = 13.5 Hz, C9-H), 1.76 (d, 1H, *J* = 13.5 Hz, C9-H); **^{13}C NMR (100 MHz, D_2O, δ_C):**169.1 (C14), 164.6 (CO), 149.2 (C4), 147.6 (C6), 133.0 (C19), 132.6 (C16), 128.7 (C18, C20), 127.5 (C17, C21), 104.1 (C5), 102.8 (C3), 49.2 (C11 or C12), 48.6 (C7), 48.2 (C11 or C12), 31.5 (C10), 24.6 (C8), 22.5 (C9); **HRMS (ESI$^+$):** calculated for $C_{18}H_{20}N_3O_2$: 310.1550, found $[M+H-HCl]^+$: 310.1549.

Example 21a - *N*-Boc 4-(*N*-acetylamino)cytisine (93)

[0258]



93

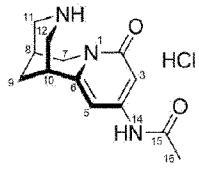
[0259] To a mixture of *N*-Boc-4-bromo-cytisine **61** (369 mg, 1.0 mmol), CuI (19 mg, 10 mol%), acetamide (70 mg, 1.2 mmol) and K_2CO_3 (276 mg, 2.0 mmol) in dry toluene (5.0 mL) was added *N*,*N'*-dimethylethylenediamine (11 µL, 10 mol%). The mixture was heated at 110 °C for 24 h. After cooling to r.t., the mixture was diluted with H_2O (10 mL), then extracted with DCM (5 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [DCM/MeOH/NH_4OH (95:5:0.1)] to give **93** (340 mg, 98%) as a pale yellow foam with few impurities. The product was used in the next step without further purification.

[0260] R_f: 0.49 [DCM/MeOH (10% MeOH)]; **FTIR ν_{max} / cm^{-1} (neat):** 2971, 2929, 1688, 1644, 1556, 1422; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 7.11/6.74 (2x s, 1H, C3-H, rotamers), 6.58/6.23 (2 × s, 1H, H5, rotamers), 4.34-4.12 (m, 3H, C7-H_a, C11-H, C12-H), 3.77 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.04-2.97 (m, 3H, C10-H, C11-H, C12-H), 2.51 (s, 1H, C8-H), 2.09 (s, 3H, C16-H), 2.01-1.89 (m, 2H, C9-H), 1.33-1.21 (m, 9H, Boc); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 170.2 (C15), 164.4 (CO), 154.8/154.5 (CO Boc, rotamers), 148.5, 148.3 (C6, C4), 101.9 (C3), 100.4 (C5), 80.7/79.6 (q Boc, rotamers), 51.6/50.7/50.5/49.3 (C11, C12, rotamers), 48.6 (C7), 35.0 (C10), 28.1 (3C, Boc), 27.5 (C8), 26.2 (C9), 24.6 (C16); **HRMS (ESI$^+$):** calculated for $C_{18}H_{26}N_3O_4$: 348.1918, found $[M+H]^+$: 348.1916, $C_{18}H_{25}N_3NaO_4$: 370.1737, found $[M+Na]^+$:

370.1737.

Example 21b - (+)4-(*N*-acetylamino)cytisine (94)

[0261]



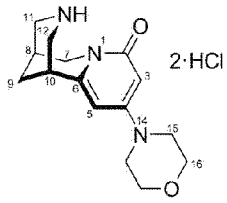
94

[0262] Following the general procedure B, *N*-Boc-4-(*N*-acetamide)-cytisine **93** (306 mg, 0.88 mmol) gave **94** (250 mg, quantitative) as a pale yellow solid.

[0263] mp: >200 °C, colourless powder; **$[\alpha]_D^{25}$** = +30 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1} (neat):** 2457, 2374, 1612, 1530, 1506; **^{1}H NMR (400 MHz, D_2O, δ_H):** 6.79 (d, 1H, *J* = 2.0 Hz, C3-H), 6.64 (d, 1H, *J* = 2.0 Hz, C5-H), 4.04 (d, 1H, *J* = 15.5 Hz, C7-H_a), 3.88 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.40-3.25 (m, 5H, C10-H, C11-H, C12-H), 2.70 (s, 1H, C8-H), 2.05-1.91 (m, 5H, C9-H, C16-H); **^{13}C NMR (100 MHz, D_2O, δ_C):** 173.6 (C15), 164.5 (CO), 149.4 (C4), 148.1 (C6), 104.4 (C5), 101.7 (C3), 49.2 (C11 or C12), 48.8 (C7), 48.1 (C11 or C12), 31.5 (C10), 24.6 (C8), 23.6 (C16), 22.5 (C9); **HRMS (ESI^+):** calculated for $C_{13}H_{18}N_3O_2$: 248.1394, found $[M+H-HCl]^+$: 248.1394.

Example 22 - (+)4-*N*-morpholinecytisine dihydrochloride salt (92)

[0264]



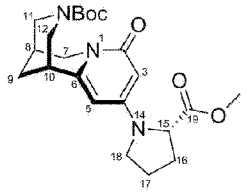
92

[0265] A sealed tube was charged with *N*-Boc-4-bromo-cytisine **61** (370 mg, 1.0 mmol), copper (II) oxide (15 mg, 0.1 eq.) and morpholine (0.4 mL, 5 eq.), and the reaction mixture was dissolved in water (2.0 mL, 0.5 M) and heated at 100 °C under air for 18 h. The reaction mixture was cooled to r.t. and the aqueous phase was extracted with DCM (4 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The resulting *N*-Boc protected cytisine derivative was deprotected and converted into the HCl salt using the general procedure A, yielding **92** (180 mg, 85%) as a colourless solid.

[0266] mp: >200 °C, colourless powder; **$[\alpha]_D^{25}$** = +61 [c 1.0, MeOH]; **FTIR ν_{max} / cm^{-1}(neat):** 2560, 1641, 1541; **^{1}H NMR (500 MHz, D_2O, δ_H):** 6.48 (s, 1H, C3-H), 4.09 (d, 1H, *J* = 16.0 Hz, C7-H), 3.96 (dd, 1H, *J* = 16.0, 5.5 Hz, C7-H), 3.74 (s, 4H, C11-H, C12-H), 3.39 (m, 9H, CH_2 morpholine, C10-H), 2.71 (s, 1H, C8-H), 2.04 (m, 2H, C9-H); C5-H is not visible due to H-solvent exchange; **^{13}C NMR (125 MHz, D_2O, δ_C):** 162.5 (CO), 157.9 (C6), 147.4 (C4), 101.6 (C3), 91.7 (C5), 65.8 (2C, C15), 49.4, 48.2 (C11, C12), 48.4 (C7), 45.7 (2C, C16), 31.7 (C10), 24.6 (C8), 22.7 (C9); **HRMS (ESI^+):** calculated for $C_{15}H_{22}N_3O_2$: 276.1707, found $[M+H-HCl]^+$: 276.1718.

Example 23a - *N*-Boc 4-(*N*-(*L*-proline methyl ester)cytisine (136)

[0267]



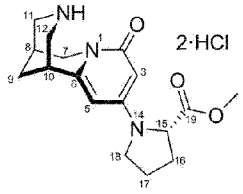
136

[0268] A mixture of *N*-Boc 4-bromocytisine **61** (369 mg, 1.0 mmol), L-proline methyl ester hydrochloride (198 mg, 1.2 mmol), Cs_2CO_3 (814 mg, 2.5 mmol), $Pd(OAc)_2$ (11 mg, 5 mol%) and (±)-BINAP (44 mg, 7 mol%) in dry toluene (5.0 mL) was stirred for 48 h at 100 °C. The mixture was cooled to r.t., filtered through a short pad of Celite®, washed with EtOAc and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [DCM/MeOH/NH_4OH (95:5:0.1)] to give **136** (371 mg, 89%) as an off-white foam with few impurities.

[0269] R_f: 0.11 [DCM/MeOH (5% MeOH)]; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 5.55 (s, 1H, C3-H), 5.28 (s, 1H, C5-H), 4.27-4.02 (m, 4H, C7-H_a, C11-H, C12-H, C15-H), 3.73-3.67 (m, 4H, C7-H_b, C20-H), 3.48 (s, 1H, C18-H), 3.36 (s, 1H, C18-H), 3.00-2.85 (m, 3H, C10-H, C11-H, C12-H), 2.31-2.16 (m, 2H, C18-H, C16H), 2.08-1.99 (m, 3H, C16-H, C17-H), 1.91-1.81 (m, 2H, C9-H), 1.31-1.18 (m, 9H, Boc); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C):** 173.3 (C19), 164.0 (CO), 154.7/154.4 (CO Boc, rotamers), 153.0 (C4), 148.6/148.2 (C6, rotamers), 96.2/95.5 (C3, rotamers), 92.3 (C5), 80.2/79.6 (q Boc, rotamers), 60.0 (C15), 52.3 (C20), 50.7/50.6/50.4/49.4 (C11, C12, rotamers), 47.9 (C18), 47.8 (C7), 35.1 (C10), 30.6 (C16), 28.1 (3C, Boc), 27.5 (C8), 26.3 (C9), 23.5 (C17); **HRMS (ESI^+):** calculated for $C_{22}H_{32}N_3O_5$: 418.2336, found $[M+H]^+$: 418.2340, calculated for $C_{22}H_{31}N_3NaO_5$: 440.2156, found $[M+Na]^+$: 440.2161.

Example 23b - (+)4-(*N*-(*L*-proline methyl ester)cytisine dihydrochloride salt (137)

[0270]



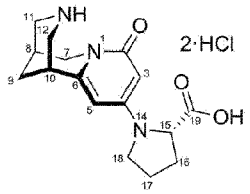
137

[0271] Following the general procedure B, *N*-Boc-4-(*N*-(*L*-proline methyl ester)-cytisine **136** (0.88 mmol) gave **137** (304 mg, 89%) as a colourless solid.

[0272] mp: >200 °C, colourless powder; **$[\alpha]_D^{26}$** = +2 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1} (neat):** 2951, 2714, 2385, 1740, 1637, 1538, 1484,; **^{1}H NMR (400 MHz, D_2O, δ_H):** 6.38 (s, 1H, C3-H), 4.62 (s, 1H, C15-H), 4.25 (d, 1H, *J* = 15.0 Hz, C7-H_a), 4.12 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.79 (s, 3H, C20-H), 3.60-3.40 (m, 7H, C10-H, C11-H, C12-H, C18-H), 2.82 (s, 1H, C8-H), 2.43-2.26 (m, 2H, C16-H), 2.18-1.99 (m, 4H, C14-H, C17-H), H3 not detected due to deuterium exchange; **^{13}C NMR (100 MHz, D_2O, δ_C):** 174.6 (C19), 160.9 (CO), 155.2 (C4), 147.8 (C6), 102.9 (C3), 60.5 (C15), 53.2 (C20), 49.3, 48.7, 48.6, 48.0 (C7, C11, C12, C18), 31.4 (C10), 30.1 (C16), 24.5 (C8), 23.0 (C17), 22.5 (C20), C3 not detected due to deuterium exchange; **HRMS (ESI^+):** calculated for $C_{17}H_{24}N_3O_3$: 318.1812, found $[M+H-2HCl]^+$: 318.1802.

Example 24 - (-)4-(*N*-(*L*-proline)cytisine dihydrochloride salt (138)

[0273]



138

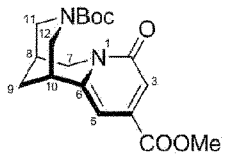
[0274] A mixture of *N*-Boc-4-(*N*-(*L*-proline methyl ester)-cytisine **138** (341 mg, 0.82 mmol) in HCl (37% in water, 8.2 mL) was heated at reflux for 48 h. The mixture was cooled to r.t. and concentrated *in vacuo.* The crude was solubilized in MeOH (4 mL) and then acetone was slowly added (40 mL). The resulting suspension was stirred for 1 h. The solid was filtered off, washed with acetone and dried under vacuum to give **138** (261 mg, 85%) as a pale brown solid.

[0275] mp: >200 °C, colourless powder; **$[\alpha]_D^{26}$** = -32 [c 0.5, water]; **FTIR ν_{max} / cm^{-1} (neat):**

2908, 2754, 2583, 1719, 1640, 1546; **^{1}H NMR (400 MHz, D_2O, δ_H):** 6.28 (s, 1H, C3-H), 4.51 (s, 1H, C15-H), 4.21 (d, 1H, *J* = 15.0 Hz, C7-H_a,), 4.07 (dd, 1H, *J* = 6.5, 15.0 Hz, C7-H_b), 3.59-3.39 (m, 7H, C10-H, C11-H, C12-H, C18-H), 2.81 (s, 1H, C8-H), 2.46-2.36 (m, 1H, C16-H), 2.28-2.22 (m, 1H, C16-H), 2.17-2.01 (m, 4H, C14-H, C17-H), H5 not detected due to deuterium exchange; **^{13}C NMR (100 MHz, D_2O, δ_C):** 176.1 (C19), 160.8 (CO), 155.2 (C4), 147.8 (C6), 102.8 (C3), 60.6 (C15), 49.3, 48.8, 48.6, 48.0 (C7, C11, C12, C18), 31.4 (C10), 30.3 (C16), 24.5 (C8), 23.0 (C17), 22.5 (C9), C3 not detected; **HRMS (ESI$^+$):** calculated for $C_{16}H_{22}N_3O_3$ $[M+H-2HCl]^+$: 304.1656, found: 304.1651.

Example 25a - *N*-Boc 4-(carboxymethyl)cytisine (119)

[0276]



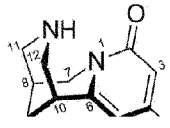
119

[0277] A solution of *N*-Boc-4-bromo-cytisine **61** (369 mg, 1.0 mmol), Et_3N (0.4 mL, 2.5 mmol), dppp (82 mg, 0.2 mmol) and $Pd(OAc)_2$ (45 mg, 0.2 mmol) in DMF/MeOH (1:1) (5 mL) was stirred at 80 °C under 1 atm of CO for 24 h. The mixture was cooled to r.t., filtered through Celite® and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [EtOAc] to give **119** (300 mg, 86%) as a yellow foam.

[0278] **R_f:** 0.25 [EtOAc]; **FTIR ν_{max} / cm^{-1} (neat):** 2931, 1683, 1657, 1575, 1547; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 7.00 (s, 1H, C3-H), 6.54 (s, 1H, C5-H), 4.31-4.06 (m, 3H, C7-H_a, C11-H, C12-H), 3.85 (s, 3H, Me), 3.79 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.14-2.88 (m, 3H, C10-H, C11-H, C12-H), 2.41 (s, 1H, C8-H), 1.98-1.91 (m, 2H, C9-H), 1.28-1.15 (m, 9H, Boc); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 165.4 (C14), 163.2 (CO), 154.32 (CO Boc), 150.0/149.5 (C4, rotamers) 139.5 (C6), 118.4 (C3), 104.1/103.5 (C5, rotamers), 80.4/79.9 (q Boc, rotamers), 52.7 (C7), 51.5/50.5/50.3 (C11, C12, rotamers), 49.2 (Me), 35.0 (C10), 28.0 (3C, Boc), 27.4 (C8), 26.0 (C9); **HRMS (ESI$^+$):** calculated for $C_{18}H_{25}N_2O_5$: 349.1758, found $[M+H]^+$: 349.1750.

Example 25b - (-)4-carboxymethycytisine (120)

[0279]



120

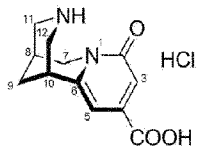


[0280] To a solution of *N*-Boc-4-methyl-ester-cytisine **119** (95 mg, 0.27 mmol) in DCM (1.3 mL) was added TFA (0.21 mL, 2.7 mmol). The mixture was stirred for 24 h then concentrated *in vacuo.* The crude was partitioned between HCl 3M (5 mL) and DCM (5 mL). The aqueous layer was washed with DCM (2 × 5 mL), basified with Na_2CO_3 to pH 9 and then extracted with DCM (5 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give **120** (55 mg, 81%) as an off-white solid. An analytic pure sample was obtained by recrystallization in toluene.

[0281] R_f**:** 0.23 [DCM/MeOH (10% MeOH)]; **mp:** 141-142 °C, (toluene); $[\alpha]_D^{25}$ = -96 [c 0.3, water]; **FTIR** ν_{max} / cm^{-1} **(neat):** 3300, 2926, 2893, 2847, 1719 (w), 1648, 1571; ^{1}**H NMR (400 MHz,** $CDCl_3$**,** δ_H**):** 7.02 (d, 1H, *J* = 1.5 Hz, C3-H), 6.49 (d, 1H, *J* = 1.5 Hz, C5-H), 4.08 (d, 1H, J= 15.5 Hz, C7-H_a), 3.88 (dd, 1H, J= 6.5, 15.5 Hz, C7-H_b), 3.87 (s, 3H, Me), 3.08-2.95 (m, 5H, C10-H, C11-H, C12-H), 2.33 (s, 1H, C8-H), 1.97-1.90 (m, 2H, C9-H), 1.50 (s, 1H, NH); ^{13}**C NMR (100 MHz,** $CDCl_3$**,** δ_C**):** 165.6 (COOMe), 163.4 (CO), 151.9 (C6), 139.4 (C4), 118.0 (C3), 103.3 (C5), 53.8, 52.9 (C12, C11), 52.7 (Me), 50.2 (C7), 35.8 (C10), 27.7 (C8), 26.2 (C9); **HRMS (ESI$^+$):** calculated for $C_{13}H_{17}N_2O_3$: 249.1234, found $[M+H]^+$: 249.1245.

Example 26 - (-)4-Carboxylic acidcytisine, hydrochloride salt (229)

[0282]



229

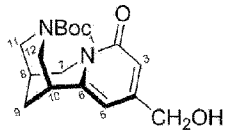
[0283] A solution of *N*-Boc-4-methyl-ester-cytisine **119** (263 mg, 0.75 mmol) in HCl (37% aq.sol. 7.5 mL) was heated at reflux for 24 h. The mixture was cooled to r.t. then concentrated *in vacuo.* The crude reaction mixture was solubilized in MeOH (30 mL) and then acetone was slowly added (300 mL). The resulting suspension was stirred for 1 h. The solids were filtered off, washed with acetone and dried under vacuum to give **229** (164 mg, 81%) as a colourless solid.

[0284] mp: > 200 °C, colourless powder; $[\alpha]_D^{22}$ = -33 [c 0.3, water]; **FTIR** ν_{max} / cm^{-1} **(neat):** 1698, 1648, 1543, 1471; ^{1}**H NMR (400 MHz,** D_2O**,** δ_H**):** 6.88 (s, 1H, C3-H), 6.79 (s, 1H, C5-H), 4.06 (d, 1H, *J* = 15.5 Hz, C7-H_a), 3.91 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.44-3.27 (m, 5H, C10-H, C11-H, C12-H), 2.75 (s, 1H, C8-H), 2.08-1.96 (m, 2H, C9-H); ^{13}**C NMR (100 MHz,** D_2O**,**

δ_C):167.7 (COOH), 164.8 (CO), 148.0 (C6), 142.1 (C4), 118.1 (C3), 107.8 (C5), 49.4 (C11 or C12), 49.0 (C7), 48.2 (C11 or C12), 31.7 (C10), 24.7 (C8), 22.5 (C9); **HRMS (ESI^+):** calculated for $C_{12}H_{15}N_2O_3$: 235.1077, found $[M+H-HCl]^+$: 235.1078.

Example 27a - *N*-Boc 4-(hydroxymethyl)cytisine (121)

[0285]



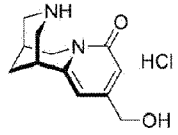
121

[0286] To a solution of *N*-Boc-4-methyl ester-cytisine **119** (350 mg, 1.00 mmol) in THF (4 mL) was added $LiAlH_4$ (1.0 M in Et_2O) dropwise at -78°C during 5 min. and the reaction mixture was stirred for 3.5 h. EtOAc (2 mL) was added dropwise followed by the addition of a saturated Rochelle's salt solution (10 mL). The reaction mixture was stirred for 30 min, and the aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography [DCM/MeOH (2% MeOH to 5% MeOH)] yielded **121** (194 mg, 62%) as a colourless foam.

[0287] mp: 201-203 °C, colourless solid (toluene); **^{1}H NMR (500 MHz, $CDCl_3$, δ_H):** 6.49 (s, 1H, C3-H), 6.16 (s, 1H, C5-H), 4.55 (s, 2H, C14-H), 4.28-4.16 (m, 3H, C7-H, C11-H, C12-H), 3.86 (dd, 1H, *J* = 6.5, 16.0 Hz, C7-H), 3.19-2.92 (m, 3H, C11-H, C12-H, C10-H), 2.45 (s, 1H, C8-H), 1.99 (m, 2H, C9-H), 1.41-1.18 (m, 9H, Boc). **^{13}C NMR (125 MHz, $CDCl_3$, δ_C):** 163.5 (CO), 154.6 (C6), 153.5 (C4), 112.7 (C3), 104.5 (C5), 80.6, 80.5 (C11, C12), 63.2 (C13), 48.8 (C7), 34.9 (C8), 28.0 (3C, Boc), 27.6 (C10), 26.2 (C9). The quaternary carbon of the boc group has not been found.

Example 27b - (-)4-(Hydroxymethyl)cytisine hydrochloride salt (122)

[0288]



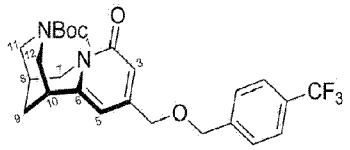
122

[0289] Following the general procedure A, *N*-Boc 4-hydroxymethylcytisine **121** (0.60 mmol) gave alcohol **122** (120 mg, 90%) as a colourless solid.

[0290] mp: >200 °C, colourless solid; **$[\alpha]_D^{23}$** = -24 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1}(neat):** 3292, 2726, 2323, 1643, 1571; **^{1}H NMR (500 MHz, D_2O, δ_H):** 6.50 (s, 1H, C3-H), 6.47 (s, 1H, C5-H), 4.50 (s, 2H, C14-H), 4.10 (d, 1H, *J* = 15.0 Hz, C7-H), 3.96 (dd, 1H, *J* = 15.0, 6.0 Hz, C7-H), 3.48-3.31 (m, 5H, C11-H C12-H C10-H), 2.77 (s, 1H, C8-H), 2.11-1.99 (m, 2H, C9-H); **^{13}C NMR (125 MHz, D_2O, δ_C):** 164.8 (CO), 156.1 (C4), 147.0 (C6), 112.5 (C3), 108.4 (C5), 61.5 (C13), 49.6 (C7), 48.5, 48.3 (C11, C12), 31.5 (C10), 24.7 (C8), 22.6 (C9); m/z **(ESI^+):** 224 $[M+H-HCl]^+$; **HRMS (ESI^+):** calculated for $C_{12}H_{16}N_2O_2$: 224.1757, found $[M+H-HCl]^+$: 224.1758.

Example 28a - *N*-Boc 4-(4-(Trifluoromethyl)benzyl)oxycytisine (123)

[0291]



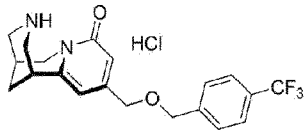
123

[0292] To a solution of the alcohol **121** (240 mg, 0.75 mmol) in dry THF (7.5 mL) was added NaH (33 mg, 1.1 eq., 60% dispersion in mineral oil) and the mixture was stirred at 0 °C. After 30 min, TBAI (14 mg, 0.05 eq.) and 4-(trifluoromethyl) benzyl bromide (358 mg, 2 eq.) were added. The reaction was allowed to warm up to r.t. and stirred for 18 h. The reaction was quenched with water (10 mL) and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude reaction mixtuer was purified by flash column chromatography on silica gel [DCM/MeOH (1% MeOH)] to give **123** (250 mg, 71%) as colourless solid, which was used in the next step without further purification.

[0293] FTIR ν_{max} / cm^{-1}(neat): 2975, 2931, 2864, 1686, 1660, 1545; **^{1}H NMR (500 MHz, $CDCl_3$, δ_H):** 7.60 (d, 2H, *J* = 8.5 Hz, C18-H), 7.46 (d, 2H, *J* = 8.5 Hz, C17-H), 6.42 (s, 1H, C3-H), 6.06 (d, 1H, *J* = 1.5 Hz, C5-H), 4.58 (s, 2H, CH_2), 4.37 (s, 2H, CH_2), 4.26-4.08 (m, 3H, C7-H, C11-H, C12-H), 3.80 (dd, 1H, *J* = 15.0, 6.5 Hz, C7-H), 3.13-2.89 (m, 3H, C10-H, C11-H, C12-H), 2.40 (s, 1H, C8-H), 1.95 (m, 2H, C9-H), 1.39-1.12 (s, 9H, Boc); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C):** 163.4 (CO), 154.6 (CO), 149.9 (C4), 148.5 (C6), 141.7 (CF_3), 129.3 (q, *J* = 33.8 Hz, Ar), 127.7 (2C, Ar), 125.4 (2C, Ar), 123.3 (Ar), 114.2 (C3), 104.5/103.7 (C5 rotamers), 80.4/79.4 (q Boc rotamers), 71.5 (CH_2), 70.5 (CH_2), 51.6/50.6/50.5/49.3 (C11, C12 rotamers), 48.8 (C7), 34.9 (C10), 28.1 (3C, Boc), 27.5 (C8), 26.2 (C9); **HRMS (ESI^+):** found $[M+H]^+$: 479.2142, calculated $C_{25}H_{30}F_3N_2O_4$: 479.2152.

Example 28b - (-)4-(4-(Trifluoromethyl)benzyl)oxycytisine (124)

[0294]



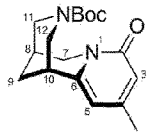
124

[0295] Eter **123** (0.25 g, 0.52 mmol) was converted into the HCl salt using the general procedure A yielding **124** (110 mg, 60%) as a colourless solid.

[0296] mp: >200 °C, colourless solid; **$[\alpha]_D^{25}$** = -18 [c 1.0, MeOH]; **FTIR ν_{max} / cm^{-1}(neat):** 2974, 2930, 1687, 1658, 1545, 1421; **^{1}H NMR (500 MHz, D_2O, δ_H):** 7.65 (d, 2H, *J* = 9.0 Hz, Ar), 7.50 (d, 2H, *J* = 9.0, Ar), 6.47 (s, 1H, C3-H), 6.45 (s, 1H, C5-H), 4.64 (s, 2H, CH_2), 4.48 (s, 2H, CH_2), 4.07 (d, 1H, *J* = 15.0 Hz, C7-H), 3.92 (dd, 1H, *J* = 15.0, 6.0 Hz, C7-H), 3.47-3.28 (m, 5H, C10-H, C11-H, C12-H), 2.76 (s, 1H, C8-H), 2.07 (d, 1H, *J* = 13.5 Hz, C9-H), 1.99 (d, 1H, J= 13.5 Hz, C9-H) ; **^{13}C NMR (125 MHz, D_2O, δ_C):** 164.8 (CO), 152.4 (C4), 146.9 (C6), 141.2 (CF_3), 129.6 (q, *J* = 30 Hz, C-CF_3), 128.7 (2C, Ar), 125.4 (2C, Ar), 123.4 (Ar), 114.4 (C3), 108.7 (C5), 72.1 (CH_2), 70.0 (CH_2), 49.5, 48.3 (C11, C12), 48.6 (C7), 31.5 (C10), 24.8 (C8), 22.6 (C9); **^{19}F NMR (376 MHz, D_2O, δ_F):** -63.2 (s); **HRMS (ESI^+):** calculated for $C_{26}H_{22}F_3N_2O_2$: 379.1628, found $[M+H^+-HCl]^+$: 379.1623.

Example 29a - N-Boc 4-Methyl cytisine (109)

[0297]



109

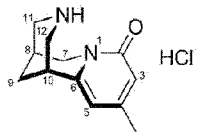
[0298] To a mixture of *N*-Boc-4-bromo-cytisine **61** (369 mg, 1.0 mmol) and $PdCl_2(PPh_3)_2$ (35 mg, 5 mol%) in dry toluene (5.0 mL) was added Me_4Sn (0.35 mL, 2.5 mmol). The mixture was stirred at 100 °C for 24 h under N_2. The mixture was cooled to r.t., filtered through Celite®, washed with EtOAc (50 mL) and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [DCM/MeOH (97:3)] to give **109** (308 mg, quantitative) as a pale yellow solid with few impurities.

[0299] **R_f:** 0.26 [DCM/MeOH (5% MeOH)]; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 6.19 (s, 1H, C3-H), 5.87 (s, 1H, C5-H), 4.30-4.06 (m, 3H, C7-H_a, C11-H, C12-H), 3.74 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.06-2.90 (m, 3H, C10-H, C11-H, C12-H), 2.35 (s, 1H, C8-H), 2.09 (s, 3H, Me), 1.94-

1.85 (m, 2H, C9-H), 1.29-1.16 (m, 9H, Boc); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 163.5 (CO), 154.7/154.3 (CO Boc, rotamers), 150.4/149.8 (C4, rotamers), 148.0/147.5 (C6, rotamers), 116.0 (C3), 108.3/107.6 (C5, rotamers), 80.4/79.7 (q Boc, rotamers), 51.8/50.7/50.5/49.4 (C11, C12, rotamers), 48.6 (C7), 34.8 (C10), 28.1 (3C, Boc), 27.6 (C8), 26.3 (C9), 21.2 (Me); **HRMS (ESI$^+$):** calculated for $C_{17}H_{25}N_2O_3$: 305.1860, found $[M+H]^+$: 305.1864, calculated for $C_{17}H_{24}N_2NaO_3$: 327.1679, found $[M+Na]^+$: 327.1684.

Example 29b - (-)4-Methylcytisine hydrochloride salt (110)

[0300]



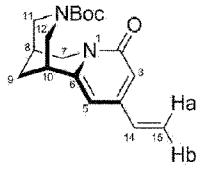
110

[0301] Following the general procedure A, N-Boc 4-Methylcytisine **109** (1.40 mmol) gave **110** (337 mg, quantitative) as a colourless solid.

[0302] mp: >200 °C, colourless powder; **$[\alpha]_D^{26}$** = -28 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1} (neat):** 2714, 2604, 2038, 1727, 1643, 1567; **^{1}H NMR (400 MHz, D_2O, δ_H):** 6.67 (s, 1H, C3-H), 6.59 (s, 1H, C5-H), 4.21 (d, 1H, *J* = 15.5 Hz, C7-H_a,), 4.07 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.52-3.37 (m, 5H, C10-H, C11-H, C12-H), 2.83 (s, 1H, C8-H), 2.27 (s, 3H, Me), 2.16-2.13 (m, 2H, C9-H); **^{13}C NMR (100 MHz, D_2O, δ_C):** 163.3 (CO), 156.0 (C4), 146.5 (C6), 114.6 (C3), 114.5 (C5), 49.3 (C11 or C12), 49.0 (C7), 48.1 (C11 or C12), 31.2 (C10), 24.7 (C8), 22.4 (C9), 20.4 (Me); **HRMS (ESI$^+$):** calculated for $C_{12}H_{17}N_2O$: 205.1335, found $[M+H^+-HCl]^+$: 205.1336.

Example 30a - (-)*N*-Boc 4-Vinylcytisine (115)

[0303]



115

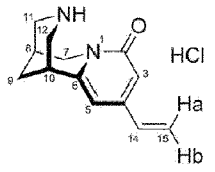
[0304] A mixture of *N*-Boc-4-bromo-cytisine **61** (369 mg, 1.0 mmol), 2, 4, 6-trivinylcyclotriboroxane pyridine complex (194 mg , 1.2 mmol), K_2CO_3 (276, 2.0 mmol) and $PdCl_2(PPh_3)_2$ (35 mg, 5 mol%) in dioxane/H_2O (8:2) (5.0 mL) was stirred at 90 °C for 24 h

under N_2. The mixture was cooled to r.t., filtered through Celite®, and washed with EtOAc (50 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude reaction mixture was purified by flash column chromatography on silica gel [DCM/MeOH (97:3)] to give **115** (271 mg, 86%) as a pale yellow foam, which was used in the next step without further purification.

[0305] **R_f:** 0.22 [DCM/MeOH (5% MeOH)]; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 6.44 (s, 1H, C14-H), 6.32 (s, 1H, C3-H), 6.14 (s, 1H, C5-H), 5.77 (d, 1H, *J* = 17.5 Hz, C15-H_A), 5.39 (d, 1H, *J* = 11.0 Hz, C15-H_B), 4.33-4.10 (m, 3H, C7-H_a, C11-H, C12-H), 3.77 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.09-2.89 (m, 3H, C10-H, C11-H, C12-H), 2.38 (s, 1H, C8-H), 1.97-1.88 (m, 2H, C9-H), 1.30-1.15 (m, 9H, Boc); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 163.8 (CO), 154.6/154.3 (CO Boc, rotamers), 148.6/148.2 (C6, rotamers), 147.1/146.9 (C4, rotamers), 134.8 (C14), 118.9 (C15), 114.7 (C3), 102.9/102.2 (C5, rotamers), 80.4/79.7 (q Boc, rotamers), 51.9/50.7/50.4/49.3 (C11, C12, rotamers), 48.8 (C7), 35.0 (C10), 28.1 (3C, Boc), 27.6 (C8), 26.3 (C9); **HRMS (ESI^+):** calculated for $C_{18}H_{25}N_2O_3$: 317.1860, found $[M+H]^+$: 317.1844, calculated for $C_{18}H_{24}N_2NaO_3$: 339.1679, found $[M+Na]^+$: 339.1665.

Example 30b - (+)4-Vinylcytisine hydrochloride salt (116)

[0306]



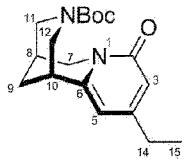
116

[0307] Following the general procedure B, *N*-Boc-4-Vinyl-cytisine **115** (271 mg, 0.86 mmol) gave **116** (214 mg, 99%) as a colourless solid.

[0308] **mp:** >200 °C, colourless powder; **$[\alpha]_D^{26}$** = +18 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1} (neat):** 3376, 2938, 2717, 2574, 2386, 1643, 1552; **^{1}H NMR (400 MHz, D_2O, δ_H):** 6.82 (d, 1H, *J* = 1.5 Hz, C3-H), 6.63-6.55 (m, 2H, C5-H, C14-H), 6.03 (d, 1H, *J* = 17.5 Hz, C15-H_A), 5.60 (d, 1H, J= 11.0 Hz, C15-H_B), 4.16 (d, 1H, J= 15.5 Hz, C7-H_a), 4.00 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.52-3.37 (m, 5H, C10-H, C11-H, C12-H), 2.83 (s, 1H, C8-H), 2.18-2.04 (m, 2H, C9-H); **^{13}C NMR (100 MHz, D_2O, δ_C):** 164.5 (CO), 150.3 (C4), 146.8 (C6), 133.2 (C14), 122.0 (C15), 113.2 (C5), 108.0 (C3), 49.4 (C11 or C12), 48.8 (C7), 48.1 (C11 or C12), 31.5 (C10), 24.7 (C8), 22.6 (C9); **HRMS (ESI^+):** calculated for $C_{13}H_{17}N_2O$: 217.1335, found $[M+H-HCl]^+$: 217.1332.

Example 31a - *N*-Boc 4-Ethylcytisine (117)

[0309]



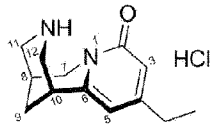
117

[0310] To a solution of 4-vinyl-*N*-Boc-cytisine **115** (353 mg, 1.1 mmol) in methanol (22 mL) was added Pd/C 10% w/w (35 mg). The reaction vessel was placed under vacuum and backfilled with hydrogen three times. The mixture was stirred at r.t. for 24 h under 1 atm of H_2. The mixture was filtered through Celite®, washed with EtOAc (50 mL) and concentrated *in vacuo* to give **117** (337 mg, 95%) as an off-white solid.

[0311] **R_f**: 0.17 [DCM/MeOH (5% MeOH)]; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 6.22 (s, 1H, C3-H), 5.88 (s, 1H, C5-H), 4.33-4.30 (m, 3H, C7-H_a, C11-H, C12-H), 3.74 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.05-2.91 (m, 3H, C10-H, C11-H, C12-H), 2.41-2.34 (m, 3H, C8-H, C14-H), 1.94-1.85 (m, 2H, C9-H), 1.28-1.14 (m, 12H, C15-H, Boc); **^{13}C NMR (100 MHz, $CDCl_3$,** δ_C): 163.8 (CO), 156.0/155.5 (CO Boc, rotamers), 154.7/154.3 (C4, rotamers), 148.1/147.6 (C6, rotamers), 114.5 (C3), 107.3/106.4 (C5, rotamers), 80.3/79.7 (q Boc, rotamers), 51.7/50.7/50.5/49.3 (C11, C12, rotamers), 48.7 (C7), 34.8 (C10), 28.1 (3C, Boc), 27.6 (C8), 26.5 (C14), 26.3 (C9), 13.7/13.3 (C15, rotamers); **HRMS (ESI$^+$):** calculated for $C_{18}H_{27}N_2O_3$: 319.2016, found $[M+H]^+$: 319.2015, calculated for $C_{18}H_{26}N_2NaO_3$: 341.1836, found $[M+Na]^+$: 341.1840.

Example 31b - (-)4-Ethylcytisine hydrochloride salt (118)

[0312]



118

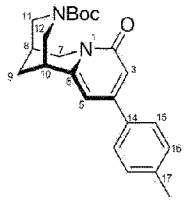
[0313] Following the general procedure A, *N*-Boc-4-ethyl-cytisine **117** (0.92 mmol) gave **118** (227 mg, 97%) as a colourless solid.

[0314] **mp**: > 200 °C, colourless powder; **$[\alpha]_D^{26}$ =** -16 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1} (neat):** 2724, 2603, 1716, 1634, 1555; **^{1}H NMR (400 MHz, D_2O, δ_H):** 6.67 (d, 1H, *J* = 1.5 Hz, C3-H),

6.57 (s, 1H, C5-H), 4.21 (d, 1H, *J* = 15.5 Hz, C7-H_a), 4.06 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.53-3.39 (m, 5H, C10-H, C11-H, C12-H), 2.83 (s, 1H, C8-H), 2.58 (q, 2H, *J* = 7.5 Hz, C14-H), 2.17-2.06 (m, 2H, H9), 1.16 (t, 3H, *J* = 7.5 Hz, C15-H); **^{13}C NMR (100 MHz, D_2O, δ_C):** 163.9 (CO), 161.1 (C4), 146.5 (C6), 113.5 (C5), 112.9 (C3), 49.4 (C11 or C12), 48.9 (C7), 48.1 (C11 or C12), 31.3 (C10), 27.7 (C14), 24.7 (C8), 22.5 (C9), 12.6 (C15); **HRMS (ESI$^+$):** calculated for $C_{13}H_{19}N_2O$: 219.1492, found $[M+H^+-HCl]^+$: 219.1494.

Example 32a - *N*-Boc 4-*p*-tolylcytisine (72)

[0315]



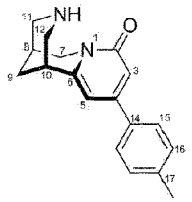
72

[0316] A Schlenk tube was charged with *N*-Boc-4-bromo-cytisine **61** (370 mg, 1.0 mmol), potassium carbonate (250 mg, 1.8 eq.), tetrakis (triphenylphosphine) palladium (0) (58 mg, 5 mol%) and p-tolylboronic acid (160 mg, 1.2 eq. and a mixture of DME/water (5:1, 10 mL) was added. The reaction mixture was heated at 80 °C for 18 h. The solution was cooled and the solvent was removed *in vacuo*. The crude of the reaction was partitioned between water (15 mL) and DCM (15 mL), and the aqueous phase was extracted with DCM (3 × 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification of the crude reaction mixture by flash column chromatography [DCM/MeOH (1.5% MeOH)] afforded **72** as a colourless solid. Recrystallization of the crude in hot toluene afforded **72** (260 mg, 71%) as a colourless foam.

[0317] mp: 194-195 °C, colourless foam (toluene); **FTIR ν_{max} / cm^{-1}(neat):** 2922, 1678, 1648, 1431; **^{1}H NMR (500 MHz, $CDCl_3$, δ_H):** 7.44 (d, 2H, *J* = 8.0 Hz, Ar), 7.20 (d, 2H, *J* = 8.0 Hz, Ar), 6.62 (s, 1H, C3-H), 6.28 (s, 1H, C5-H), 4.41-4.13 (m, 3H, C11-H, C12-H, C7-H), 3.83 (dd, 1H, *J* = 15.0, 6.5 Hz, C7-H), 3.15-2.91 (m, 3H, C11-H, C12-H, C10-H), 2.39 (s, 1H, C8-H), 2.36 (s, 3H, Me), 1.99 (d, 1H, *J* = 13.5 Hz, C9-H), 1.93 (d, 1H, *J* = 13.5 Hz, C9-H), 1.23 (s, 9H, Boc); **^{13}C NMR (125 MHz, $CDCl_3$, δ_c):** 163.5 (CO), 154.3 (CO), 150.5 (C3), 148.6 (C5), 139.2 (Ar), 134.9 (Ar), 129.5 (2C, Ar), 126.5 (2C, Ar), 113.2 (C3), 104.6 (C5), 79.8 (q Boc), 51.0, 50.6 (C11, C12), 48.6 (C7), 35.0 (C10), 28.0 (3C, Boc), 27.7 (C8), 26.4 (C9), 21.1 (Me); **HRMS (ESI$^+$):** calculated for $C_{23}H_{29}N_2O_3$: 381.2173, found $[M+H]^+$: 381.2164; calculated for $C_{23}H_{28}N_2NaO_3$: 403.1992, found $[M+Na]^+$: 403.1984.

Example 32b - (+)4-*p*-Tolylcytisine (73)

[0318]



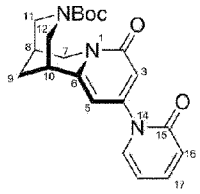
73

[0319] In a schlenk flask *N*-Boc-4-*p*-tolyl-cytisine **72** (270 mg, 0.71 mmol) was dissolved in DCM (7.0 mL) and TFA (0.3 mL, 10 eq.) was added. The reaction mixture was stirred for 18 h at r.t. Then, water (10 mL) was added over the reaction mixture and the aqueous phase was washed with DCM (3 × 15 mL). Then, ammonia solution (20 mL, 15% aq. sol.) was added and the aqueous phase was extracted with DCM (3 × 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated, yielding **73** (140 mg, 74 %) as a colourless solid. Recrystallization of the product in hot toluene afforded **73** (73 mg, 40 %) as a colourless solid.

[0320] mp: > 200°C, colourless solid (toluene); **$[\alpha]_D^{25}$**=+44 [c 1.0, MeOH]; **FTIR ν_{max} /cm^{-1}(neat):** 1638, 1552, 1531; **^{1}H NMR (500 MHz, MeOD, δ_H):** 7.56 (d, 2H, *J* = 8.0 Hz, Ar), 7.27 (d, 2H, *J* = 8.0 Hz, Ar), 6.65 (d, 1H, *J* = 2.0 Hz, C3-H), 6.58 (d, 1H, *J* = 2.0 Hz, C5-H), 4.10 (d, 1H, *J* = 15.5 Hz, C7-H), 3.93 (dd, 1H, *J* = 15.5, 7.0 Hz, C7-H), 3.10-2.97 (m, 5H, C11-H, C12-H, C10-H), 2.38 (s, 3H, Me), 2.34 (s, 1H, C8-H), 2.01 (m, 2H, C9-H); **^{13}C NMR (125 MHz, MeOD, δ_C):** 164.5 (CO), 152.0 (C4), 151.4 (C6), 139.5 (Ar), 134.4 (Ar, 2C), 129.3 (Ar, 2C), 126.2 (Ar), 111.2 (C3), 105.6 (C5), 53.0, 51.9 (C11, C12), 49.5 (C7), 35.4 (C10), 27.6 (C8), 25.5 (C9), 19.7 (Me); **HRMS (ESI$^+$):** calculated for $C_{18}H_{21}N_2O$: 281.1648, found $[M+H]^+$: 281.1653.

Example 33a - *N*-Boc 4-(*N*-2-pyridone)cytisine (107)

[0321]



107

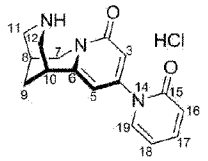
[0322] To a mixture of *N*-Boc-4-bromo-cytisine **61** (369 mg, 1.0 mmol), CuI (19 mg, 10 mol%), 2-hydroxypyridine (114 mg, 1.2 mmol) and K_2CO_3 (277 mg, 2.0 mmol) in dry toluene (5.0 mL) was added *N,N'*-dimethylethylenediamine (22 µL, 20 mol%). The mixture was heated at 110 °C for 24 h under nitrogen. More CuI (19 mg, 10 mol%) and *N,N'*-dimethylethylenediamine

(DMEDA) (22 µL, 20 mol%) were added, and the stirring was carried on for 36 h. After cooling, the mixture was diluted with EtOAc (50mL) then filtered through Celite®. The organic layer was washed with NH_4OH (2 × 10 mL, 15% aq.sol.). The combined aqueous layers were extracted with DCM (5 × 10 mL). The combined organic layers (EtOAc and DCM) were dried on Na_2SO_4, filtered and concentrated *in vacuo.* The crude reaction mixture was purified by flash column chromatography on silica gel [DCM/MeOH (95:5)] to give **107** (336 mg, 88%) as a pale yellow solid, which was used in the next step without further purification.

[0323] R_f: 0.17 [DCM/MeOH (5% MeOH)]; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 7.37-7.33 (m, 1H, C17-H), 7.22 (d, 1H, *J* = 6.0 Hz, C19-H), 6.57 (d, 1H, *J* = 9.0 Hz, C16-H), 6.33-6.32 (m, 2H, C3-H, C5-H), 6.24-6.21 (m, 1H, C18-H), 4.36-4.15 (m, 3H, C7-H_a, C11-H, C12-H), 3.76 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.04-2.98 (m, 3H, C10-H, C11-H, C12-H), 2.41 (s, 1H, C8-H), 2.04-1.90 (m, 2H, C9-H), 1.31-1.24 (m, 9H, Boc); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C):** 163.6 (CO py), 161.5 (CO), 154.7/154.4 (CO Boc, rotamers), 151.1 (C4), 149.7 (C6), 140.4 (C17), 136.7/136.2 (C19, rotamers), 122.3/122.0 (C16, rotamers), 113.0/112.7 (C3, rotamers), 106.7 (C18), 104.9/104.3 (C5, rotamers), 80.5/80.0 (q Boc, rotamers), 51.4/50.6/50.5/49.3 (C11, C12, rotamers), 49.1 (C7), 35.1 (C10), 28.1 (3C, Boc), 27.4 (C8), 26.0 (C9); **HRMS (ESI$^+$):** calculated for $C_{21}H_{26}N_3O_4$: 384.1918, found $[M+H]^+$: 384.1921, calculated for $C_{21}H_{25}N_3NaO_4$: 406.1737, found $[M+Na]^+$: 406.1747.

Example 33b - (-)4-(*N*-2-pyridone)cytisine hydrochloride salt (108)

[0324]



108

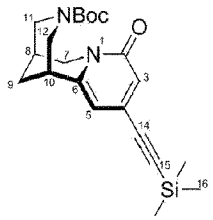
[0325] Following the general procedure B, *N*-Boc 4-(*N*-2-pyridone)-cytisine **107** (289 mg, 0.75 mol) gave **108** (182 mg, 76%) as a pale orange solid.

[0326] mp: >200 °C, colourless powder (toluene); **$[\alpha]_D^{25}$** = -20 [c 0.5, water]; **FTIR ν_{max}/cm^{-1} (neat):** 2922, 2710, 2601, 1662, 1638, 1595; ^{1}H **NMR (400 MHz, D_2O, δ_H):** 7.74-7.70 (m, 1H, C17-H), 7.60 (dd, 1H, *J* = 1.5, 7.0 Hz, C19-H), 6.69-6.62 (m, 4H, C3-H, C5-H, C16-H, C18-H), 4.23 (d, 1H, *J* = 15.5 Hz, C7-H_a), 4.07 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.57-3.40 (m, 5H, C10-H, C11-H, C12-H), 2.87 (s, 1H, C8-H), 2.20-2.10 (m, 2H, C9-H); **^{13}C NMR (100 MHz, D_2O, δ_C):** 165.1 (CO), 163.1 (CO py), 151.4 (C4), 148.8 (C6), 143.6 (C17), 137.3 (C19), 119.8 (C16), 114.3 (C3), 109.4 (C18), 108.0 (C5), 49.2 (C11 or C12), 48.9 (C7), 48.1 (C11 or C12),

31.7 (C10), 24.7 (C8), 22.4 (C9); **HRMS (ESI$^+$):** calculated for $C_{16}H_{18}N_3O_2$: 284.1394, found $[M+H-HCl]^+$: 284.1388.

Example 34a - *N*-Boc 4-(trimethylsilylacetylene)cytisine (125)

[0327]



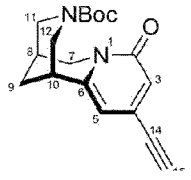
125

[0328] To a mixture of *N*-Boc-4-bromo-cytisine 61 (369 mg, 1.0 mmol), CuI (19 mg, 10 mol%) and $PdCl_2(PPh_3)_2$ (35 mg, 5 mol%) in dry THF (10.0 mL) was added i-Pr_2NH (0.42 mL, 3.0 mmol) followed by trimethylsilylacetylene (0.16 mL, 1.1 mmol). The mixture was stirred at r.t. for 24 h under nitrogen. The mixture was diluted with DCM (50 mL). The organic layer was washed with NH_4Cl (10 mL, sat. sol.), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [EtOAc] to give **125** (406 mg, quantitative) as a pale brown foam with few impurities (palladium catalyst). The product was used in the next step without further purification.

[0329] R_f: 0.21 [EtOAc]; **FTIR ν_{max} / cm^{-1} (neat):** 2972, 2932, 1689, 1651, 1574; ^{1}H **NMR (400 MHz, $CDCl_3$, δ_H):** 6.48 (s, 1H, C3-H), 6.05 (s, 1H, C5-H), 4.32-4.09 (m, 3H, C7-H_a, C11-H, C12-H), 3.78 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.08-2.92 (m, 3H, C10-H, C11-H, C12-H), 2.38 (s, 1H, C8-H), 1.96-1.88 (m, 2H, C9-H), 1.30-1.23 (m, 9H, Boc), 0.21 (s, 9H, C16-H); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 162.7 (CO), 154.4 (CO Boc), 148.8, 148.5 (C6, C4), 119.7 (C3), 107.9, 107.3 (C5, rotamers), 107.9 (C14), 100.2 (C15), 80.4, 79.9 (q Boc, rotamers), 51.5, 50.5, 50.3, 49.3 (C11, C12, rotamers), 48.8 (C7), 34.7 (C10), 28.0 (3C, Boc), 27.5 (C8), 26.1 (C9), -0.35 (3C, C16); **HRMS (ESI$^+$):** calculated for $C_{21}H_{31}N_2O_3Si$: 387.2098, found $[M+H]^+$: 387.2094, calculated for $C_{21}H_{30}N_2NaO_3Si$: 409.1918, found $[M+Na]^+$: 409.1910.

Example 34b - *N*-Boc 4-(acetylene)cytisine 126

[0330]



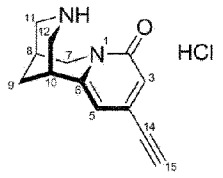
126

[0331] To a solution of *N*-Boc-4-(trimethylsilylacetylene)-cytisine **125** (379 mg, 0.98 mmol) in a mixture of MeOH (14 mL) and DCM (7 mL) was added K_2CO_3 (270 mg, 1.96 mmol). The mixture was stirred for 24 h. Water was added (10 mL) and the aqueous phase was extracted with DCM (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [EtOAc] to give **126** (275 mg, 89%) as a white solid together with few impurities (palladium catalyst). The product was used in the next step without further purification.

[0332] **R_f:** 0.21 [EtOAc]; **FTIR ν_{max} / cm^{-1} (neat):** 3225, 2915, 2862, 1686, 1654, 1574; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 6.52 (s, 1H, C3-H), 6.06 (s, 1H, C5-H), 4.31-4.09 (m, 3H, C7-H_a, C11-H, C12-H), 3.76 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.23 (s, 1H, C15-H), 3.04-2.93 (m, 3H, C10-H, C11-H, C12-H), 2.38 (s, 1H, C8-H), 1.96-1.88 (m, 2H, C9-H), 1.30-1.21 (m, 9H, Boc); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 162.5 (CO), 154.4/154.3 (CO Boc, rotamers), 149.3, 148.8 (C6, C4), 120.3 (C3), 107.8/107.1 (C5, rotamers), 82.1 (C15), 80.8 (C14), 80.3/79.9 (q Boc, rotamers), 51.6/50.5/50.2/49.3 (C11, C12, rotamers), 48.9 (C7), 34.7 (C10), 28.0 (3C, Boc), 27.4 (C8), 26.0 (C9); **HRMS (ESI^+):** calculated for $C_{18}H_{23}N_2O_3$: 315.1703, found $[M+H]^+$: 315.1696, calculated for $C_{18}H_{22}N_2NaO_3$: 337.1523, found $[M+Na]^+$: 337.1516.

Example 34c - (-)4-(acetylenyl)cytisine hydrochloride salt (127)

[0333]



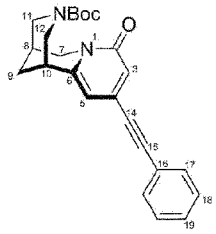
127

[0334] Following the general procedure B, *N*-Boc 4-(acetylene)cytisine **126** (0.77 mmol) gave 127 (150 mg, 78%) as a pale yellow solid.

[0335] mp: >200 °C, pale yellow solid; **$[\alpha]_D^{26}$** = -32 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1} (neat):** 2726, 2604, 1631, 1540; **^{1}H NMR (400 MHz, D_2O, δ_H):** 6.55 (s, 1H, C3-H), 6.48 (s, 1H, C5-H), 4.00 (d, 1H, *J* = 15.5 Hz, C7-H_a), 3.86 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.74 (s, 1H, C15-H), 3.39-3.23 (m, 5H, C10-H, C11-H, C12-H), 2.70 (s, 1H, C8-H), 2.03-1.91 (m, 2H, C9-H); **^{13}C NMR (100 MHz, D_2O, δ_C):** 164.0 (CO), 147.4 (C4), 135.0 (C6), 119.8 (C3), 111.9 (C5), 85.2 (C15), 79.7 (C14), 49.3 (C11 or C12), 48.8 (C7), 48.1 (C11 or C12), 31.4 (C10), 24.7 (C8), 22.4 (C9); **HRMS (ESI^+):** calculated for $C_{13}H_{15}N_2O$: 215.1179, found $[M+H-HCl]^+$: 215.1176.

Example 35a - *N*-Boc 4-(phenylacetylene)cytisine (128)

[0336]



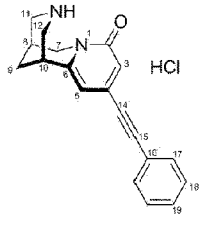
128

[0337] To a mixture of *N*-Boc 4-bromo cytisine **61** (369 mg, 1.0 mmol), CuI (38 mg, 20 mol%) and $PdCl_2(PPh_3)_2$ (70 mg, 10 mol%) in dry THF (5.0 mL) was added *i*-Pr_2NH (0.42 mL, 3.0 mmol) followed by phenylacetylene (0.22 mL, 2.0 mmol). The mixture was stirred at r.t. for 24 h under nitrogen. The mixture was diluted with EtOAc (50 mL). The organic layer was washed with NH_4Cl (10 mL, saturated solution), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [EtOAc] to give **128** (376 mg, 96%) as a pale brown foam with few impurities (palladium catalyst). The product was used in the next step without further purification.

[0338] **R_f:** 0.14 [EtOAc]; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 7.50-7.48 (m, 2H, C17-H), 7.34-7.33 (m, 3H, C18-H, C19-H), 6.56 (s, 1H, C3-H), 6.13 (s, 1H, C5-H), 4.34-4.12 (m, 3H, C7-H_a, C11-H, C12-H), 3.79 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.05-2.96 (m, 3H, C10-H, C11-H, C12-H), 2.40 (s, 1H, C8-H), 1.98-1.89 (m, 2H, C9-H), 1.32-1.23 (m, 9H, Boc); **^{13}C NMR (100 MHz, $CDCl_3$, δ_C):** 162.7 (CO), 154.4 (CO Boc), 148.9/148.5 (C6, rotamers), 134.0/133.7 (C4, rotamers), 131.8 (C17, C21), 129.1 (C19), 128.4 (C18, C20), 122.1 (C16), 119.2 (C3), 107.8/107.1 (C5, rotamers), 94.2 (C15), 86.6 (C14), 80.4/79.9 (q Boc, rotamers), 51.6/50.5/50.4/49.3 (C11, C12, rotamers), 48.8 (C7), 34.8 (C10), 28.1 (3C, Boc), 27.5 (C8), 26.1 (C9); **HRMS (ESI^+):** calculated for $C_{24}H_{27}N_2O_3$: 391.2016, found $[M+H]^+$: 391.2024, calculated for $C_{24}H_{26}N_2NaO_3$: 413.1836, found $[M+Na]^+$: 413.1876.

Example 35b - (+)4-(phenylacetylene)cytisine hydrochloride salt (129)

[0339]



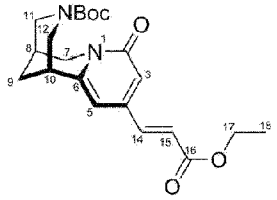
129

[0340] Following the general procedure B, *N*-Boc-4-(phenylacetylene)-cytisine **128** (0.88 mmol) gave **129** (267 mg, 92%) as a pale yellow solid.

[0341] mp: >200 °C, pale yellow solid; **$[\alpha]_D^{26}$** = +42 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1} (neat):** 2925, 2717, 2214, 1630, 1537; **^{1}H NMR (400 MHz, MeOH, δ_H):** 7.51-7.49 (m, 2H, C17-H), 7.41-7.33 (m, 3H, C18-H, C19-H), 7.00 (s, 1H, C3-H), 6.89 (s, 1H, C5-H), 4.33 (d, 1H, *J* = 15.5 Hz, C7-H_a), 4.17 (dd, 1H, *J* = 6.5,15.5 Hz, C7-H_b), 3.56-3.22 (m, 5H, C10-H, C11-H, C12-H), 2.78 (s, 1H, C8-H), 2.17 (d, 1H, *J* = 13.0 Hz, C9-H_a), 2.07 (d, 1H, *J* = 13.0 Hz, C9-H_b); **^{13}C NMR (100 MHz, MeOD, δ_C):** 163.8 (CO), 150.3 (C6), 139.4 (C4), 133.2 (C17, C21), 131.4 (C19), 129.9 (C18, C20), 122.4 (C16), 117.5 (C5), 116.6 (C3), 99.4 (C15), 86.3 (C14), 51.4 (C7), 50.3 (C11, C12), 33.0 (C10), 26.4 (C8), 23.6 (C9); **HRMS (ESI^+):** calculated for $C_{19}H_{19}N_2O$: 291.1492, found $[M+H-HCl]^+$: 291.1486.

Example 36a - *N*-Boc 4-(E-2-propenoate methyl ester)cytisine (111)

[0342]



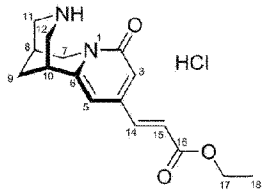
[0343] To a mixture of *N*-Boc 4-bromocytisine **61** (369 mg, 1.0 mmol) and $Pd_2(dba)_3$ (12 mg, 2.5 mol%) in dry dioxane (5.0 mL) was added Cy_2NMe (0.2 mL, 1.1 mmol), P(*t*-Bu)$_3$(0.1M in dioxane, 0.5 mL, 5 mol%) and ethyl acrylate (0.2 mL, 2.0 mmol). The mixture was stirred at r.t. for 24 h under nitrogen. $Pd_2(dba)_3$ (12 mg, 2.5 mol%), P(*t*-Bu)$_3$ (0.1M in dioxane, 0.50 mL, 5 mol%) and ethyl acrylate (0.2 mL, 2.0 mmol) were added again and the mixture stirred for 24 h more. The mixture was filtered through Celite®, washed with EtOAc and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [DCM/MeOH (97:3)] to give **111** (321 mg, 83%) as a pale yellow solid.

[0344] R_f: 0.26 [DCM/MeOH (5% MeOH)]; **mp**: >200 °C, colourless powder; **FTIR** ν_{max} / cm^{-1} **(neat):** 2973, 2934, 1723, 1679, 1655, 1640, 1567, 1431; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 7.35 (d, 1H, *J* = 16.0 Hz, C14-H), 6.47 (s, 1H, C3-H), 6.38 (d, 1H, *J* = 16.0 Hz, C15-H), 6.15 (s, 1H, C5-H), 4.34-4.07 (m, 5H, C7-H_a, C11-H, C12-H, C17-H), 3.77 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.10-2.90 (m, 3H, C10-H, C11-H, C12-H), 2.39 (s, 1H, C8-H), 1.98-1.90 (m, 2H, C9-H),

1.31-1.14 (m, 12H, Boc, C18-H); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C):** 165.9 (C16), 163.3 (CO), 154.5/154.2 (CO Boc, rotamers), 149.8/148.9 (C6, rotamers), 144.1/143.8 (C4, rotamers), 141.7 (C14), 123.1 (C15), 117.4 (C3), 102.9/102.0 (C5, rotamers), 80.4/79.8 (q Boc, rotamers), 60.9 (C17), 51.7/50.6/50.4/49.2 (C11, C12, rotamers), 49.0 (C7), 35.1 (C10), 28.1 (3C, Boc), 27.5 (C8), 26.2 (C9), 14.2 (C18); **HRMS (ESI^+):** calculated for $C_{21}H_{29}N_2O_5$: 389.2071, found $[M+H]^+$: 389.2059, calculated for $C_{21}H_{28}N_2NaO_5$: 411.1890, found $[M+Na]^+$: 411.1880.

Example 36b - (+)4-(*E*-2-propenoate methyl ester)cytisine hydrochloride salt (112)

[0345]



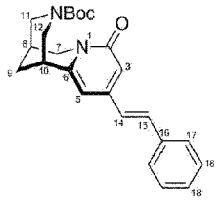
112

[0346] Following the general procedure B, **111** (1.00 mmol) gave **112** (300 mg, 92%) as a pale yellow solid.

[0347] mp: >200 °C, pale yellow solid; **$[\alpha]_D^{26}$** = +22 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1} (neat):** 2943, 2751, 1706, 1655, 1637, 1570; **^{1}H NMR (400 MHz, D_2O, δ_H):** 7.28(d, 1H, *J* = 16.0 Hz, C14-H), 6.62 (d, 1H, *J* = 1.5 Hz, C3-H), 6.47-6.43 (m, 2H, C5-H, C15-H), 4.11 (q, 2H, *J* = 7.0 Hz, C17-H), 4.00 (d, 1H, *J* = 16.0 Hz, C7-H_a), 3.83 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.40-3.24 (m, 5H, C10-H, C11-H, C12-H), 2.69 (s, 1H, C8-H), 2.05-1.92 (m, 2H, C9-H), 1.16 (t, 3H, *J* = 7.0 Hz, C18-H); **^{13}C NMR (100 MHz, D_2O, δ_C):** 167.9 (C16), 164.7 (CO), 147.2 (C4), 146.2 (C6), 141.1 (C14), 124.0 (C15), 116.9 (C3), 106.9 (C5), 62.1 (C17), 49.4 (C11 or C12), 48.7 (C7), 48.2 (C11 or C12), 31.6 (C10), 24.7 (C8), 22.6 (C9), 13.2 (C18); **HRMS (ESI^+):** calculated for $C_{16}H_{21}N_2O_3$: 289.1547, found $[M+H^+-HCl]^+$: 289.1561.

Example 37a - N-Boc-4-(*E*-(2-phenylethenyl))cytisine (113)

[0348]



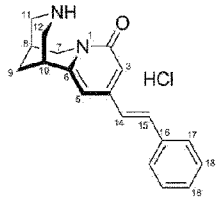
113

[0349] To a mixture of *N*-Boc-4-bromo-cytisine **61** (369 mg, 1.0 mmol) and $Pd_2(dba)_3$ (12 mg, 2.5 mol%) in dry dioxane (5.0 mL) was added Cy_2NMe (0.2 mL, 1.1 mmol), P(*t*-Bu)$_3$ (0.1M in dioxane, 0.50 mL, 5 mol%) and styrene (0.2 mL, 2.0 mmol). The mixture was stirred at r.t. for 24 h under nitrogen. $Pd_2(dba)_3$ (12 mg, 2.5 mol%), P(*t*-Bu)$_3$(0.1M in dioxane, 0.50 mL, 5 mol%) and styrene (0.2 mL, 2.0 mmol) were added again and the mixture stirred for 24 h more. The mixture was filtered through Celite®, washed with EtOAc and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [DCM/MeOH (97:3)] to give **113** (373 mg, 95%) as a pale yellow foam. The product was used in the next step without further purification.

[0350] R_f**:** 0.19 [DCM/MeOH (5% MeOH)]; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 7.49-7.47 (m, 2H, C17-H, C21-H), 7.36-7.25 (m, 3H, C18-H, C19-H, C20-H), 7.11 (d, 1H, *J* = 16.0 Hz, C15-H), 6.81 (s, 1H, C14-H), 6.43 (s, 1H, C3-H), 6.28 (s, 1H, C5-H), 4.39-4.13 (m, 3H, C7-H_a, C11-H, C12-H), 3.80 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.12-2.92 (m, 3H, C10-H, C11-H, C12-H), 2.39 (s, 1H, C8-H), 2.00-1.91 (m, 2H, C9-H), 1.37-1.17 (m, 9H, Boc); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C):** 163.8 (CO), 154.6/154.3 (CO Boc, rotamers), 148.5/148.1 (C6, rotamers), 147.0/146.7 (C4, rotamers), 136.1 (C16), 133.4/133.3 (C15, rotamers), 128.8 (C18, C20), 128.7 (C19), 127.0 (C17, C21), 126.0 (C14), 114.6 (C3), 103.1/102.3 (C5, rotamers), 80.3/79.7 (q Boc, rotamers), 51.8/50.6/50.5/49.3 (C11, C12, rotamers), 48.7 (C7), 35.0 (C10), 28.1 (3C, Boc), 27.5 (C8), 26.3 (C9); **HRMS (ESI$^+$)** calculated for $C_{24}H_{29}N_2O_3$: 393.2173, found $[M+H]^+$: 393.2173, calculated for $C_{24}H_{28}N_2NaO_3$: 415.1992, found $[M+Na]^+$: 415.1991.

Example 37b - - (+)4-(*E*-(2-phenylethenyl))cytisine hydrochloride salt (114)

[0351]



114

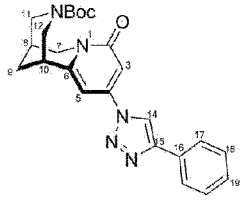
[0352] Following the general procedure B, **113** (0.88 mmol) gave **114** (259 mg, 89%) as an off-white solid.

[0353] mp: >200 °C, off-white solid; **$[\alpha]_D^{26}$** = +90 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1} (neat):** 2925, 2713, 2606, 1629, 1553; **^{1}H NMR (400 MHz, D_2O, δ_H):** 7.26-7.16 (m, 5H, C17-H, C18-H, C19-H), 6.99 (d, 1H, *J* = 16.5 Hz, C15-H), 6.59 (d, 1H, *J* = 16.5 Hz, C14-H), 6.51 (s, 1H, C3-H),

6.23 (s, 1H, C5-H), 3.87 (d, 1H, *J* = 15.5 Hz, C7-H_a), 3.54 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.31-3.16 (m, 5H, C10-H, C11-H, C12-H), 2.56 (s, 1H, C8-H), 1.91 (d, 1H, *J* = 13.5 Hz, C9-H), 1.67 (d, 1H, *J* = 13.5 Hz, C9-H); **^{13}C NMR (100 MHz, D_2O, δ_C):** 164.1 (CO), 149.8 (C16), 146.3 (C6), 135.4 (C15), 135.3 (C14), 129.2 (C19), 128.8 (C18, C20), 127.2 (C17, C21), 124.3 (C4), 113.1 (C3), 107.7 (C5), 49.5 (C11 or C12), 48.5 (C7), 48.1 (C11 or C12), 31.4 (C10), 24.6 (C8), 22.5 (C9); **HRMS (ESI^+):** calculated for $C_{19}H_{21}N_2O$: 293.1648, found $[M+H-HCl]^+$: 293.1655.

Example 38a - *N*-Boc 4-(1-(4-pheny))-*N*H-1, 2, 3-triazolyl)cytisine (134)

[0354]



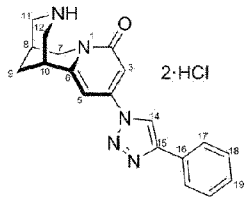
134

[0355] To a mixture of *N*-Boc-4-bromo-cytisine **61** (369 mg, 1.00 mmol), NaN_3 (130 mg, 2.0 mmol), sodium ascorbate (20 mg, 10 mol%) and CuI (19 mg, 10 mol%) in EtOH/H_2O (7:3) (5.0 mL) was added DMEDA (22 µL, 20 mol%) then phenylacetylene (132 µL, 1.2 mmol). The mixture was stirred at 50 °C for 24 h under nitrogen. The mixture was cooled to r.t., diluted with NH_4OH solution (20 mL, 15% aq.sol.) and then extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude (86-93% conversion based on ^{1}H NMR) was purified by flash column chromatography on silica gel [EtOAc then DCM/MeOH/NH_4OH (97:3:0.1)] to give **134** (214 mg, 49%) as an off-white solid, which was used in the next step without further purification.

[0356] **R_f:** 0.11 [EtOAc]; **^{1}H NMR (400 MHz, $CDCl_3$, δ_H):** 8.22 (s, 1H, C14-H), 7.89 (d, 2H, *J* = 7.0 Hz, C17-H, C21-H), 7.47-7.44 (m, 2H, C18-H, C20-H), 7.39- 7.36 (m, 1H, C19-H), 6.91 (s, 1H, C3-H), 6.70 (s, 1H, C5-H), 4.39-4.20 (m, 3H, C7-H_a, C11-H, C12-H), 3.87 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.15-3.00 (m, 3H, C10-H, C11-H, C12-H), 2.47 (s, 1H, C8-H), 2.06-1.98 (m, 2H, C9-H), 1.34-1.19 (m, 9H, Boc); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C):** 163.3 (CO), 154.6 (CO Boc), 152.0/151.5 (C6, rotamers), 149.0 (C15), 145.0 (C4), 129.7 (C16), 129.1 (C18, C20), 128.9 (C19), 126.1 (C17, C21), 116.9 (C14), 103.8 (C5), 98.3/97.8 (C3, rotamers), 80.7/80.1 (q Boc, rotamers), 51.6/50.8/50.3/49.4 (C11, C12, rotamers), 49.3 (C7), 35.5 (C10), 28.2 (3C, Boc), 27.5 (C8), 26.1 (C9); **HRMS (ESI^+):** calculated for $C_{24}H_{27}N_5NaO_3$: 456.2006, found $[M+Na]^+$: 456.1993.

Example 38b - (+)4-(1-(4-pheny))-*N*H-1, 2, 3-triazolyl)cytisine dihydrochloride salt (135)

[0357]



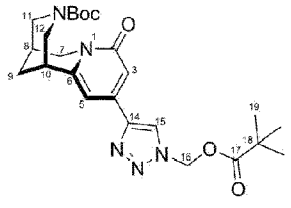
135

[0358] Following the general procedure B, *N*-Boc-4-((4-phenyl)-*N*H-1, 2, 3, triazole)-cytisine **134** (0.46 mmol) gave **135** (151 mg, 81%) as a colourless solid.

[0359] mp: >200 °C, colourless powder; **$[\alpha]_D^{22}$** = +36 [c 0.5, water]; **FTIR** v_{max}/ cm^{-1} **(neat):** 3436, 3034, 2565, 1656, 1563; **^{1}H NMR (400 MHz, DMSO-d6, δ_H):** 9.50 (s, 1H, C14-H), 8.58 (s, 1H, NH), 7.94 (d, 2H, *J* = 7.5 Hz, C17-H, C21-H), 7.50 (app t, 2H, *J* = 7.5 Hz, C18-H, C20-H), 7.40 (app t, 1H, *J* = 7.5 Hz, C19-H), 7.10 (d, 1H, *J* = 2.5 Hz, C3-H), 6.93 (d, 1H, *J* = 2.5 Hz, C5-H), 4.01 (d, 1H, *J* = 15.5 Hz, C7-H_a), 3.85 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.46 (s, 1H, C10-H), 3.35-3.16 (m, 4H, C11-H, C12-H), 2.67 (s, 1H, C8-H), 2.07 (d, 1H, *J* = 13.0 Hz, C9-H), 1.94 (d, 1H, *J* = 13.0 Hz, C9-H); **^{13}C NMR (100 MHz, DMSO-d6, δ_C)**:162.7 (CO), 150.2 (C4), 147.8 (C15), 144.4 (C6), 129.7 (C19), 129.1 (C18, C20), 128.6 (C16), 125.5 (C17, C21), 119.5 (C14), 103.8 (C5), 97.6 (C3), 48.4 (C11 or C12), 48.1 (C7), 47.4 (C11 or C12), 31.6 (C10), 24.5 (C8), 22.7 (C9); **HRMS (ESI^+):** calculated for $C_{19}H_{20}N_5O$: 334.1662, found $[M+H^+-2HCl]^+$: 334.1676; calculated for $C_{19}H_{19}N_5NaO$: 356.1482, found $[M+Na-2HCl]^+$: 356.1503.

Example 39a - N-Boc 4-(1, 2, 3-triazol-1-yl)methyl pivalate)cytisine (131)

[0360]



131

[0361] To a solution of *N*-Boc-4-(acetylene)-cytisine 126 (544 mg, 1.73 mmol) in a mixture of tBuOH/H_2O (1:1) (8.6 mL) were successively added azidomethyl pivalate (0.3 mL, 2.08 mmol), $CuSO_4 \cdot 5\ H_2O$ (22 mg, 5 mol%) and sodium ascorbate (102 mg, 30 mol%). The mixture was stirred at r.t. for 48 h. The mixture was diluted with NH_4OH (10 mL, 15% aq. sol.) then

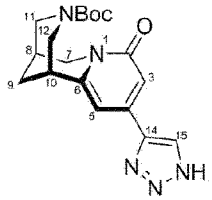
extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [DCM/MeOH/NH_4OH (95:5:0.1)] to give **131** (722 mg, 89%) with few impurities as a pale yellow oil, which was used in the next step without further purification.

[0362] **R_f:** 0.08 [DCM/MeOH (5% MeOH)]; **^{1}H NMR (500 MHz, $CDCl_3$, δ_H):** 8.07 (s, 1H, C15-H), 6.78-6.72 (m, 2H, C3-H, C5-H), 6.26 (s, 2H, C16-H), 4.37-4.16 (m, 3H, C7-H_a, C11-H, C12-H), 3.84 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.08-2.95 (m, 3H, C10-H, C11-H, C12-H), 2.43 (s, 1H, C8-H), 2.02-1.94 (m, 2H, C9-H), 1.32-1.13 (m, 18H, Boc, C19-H); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C):** 178.0 (C17), 163.5 (CO), 154.7/154.5 (CO Boc, rotamers), 150.1/149.5 (C4, rotamers), 145.5 (C14), 140.1/139.9 (C6, rotamers), 123.2/123.0 (C15, rotamers), 112.4 (C3), 103.5/102.9 (C5, rotamers), 80.5/79.9 (q Boc, rotamers), 69.9 (C16), 51.7/50.8/50.4/49.4 (C11, C12, rotamers), 49.0 (C7), 38.9 (C18), 35.1 (C10), 28.2 (3C, Boc), 27.7 (C8), 26.9 (3C, C19), 26.3 (C9); **HRMS (ESI$^+$):** calculated for $C_{24}H_{34}N_5O_5$: 472.2554, found $[M+H]^+$: 472.2551; calculated for $C_{24}H_{33}N_5NaO_5$: 494.2374, found [M+Na]+: 494.2371.

Example 39b - *N*-Boc4-(*N*H-1, 2, 3-triazolyl))-cytisine (132)

[0363]

132



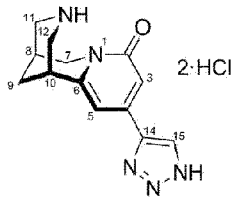
[0364] To a solution of N-Boc-4-(1, 2, 3-triazol-1-yl)methyl pivalate)-cytisine **131** (688 mg, 1.46 mmol) in MeOH (3.2 mL) was added NaOH (3.2 mL, 1M aq. sol.). The mixture was stirred at r.t. for 12 h. The reaction was neutralized with HCl (3.2 mL, 1M aq. sol.), diluted with water (30 mL) and extracted with EtOAc (5 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [DCM/MeOH/NH_4OH (97:3:0.1)] to give **132** (461 mg, 88%) as an off-white solid.

[0365] **R_f:** 0.32 [DCM/MeOH (10% MeOH)]; **^{1}H NMR (500 MHz, $CDCl_3$, δ_H):** 8.01-7.82 (m, 1H, C15-H), 7.03-6.92 (m, 1H, C3-H), 6.77 (s, 1H, C5-H), 4.39-4.15 (m, 3H, C7-H_a, C11-H, C12-H), 3.91 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.15-2.99 (m, 3H, C10-H, C11-H, C12-H), 2.47 (s, 1H,

C8-H), 2.06-1.97 (m, 2H, C9-H), 1.36-1.14 (m, 9H, Boc); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C):** 164.0 (CO), 155.0/154.7 (CO Boc, rotamers), 149.9/149.1 (C4, rotamers), 143.6 (C14), 141.2 (C6), 128.7/128.3 (C15, rotamers), 112.4 (C3), 104.7/104.2 (C5, rotamers), 81.3/80.1 (q Boc, rotamers), 51.8/50.9/50.8/49.5 (C11, C12, rotamers), 49.2 (C7), 35.2 (C10), 28.2 (3C, Boc), 27.3 (C8), 26.3 (C9); **HRMS (ESI^+):** calculated for $C_{18}H_{24}N_5O_3$: 358.1874, found $[M+H]^+$: 358.1874; calculated for $C_{18}H_{23}N_5NaO_3$: 380.1693, found $[M+Na]^+$: 380.1703.

Example 39c - (+)4-(*N*H-1, 2, 3-triazolyl))cytisine dihydrochloride salt 133 *(A)*

[0366]



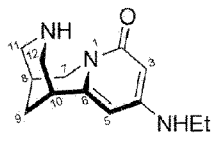
133

[0367] Following the general procedure A, *N*-Boc-4-(*N*H-1, 2, 3-triazole)-cytisine **132** (1.22 mmol) was deprotected and converted into the HCl salt using the general procedure A yielding **133** (352 mg, 87%) as an colourless solid.

[0368] mp: > 200 °C, colourless powder; **$[\alpha]_D^{22}$** = +32 [c 0.5, water]; **FTIR ν_{max} / cm^{-1} (neat):** 3094, 2905, 2723, 2396, 1651, 1552; **^{1}H NMR (400 MHz, D_2O, δ_H):** 8.19 (s, 1H, C15 H), 6.81 (d, 1H, *J* = 1.5 Hz, C3-H), 6.68 (d, 1H, *J* = 1.5 Hz, C5-H), 4.13 (d, 1H, *J* = 15.5 Hz, C7-H_a), 3.90 (dd, 1H, *J* = 6.5, 15.5 Hz, C7-H_b), 3.54-3.38 (m, 5H, C10-H, C11-H, C12-H), 2.83 (s, 1H, C8-H), 2.16 (d, 1H, *J* = 13.5 Hz, C9-H), 2.05 (d, 1H, *J* = 13.5 Hz, C9-H); **^{13}C NMR (100 MHz, D_2O, δ_C):** 164.2 (CO), 147.9 (C6), 142.1 (C14), 141.5 (C4), 125.4 (C15), 111.2 (C5), 107.0 (C3), 49.3 (C11 or C12), 48.7 (C7), 48.2 (C11 or C12), 31.6 (C10), 24.7 (C8), 22.5 (C9); **HRMS (ESI^+):** calculated for $C_{13}H_{16}N_5O$: 258.1349, found $[M+H^+-2HCl]^+$: 258.1342; calculated for $C_{13}H_{15}N_5NaO$: 280.1169, found $[M+Na-2HCl]^+$: 280.1163.

Example 40 - (+)4-(*N*-ethylamino)cytisine (87)

[0369]



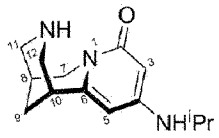
87

[0370] A mixture of *N*-Boc-4-bromo-cytisine **61** (369 mg, 1.0 mmol) and copper (7 mg, 10 mol %) in $EtNH_2$ (2.0 mL, 2.0 M in THF) was stirred in water (1 mL) at 100 °C for 24 h in a sealed tube. The mixture was cooled and extracted with DCM (5 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [DCM/MeOH (6% MeOH)] to give **87** (102 mg, 42%) as an off-white solid.

[0371] Mp: ≥ 200 °C; $[\alpha]_D^{23}$ = +50 [c 0.5, MeOH]; **FTIR** ν_{max} / **cm^{-1}(neat):** 3269, 2901, 2868, 1639, 1532; ^{1}H **NMR (500 MHz, D_2O, δ_H):** 5.92 (d, 1H, *J* = 2.0 Hz, C3-H), 5.54 (d, 1H, *J* = 2.0 Hz, C5-H), 3.92 (d, 1H, *J* = 15.0 Hz, C7-H), 3.79 (dd, 1H, *J* = 6.0, 15.0 Hz, C7-H), 3.13 (q, 2H, *J* = 7.5 Hz, CH_2), 3.06-2.90 (m, 5H, C10-H, C11-H, C12-H), 2.33 (s, 1H, C8-H), 1.98 (d, 1H, *J* = 13.5 Hz, C9-H), 1.91 (d, 1H, *J* = 13.5 Hz, C9-H), 1.10 (t, 3H, *J* = 7.5 Hz, CH_3); **^{13}C NMR (125 MHz, D_2O, δ_C):** 165.3 (CO), 157.1 (C4), 150.7 (C6), 99.5 (C3), 89.4 (C5), 52.0, 50.8 (C11, C12), 48.9 (C7), 36.8 (CH_2), 34.5 (C10), 26.8 (C8), 24.9 (C9), 13.0 (CH_3); **HRMS (ESI$^+$):** calculated $C_{13}H_{20}N_3O$: 234.1601, found $[M+H]^+$: 234.1609.

Example 41 - (+)4-(*N*-isopropylamino)cytisine 88

[0372]



88

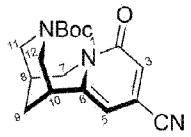
[0373] A mixture of *N*-Boc-4-bromo-cytisine **61** (369 mg, 1.0 mmol) and copper (7 mg, 10 mol%) in 40% aq. $iPrH_2$ (2.0 mL) was stirred at 100 °C for 24 h in a sealed tube. The mixture was cooled and extracted with DCM (5 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel [DCM/MeOH (6% MeOH)] to give 88 (88 mg, 33%) as an off-white solid.

[0374] Mp: ≥ 200 °C; **$[\alpha]_D^{24}$** = +50 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1}(neat):** 2969, 1639, 1535, 1276; **^{1}H NMR (500 MHz, MeOD,** δ_H): 5.76 (d, *J* = 2.5 Hz, 1H, C3-H), 5.46 (d, *J* = 2.5 Hz, 1H, C5-H), 3.97 (d, *J* = 15.0 Hz, 1H, C7-H), 3.79 (dd, *J* = 15.0, 6.0 Hz, 1H, C7-H), 3.57(hept, *J* = 6.5 Hz, 1H, C13-H), 3.07-2.92 (m, 4H, C11-H C12-H), 2.83 (s, 1H, C10-H), 2.27(s, 1H, C8-H), 1.95 (m, 2H, C9-H), 1.20 (dd, *J* = 6.5, 2.0 Hz, 6H, C14-H); **^{13}C NMR (125 MHz, MeOD,** δ_C): 165.5 (CO), 155.7 (C4), 149.7 (C6), 98.7 (C3), 89.1 (C5), 52.7, 51.6 (C11 C12), 48.5 (C7), 43.1 (C13), 35.1 (C10), 27.6 (C8), 25.6 (C9), 21.0 (2C, C14); **HRMS (ESI$^+$):** calculated

$C_{14}H_{22}N_3O$: 248.1757, found $[M+H^+-HCl]^+$: 248.1766.

Example 42a - *N*-Boc 4-cyanocytisine (139)

[0375]



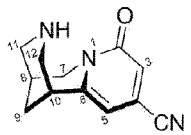
139

[0376] A Schlenk tube was charged with *N*-Boc-4-bromo-cytisine **61** (1.85 g, 5.00 mmol), $Pd((PPh_3)_4)$ (230 mg, 0.20 mmol), and zinc cyanide (350 mg, 3.00 mmol), and placed under nitrogen. DMF (6.2 mL) was added and the reaction mixture was heated at 80 °C for 18 h. The reaction mixture was cooled and the solvent was removed *in vacuo.* Purification of the crude reaction mixture by flash column chromatography [DCM:MeOH (1% MeOH)] afforded **139** (1.6 g, 99%) as a colourless solid.

[0377] **R_f:** 0.7 [DCM/MeOH (4% MeOH)]; **mp**: 153-156 °C, colourless powder (toluene); **FTIR ν_{max} / cm^{-1} (neat):** 2973, 2233 (weak peak as conjugated, CN band), 1658, 1572; **^{1}H NMR (500 MHz, $CDCl_3$, δ_H, 52.0 °C):** 6.74 (s, 1H, C3-H), 6.18 (s, 1H, C5-H), 4.42-4.07 (m, 3H, C11-H, C12-H, C7-H), 3.81 (dd, 1H, *J* = 6.5, 16.0 Hz, C7-H), 3.19-2.91 (m, 3H, C11-H, C12-H, C10-H), 2.48 (s, 1H, C8-H), 1.98 (s, 2H, C9-H), 1.38-1.17 (s, 9H, Boc); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C, 52.0 °C):** 161.3 (CO), 154.1 (C4), 151.7 (C6), 121.9 (C3), 115.9 (CN), 104.3 (C5), 80.5 (q Boc), 50.1, 49.8 (C11, C12), 49.2 (C7), 34.8 (C10), 28.4 (3C, Boc), 27.4 (C8), 25.8 (C9). (Carbonyl carbon of the Boc group not observed); **HRMS (ESI^+):** calculated $C_{17}H_{21}N_3NaO$: 338.1475, found $[M+Na]^+$: 338.1467.

Example 43 - (-)4-Cyanocytisine (140)

[0378]



140

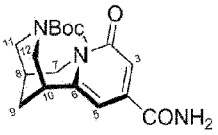
[0379] In a Schlenk flask, *N*-Boc-4-cyano-cytisine **139** (140 mg, 0.46 mmol) was dissolved in DCM (3.0 mL, 0.1 M) and TFA (0.3 mL, 10 eq.) was added. The solution was stirred at r.t. for 16 h. Water was added (10 mL) and the aqueous phase was washed with DCM (3 × 20 mL). Ammonia was added (10 mL, 15% aq. sol.) and the aqueous phase was extracted with DCM (4

× 20 mL). The combined organic lawyers were dried over $MgSO_4$, filtered and concentrated, yielding **140** (86 mg, 86%) as a colourless solid.

[0380] mp: 161-163 °C, colourless needles (toluene); **$[\alpha]_D^{23}$** = -53 [c 0.66, MeOH]; **(FTIR ν_{max} / cm^{-1}(neat):** 2233 (weak peak as conjugated, CN band), 1649, 1581; **^{1}H NMR (500 MHz, MeOD, δ_H):** 6.87 (d, 1H, *J* = 2.0 Hz, C3-H), 6.59 (d, 1H, *J* = 2.0 Hz, C5-H), 4.19 (d, 1H, *J* = 16.0 Hz, C7-H), 4.01 (dd, 1H, *J* = 16.0, 7.0 Hz, C7-H), 3.52-3.35 (m, 5H, C10-H, C11-H, C12-H), 2.78 (s, 1H, C8-H), 2.18 (d, 1H, *J* = 14.0 Hz, C9-H), 2.10 (d, 1H, *J* = 14.0 Hz, C9-H); **^{13}C NMR (125 MHz, MeOD, δ_C):** 161.6 (C2), 154.1 (C6), 122.7 (C4), 121.4 (C3), 116.4 (C13), 104.1 (C5), 53.7, 52.9 (C11, C12), 50.4 (C7), 35.7 (C10), 27.5 (C8), 25.9 (C9); **HRMS (ESI^+):** calculated $C_{12}H_{14}N_3O$: 216.1131, found $[M+H]^+$: 216.1129.

Example 44a - *N*-Boc -4-(carboxyamido)cytisine (141)

[0381]



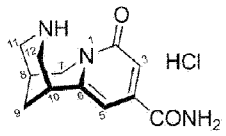
141

[0382] To a solution of *N*-Boc-4-cyano-cytisine **139** (320 mg, 1.0 mmol) in an equimolar mixture of EtOH/water (5 mL) was added $NaBH_4$ (33 mg, 0.75 mmol) and the reaction mixture was stirred at 75 °C for 18 h. The reaction mixture was cooled to r.t., and quenched with water (5 mL). Ethanol was removed *in vacuo.* Then, the aqueous phase was extracted with DCM (3 × 15 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification of the crude reaction mixture by flash column chromatography [DCM/MeOH (from 2% to 4% MeOH)] yielded **141** (150 mg, 46%) as a colourless solid which was recrystallized from toluene.

[0383] R*f*: 0.43 [DCM/MeOH (4% MeOH)] ; **mp**: > 200 °C, colourless powder; **FTIR ν_{max} / cm^{-1}(neat):** 3317, 3148, 2974, 1690, 1639, 1562; **^{1}H NMR (500 MHz, MeOD, δ_H, 52 °C):** 6.83 (s, 1H, C3-H), 6.69 (s, 1H, C5-H), 4.35-4.31 (s, 1H, C11-H), 4.20-4.16 (br s, 1H, C7-H), 4.14 (s, 1H, C12-H), 3.84 (dd, 1H, *J* = 6.0, 15.0 Hz, C7-H), 3.27-2.98 (m, 3H, C10-H C11-H C12-H), 2.49 (s, 1H, C8-H), 2.12-1.97 (m, 2H, C9-H), 1.41-1.06 (s, 9H, Boc) ; **^{13}C NMR (125 MHz, MeOD, δ_C, 52 °C):** 167.8 (CO amide), 163.4 (CO pyridone), 154.6 (CO Boc), 150.8 (C6), 144.4 (C4), 114.3 (C3), 104.6 (C5), 80.2 (q Boc), 67.4 (C11, C12), 49.3 (C7), 35.2 (C10), 27.7 (C8), 26.9 (3C, Boc), 25.1 (C9); **HRMS (ESI^+):** calculated $C_{17}H_{24}N_3O_4$: 334.1761, found $[M+H]^+$: 334.1753; calculated $C_{17}H_{23}N_3NaO_4$: 356.1581, found $[M+Na]^+$: 356.1570.

Example 44b - (-)4-(carboxyamido)cytisine hydrochloride salt (142)

[0384]



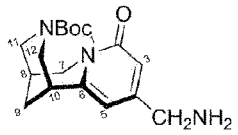
142

[0385] Following the general procedure A, *N*-Boc-4-amido-cytisine **141** (0.44 mmol) gave **142** (90 mg, 88%) as a colourless solid.

[0386] **mp**: > 200 °C, colourless powder; **$[\alpha]_D^{25}$** = -2 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1}(neat):** 1646, 1543; **^{1}H NMR (500 MHz, MeOD, δ_H):** 6.92 (d, 1H, *J* = 2.0 Hz, C3-H), 6.75 (d, 1H, *J* = 2.0 Hz, C3-H), 4.21 (d, 1H, *J* = 16.0 Hz, C7-H), 4.05 (dd, 1H, *J* = 16.0, 6.5 Hz, C7-H), 3.53-3.41 (m, 5H, C11-H, C12-H, C10-H), 2.82 (s, 1H, C8-H), 2.20 (d, 1H, *J* = 13.5 Hz, C9-H), 2.12 (d, 1H, *J* = 13.5 Hz, C9-H); **^{13}C NMR (125 MHz, MeOD, δ_C):** 167.7 (CO $CONH_2$), 164.1 (CO), 147.4 (C4), 144.8 (C6), 115.8 (C3), 105.3 (C5), 49.4 (C7), 32.1 (C10), 25.2 (C8), 22.8 (C9), (C11 and C12 are under the signal of the solvent); **HRMS (ESI^+):** calculated $C_{12}H_{16}N_3O_2$: 234.1237, found $[M+H-HCl]^+$: 234.1229.

Example 45a - N-Boc 4-(Aminomethyl)cytisine (143)

[0387]



143

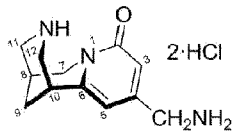
[0388] Raney Ni (0.3 mL, slurry in water) was added over a solution of *N*-Boc-4-cyano-cytisine **139** (320 mg, 1.0 mmol) and KOH (84 mg, 1.5 mmol) in EtOH (10 mL, 0.1 M). The reaction vessel was placed under vacuum and backfilled with hydrogen three times, and stirred at r.t. for 18 h. The reaction mixture was filtered through Celite® and the crude reaction mixture was concentrated. Purification by flash column chromatography [DCM:MeOH (10% MeOH) + 0.1% ammonia (35% aq. sol.)] yielded amine **143** (260 mg, 82%) as a colourless solid.

[0389] **R*f*:** 0.22 [DCM:MeOH (10% MeOH)] ; **mp**: 157-160 °C, colourless podwer (toluene); **FTIR ν_{max} / cm^{-1}(neat):** 2928, 1673, 1644, 1542; ^{1}H **NMR (500 MHz, MeOD, δ_H, 52 °C):** 6.40 (s, 1H, C3-H), 6.34 (d, 1H, *J* = 2.0 Hz, C5-H), 4.27 (s, 1H, C11-H), 4.16 (s, 1H, C12-H), 4.12 (s,

1H, C7-H), 3.30 (dd, 1H, *J* = 6.0, 15.0 Hz, C7-H), 3.67 (s, 2H, C13-H), 3.22-3.04 (m, 3H, C11-H, C12-H, C10-H), 2.45 (s, 1H, C8-H), 2.08-1.99 (m, 2H, C9-H), 1.42-1.11 (s, 9H, Boc); **^{13}C NMR (125 MHz, MeOD, δ_C, 52 °C):** 164.3 (CO), 155.6 (CO), 154.7 (C6), 149.3 (C4), 112.3 (C3), 106.5 (C5), 79.97 (q Boc), 50.3 (C11, C12), 48.9 (C7), 44.1 (C13), 34.9 (C10), 27.7 (C8), 27.0 (3C, Boc), 25.4 (C9); **HRMS (ESI$^+$):** calculated for $C_{17}H_{25}N_3O_3$: 319.1896, found $[M+H]^+$: 320.1958, calculated for $C_{17}H_{24}N_3NaO_3$: 342.1794, found $[M+Na]^+$: 342.1783.

Example 45b - (-)4-(aminomethyl)cytisine dihydrochloride salt (144)

[0390]



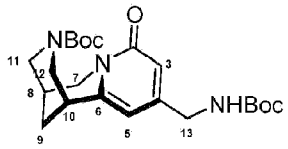
144

[0391] Following the general procedure A, *N*-Boc-4-methylamino-cytisine **143** (0.76 mmol) was converted into the HCl salt yielding **144** (150 mg, 89%) as a colourless solid.

[0392] mp: > 200 °C, colourless powder; $[\alpha]_D^{26}$ = -46 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1}(neat):** 2789, 1653, 1518; **^{1}H NMR (500 MHz, D_2O, δ_H):** 6.50 (s, 1H, C3-H), 6.46 (s, 1H, C5-H), 4.07 (d, 1H, *J* = 16.0 Hz, C7-H), 4.02 (s, 2H, C13-H), 3.94 (dd, 1H, *J* = 16.0, 6.5 Hz, C7-H), 3.45-3.29 (m, 5H, C11-H, C12-H, C8-H), 2.75 (s, 1H, C10-H), 2.06 (d, 1H, *J* = 13.6 Hz, C9-H), 2.00 (d, 1H, *J* = 13.6 Hz, C9-H); **^{13}C NMR (125 MHz, D_2O, δ_C):** 164.6 (CO), 148.0 (C4), 16.9 (C6), 115.4 (C3), 108.5 (C5), 48.7 (C7), 49.3, 48.2 (C11, C12), 41.2 (C13), 31.5 (C8), 24.8 (C10), 22.4 (C9); **HRMS (ESI$^+$):** calculated $C_{12}H_{18}N_3O$: 220.1444, found $[M+H-HCl]^+$: 220.1441.

Example 46a - *N*-Boc 4-(*N*-Boc aminomethyl)cytisine

[0393]



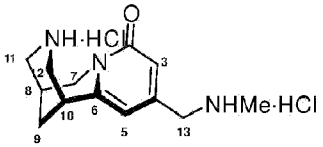
[0394] To a solution of *N*-Boc-4-aminomethyl-cytisine **143** (264 mg, 0.83 mmol) in THF (8 mL) were added Boc_2O (0.2 mL, 0.91 mmol) and triethylamine (0.16 mL, 1.16 mmol), and the reaction mixture was stirred for 18 h at r.t. Then, water (15 mL) was added and the aqueous phase was extracted with DCM (3 × 25 mL). The combined organic phases were dried over

$MgSO_4$, filtered, and concentrated. Purification by flash column chromatography [DCM:MeOH (3% MeOH)] yielded *N*-Boc-4-(*N*-Boc-aminomethyl)-cytisine (280 mg, 82%) as a colourless oil.

[0395] FTIR v_{max}/cm^{-1} (neat): 3316, 2975, 1683, 1653, 1546, 1423; **^{1}H NMR (500 MHz, $CDCl_3$, δ_H, 52°C):** 6.33 (s, 1H, C3-H), 5.98 (d, 1H, *J* = 2.0 Hz, C5-H), 4.82 (s, 1H, NH), 4.36-4.07 (m, 5H, C7-H, C11-H, C12-H, C13-H), 3.81 (dd, 1H, *J*= 5.5, 15.5 Hz, C7-H), 3.10-2.94 (m, 3H, C11-H, C12-H, C10-H), 2.41 (s, 1H, C8-H), 1.99 (d, 1H, *J* = 13.5 Hz, C9-H), 1.92 (d, 1H, *J* = 13.5 Hz, C9-H), 1.46 (s, 9H, Boc), 1.38-1.23 (s, 9H, Boc); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C, 52°C):** 166.4 (CO), 155.8 (CO Boc), 154.5 (CO Boc), 150.9 (C6), 148.7 (C4), 113.8 (C3), 104.4 (C5), 79.6 (2C, q Boc), 50.8, 50.5 (C11, C12), 48.7 (C7), 43.5 (C13), 35.0 (C10), 28.3, 28.0 (6C, Boc), 27.6 (C8), 26.3 (C9); **HRMS (ESI^+):** calculated for $C_{22}H_{34}N_3O_5$: 420.2492, found $[M+H]^+$: 420.2490.

Example 46b - (-)4-((*N*-methyl)aminomethyl)cytisine (152)

[0396]



152

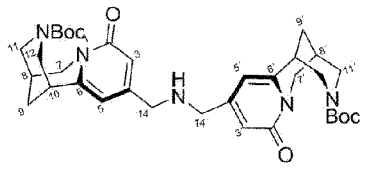
[0397] To a solution of *N*-Boc-4-(*N*-Boc-aminomethyl)-cytisine (255 mg, 0.61 mmol) in THF (6.0 mL) was added NaH (17 mg, 0.70 mmol, 60% dispersion oil) and the solution was stirred for 30 min. Iodomethane (0.05 mL, 0.70 mmol) was added and the reaction mixture was stirred for 18 h at r.t. The crude was distributed between water (10 mL) and EtOAc (10 mL) and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The resulting compound was deprotected and converted into its HCl salt using the general procedure A, yielding **152** (89 mg, 65%) as a colourless solid.

[0398] mp: >200 °C ; **FTIR v_{max} / cm^{-1}(neat):** 2728, 1651, 1548; **^{1}H NMR (500 MHz, D_2O, δ_H):** 6.57 (s, 1H, C3-H), 6.51 (s, 1H, C5-H), 4.14-4.05 (m, 3H, C7-H, CH_2), 3.97 (dd, *J* = 6.0, 15.5 Hz, 1H, C7-H), 3.50-3.31 (m, 5H, C10-H, C11-H, C12-H), 2.79 (s, 1H, C10-H), 2.70 (s, 3H, NHMe), 2.13-2.00 (m, 2H, C9-H); **^{13}C NMR (125 MHz, D_2O, δ_C):** 164.5 (CO), 148.3 (C6), 145.0 (C4), 117.2 (C3), 109.1 (C5), 50.4 (CH_2), 49.4, 48.1 (C11, C12), 48.7 (C7), 32.6 (NHMe), 31.7 (C10), 24.8 (C8), 22.5 (C9); **HRMS (ESI^+):** calculated $C_{13}H_{20}N_3O$: 234.1601, found $[M+H-HCl]^+$: 234.1595.

Example 47a - *Tert*-butyl (1R, 5R)-10-(hydroxymethyl)-8-oxo-1,5,6,8,-tetrahydro-2H-1,5-

methanopyrido[1,2-a][1,5]diazocine-3(4H)-carboxylate (153)

[0399]



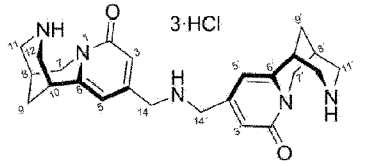
153

[0400] *N*-Boc-4-cyano-cytisine **139** (200 mg, 0.63 mmol) was dissolved in a mixture of pyridine, acetic acid and water in a proportion (2:1:1) and NaH_2PO_2 (340 mg, 3.27 mmol) and Ni Raney (1.0 mL, slurry in water) were added. The reaction mixture was stirred at 50 °C for 6 h. The solution was filtered through Celite® and concentrated. The crude was distributed between water (15 mL) and DCM (15 mL) and the aqueous phase was extracted with DCM (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification of the crude reaction mixture by column chromatography [DCM/MeOH (4% MeOH)] yielded **153** (170 mg, 86%) as a colourless pale-yellow solid.

[0401] **R*f*:** 0.10 [DCM/MeOH (4% MeOH)]; **mp**: 75-78 °C, pale-yellow solid (toluene); **FTIR ν_{max} /cm^{-1}(neat):** 2928, 1651, 1543, 1423; **^{1}H NMR (500 MHz, MeOD, δ_H, 52°C):** 6.44 (s, 2H, C3-H), 6.39 (d, 2H, *J* = 2.0 Hz, C5-H), 4.31 (m, 6H, C11-H, C12-H, NH), 4.15 (d, 2H, *J* = 15.0 Hz, C7-H), 3.80 (dd, 2H, *J* = 15.0, 6.5 Hz, C7-H), 3.64 (s, 4H, C14-H), 3.13 (s, 5H, C10-H, C11-H, C12-H), 2.45 (s, 2H, C8-H), 2.05 (m, 4H, C9-H), 1.28 (s, 18H, Boc); **^{13}C NMR (125 MHz, MeOD, δ_C, 52°C):** 164.1 (2 × CO), 157.7 (2 × CO), 153.3 (2 × C4), 149.7 (2 × C6), 113.6 (2 × C3), 107.3 (2 × C5), 80.0 (2 × q Boc), 50.8, 50.7 (4 × C11, C12), 50.6 (2 × C14), 48.8 (2 × C7), 35.0 (2 × C10), 27.7 (2 × C8), 27.0 (6 × C Boc), 25.4 (2 × C9); **HRMS (ESI$^+$):** calculated for $C_{34}H_{48}N_5O_6$: 622.3605, found $[M+H]^+$: 622.3591, calculated for $C_{34}H_{46}NaN_5O_6$: 644.3424, found $[M+Na]^+$: 644.3412.

Example 47b - Amine bis(cytisine) derivative (154)

[0402]



154

[0403] Following the general procedure A, *tert*-butyl(1*R*,5*R*)-10-(hydroxymethyl)-8-oxo-

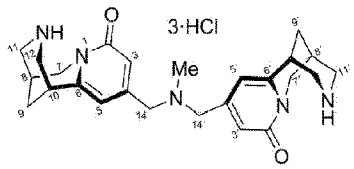
1,5,6,8,-tetrahydro-2*H*-1,5-methano- pyrido [1,2-a][1,5]diazocine-3(4*H*)-carboxylate **153** (0.53 mmol) gave **154** (113 mg, 97 %) as a colourless solid.

[0404] mp: >200 °C; colourless solid; **$[\alpha]_D^{23}$** = +116 [c 0.18, DMF]; **FTIR ν_{max} / cm^{-1} (neat):** 2955, 2590, 1654, 1584, 1547, 1099, 857; ^{1}H **NMR (500 MHz, D_2O, δ_H):** 6.47 (s, 2H, C3-H), 6.44 (s, 2H, C5-H), 4.07 (s, 4H, C13-H), 4.00 (d, *J* = 15.0Hz, 2H, C7-H), 3.86 (dd, *J* = 15.0, 6.65 Hz, 2H, C7-H), 3.40-3.20 (m, 10H, C11-H C12-H C10-H), 2.69 (s, 2H, C8-H), 1.98 (d, *J* = 14.5 Hz, 2H, C9-H), 1.94 (d, *J* = 14.5 Hz, 2H, C9-H); **^{13}C NMR (125 MHz, D_2O, δ_C):** 164.6 (2 × CO), 148.5 (2 × C4), 144.6 (2 × C6), 117.5 (2 × C3), 109.2 (2 × C5), 49.4, 48.2 (2 × C11, 2 × C12), 49.1, 48.8 (2 × C7, 2 × C13), 31.6 (2 × C10), 24.7 (2 × C8), 22.5 (2 × C9); **HRMS (ESI^+):** calculated $C_{24}H_{32}N_5O_2$:422.2550, found $[M+H]^+$: 422.2544.

Example 48 - Methylamino bis(cytisine) derivative (156)

[0405]

156



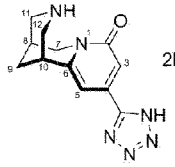
[0406] To a solution of **153** (200 mg, 0.32 mmol) in an equimolar mixture of MeOH/THF (3 mL) was added formaldehyde (0.14 mL, 6 eq., 37% aq. sol.) followed by $NaCNBH_3$ (74 mg, 3.5 eq.) and the reaction mixture was stirred for 24 h. The solution was concentrated and the crude was distributed between ammonia (20 mL, 15% aq. sol.) and DCM (20 mL), and the aqueous phase was extracted with DCM (3 × 20 mL). The combined organic lawyers were dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography [DCM/MeOH (3% MeOH)] afforded the corresponding *N*-Boc protected bis(cytisine) derivative (160 mg, 82%) as a colourless solid. Subsequent deprotection and conversion into the HCl salt using the general procedure B gave 156 (89 mg, 87%) as a colourless solid.

[0407] mp: >200 °C; colourless solid; **$[\alpha]_D^{23}$** = -30 [c 0.3, water]; **FTIR ν_{max} / cm^{-1}(neat):** 3341, 1655, 1548, 1455; **^{1}H NMR (500 MHz, D_2O, δ_H):** 6.67 (s, 2H, C3-H, C3'-H)), 6.65 (s, 2H, C5-H, C5'-H), 4.35 (s, 4H, C13-H, C13-H), 4.18 (d, 2H, *J* = 15.0 Hz, C7-H, C7'-H), 4.04 (dd, 2H, *J* = 6.0, 15.0 Hz, C7-H, C7'-H), 3.60-3.40 (m, 10H, C10-H, C10'-H, C11-H, C11'-H, C12-H, C12'-H), 2.93 (s, 3H, NMe), 2.89 (s, 2H, C8-H, C8'-H), 2.23-2.06 (m, 4H, C9-H, C9'-H); **^{13}C NMR (125 MHz, D_2O, δ_C):** 161.9 (CO, CO'), 146.5 (C4, C4'), 140.6 (C6, C6'), 117.1 (C3, C3'), 107.9 (C5, C5'), 56.2 (C13, C13'), 47.0, 46.6 (C11, C11', C12, C12'), 45.9 (C7, C7'), 38.7 (C

NMe), 29.4 (C10, C10'), 22.5 (C8, C8'), 20.2 (C9, C9') ; **HRMS (ESI$^+$):** calculated $C_{25}H_{34}N_5O_2$: 436.2707, found $[M+H]^+$: 436.2692.

Example 49 - (-)4-tetrazoylcytisine dihydrochloride salt (149)

[0408]



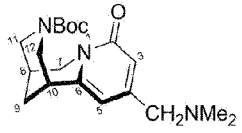
149

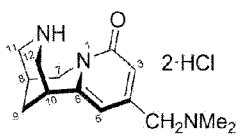
[0409] A Schlenk flask was charged with *N*-Boc-4-cyano-cytisine **139** (240 mg, 0.75 mmol), zinc bromide (170 mg, 0.75 mmol) and sodium azide (58 mg, 0.90 mmol) and placed under nitrogen. Water (2.5 mL, 0.3 M) and isopropanol (0.8 mL, 1.0 M) were added and the reaction mixture was heated at 60 °C for 18 h. The solvent was removed *in vacuo* and the residue was dissolved in DCM (20 mL) and poured over water (20 mL). The mixture was acidified with HCl (0.1 M aq. sol.) to pH ≈ 4-5 and washed with DCM (3 x 20 mL). The aqueous phase was acidified to pH ≈ 1, and extracted with DCM (3 x 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo.* The product was converted into the HCl salt using the general procedure A yielding **149** (102 mg, 53%) as a colourless solid.

[0410] mp: >200 °C, colourless solid; **$[\alpha]_D^{23}$** = -23 [c 0.13, DMF]; **FTIR ν_{max} / cm^{-1}(neat):** 3005, 2807, 1653, 1565; **^{1}H NMR (500 MHz, D_2O, δ_H):** 6.47 (s, 1H, C3-H), 6.44 (s, 1H, C5-H), 4.07 (s, 2H, C13-H), 4.00 (d, *J* =15.0Hz, 1H, C7-H), 3.86 (dd, *J* = 15.0, 6.65 Hz, 1H, C7-H), 3.40-3.20 (m, 5H, C10-H, C11-H, C12-H), 2.69 (s, 1H, C8-H), 1.98 (d, *J* = 14.5 Hz, 1H, C9-H), 1.94 (d, *J* = 14.5 Hz, 1H, C9-H); **^{13}C NMR (125 MHz, D_2O, δ_C):** 164.6 (CO), 155.9 (C4), 148.7 (C6), 137.3 (C13), 114.4 (C3), 106.7 (C5), 49.4, 48.2 (C11, C12), 48.8 (C7), 31.7 (C10), 24.8 (C8), 22.5 (C9); **HRMS (ESI$^+$):** calculated for $C_{12}H_{15}N_6O$: 259.1301, found $[M+H-2HCl]^+$: 259.1301.

Example 50 - *N*-Boc-4-(dimethylamino)methyl-cytisine, and 4-(dimethylamino)methyl-(-)-cytisine dihydrochloride salt (151)

[0411]





[0412] To a solution of amine **143** (320 mg, 1.0 mmol) in an equimolar mixture of THF/water (12 mL) were consecutively added formaldehyde (480 mg, 6 eq., 35% water sol.) and $NaCNBH_3$ (219 mg, 3.5 eq.). The reaction mixture was stirred at r.t for 18 h. The reaction was quenched with 10 mL of water and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude reaction mixture was purified by flash column chromatography on silica gel [DCM/MeOH (1% MeOH)] to give the product as green oil (207 mg, 60%).

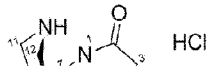
[0413] Data for *N*-Boc4-((dimethylamino)methyl)cytisine: FTIR ν_{max} / cm^{-1}(neat): 2973, 2866, 1680, 1650, 1545; **^{1}H NMR (500 MHz, $CDCl_3$, δ_H):** 6.35 (s, 1H, C3-H), 6.20 (s, 1H, C5-H), 4.44-4.08 (m, 3H, C11-H, C12-H, C7-H); 3.84 (dd, 1H, *J* = 15.0, 6.0 Hz, C7-H), 3.29 (s, 1H, C13-H), 3.20 (s, 1H, C13-H), 3.13-2.91 (m, 3H, C10-H, C11-H, C12-H), 2.41 (s, 1H, C8-H), 2.27 (s, 6H, NMe_2), 2.03-1.90 (m, 2H, C9-H), 1.41-1.15 (m, 9H, Boc); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C):** 163.5 (CO), 154.4 (C4), 150.6/148.4 (C6 rotamers), 116.1 (C3), 106.5/105.5 (C5 rotamers), 80.3/79.7 (q Boc rotamers), 63.2 (C13), 51.6/50.5/49.3 (C11, C12 rotamers), 48.8 (C7), 45.5 (2C, NMe_2), 34.8 (C10), 28.0 (3C, Boc), 27.5 (C8), 26.2 (C9) (carbonyl carbon of the Boc group has not been found); **HRMS (ESI^+):** calculated for $C_{19}H_{30}N_3O_3$: 348.2282, found $[M+H]^+$:348.2281.

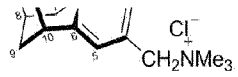
[0414] Following the general procedure A, *N*-Boc-4-(Dimethylamino)methyl-cytisine (0.60 mmol) gave **151** (120 mg, 81%) as a colourless solid, which turned into a viscous oil after several days under air.

[0415] Data for 4-((dimethylamino)methyl)cytisine: mp: >200 °C, colourless foam; **$[\alpha]_D^{26}$** = -46 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1}(neat):** 2948, 1656, 1549, 1457; **^{1}H NMR (500 MHz, D_2O, δ_H):** 6.70 (d, *J* = 1.5 Hz, 1H, C3-H), 6.62 (d, J= 1.5 Hz, 1H, C5-H), 4.24 (s, 2H, C13-H), 4.19 (d, *J* = 15.0 Hz, 1H, C7-H), 4.06 (dd, *J* = 15.0, 6.0 Hz, 1H, C7-H), 3.58-3.39 (m, 5H, C10-H, C11-H, C12-H), 2.92 (s, 6H, NMe_2), 2.88 (s, 1H, C8-H), 2.15 (m, 2H, C9-H); **^{13}C NMR (MHz, D_2O, δ_C):** 164.5 (CO), 148.6 (C6), 143.2 (C4), 118.9 (C3), 109.7 (C5), 59.1 (C13), 49.3, 48.7 (C11, C12), 48.1 (C7), 42.7 (2C, NMe_2), 31.5 (C10), 24.7 (C8), 22.4 (C9); **HRMS (ESI^+):** calculated $C_{14}H_{22}N_3O$: 248.1757, found $[M+H-HCl]^+$: 248.1755.

Example 51 - (-)4-((trimethylammonium)methyl)cytisine iodide salt (150)

[0416]





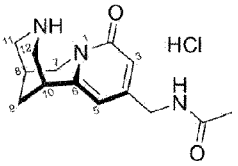
150

[0417] To a solution of amine **143** (220 mg, 0.63 mmol) in EtOH (6.3 mL) was added iodomethane (0.1 mL, 1.3 eq.) and the reaction was stirred for 18 h at 60 °C. The solution was concentrated. Deprotection and conversion into the HCl salt using the general procedure A yielding **150** (80 mg, 42%) as a off-green amorphous solid.

[0418] Mp: ≥ 200 °C; **$[\alpha]_D^{23}$ =** -65 [c 1.3, MeOH]; **FTIR ν_{max} / cm^{-1}(neat):** 1656, 1551, 1479; **^{1}H NMR (500 MHz, D_2O, δ_H):** 6.77 (s, 1 H, C3-H), 6.70 (s, 1 H, C5-H), 4.42 (s, 2H, C13-H), 4.20 (d, *J* = 15.0 Hz, 1H, C7-H), 4.09 (dd, *J* = 15.0, 6.0 Hz, 1H, C7-H), 3.60-3.41 (m, 5H, C10-H C11-H C12-H), 3.19 (s, 9H, NMe_3), 2.89 (s, 1H, C8-H), 2.20 (d, *J* = 14.0 Hz, 1H, C9-H), 2.12 (d, *J* = 14.0 Hz, 1H, C9-H); **^{13}C NMR (125 MHz, D_2O, δ_C):** 164.3 (CO), 148.4 (C4), 140.8 (C6), 121.9 (C3), 111.7 (C5), 67.5 (C13), 53.2 (3C, NMe_3), 49.4, 48.2 (C11, C12), 48.8 (C7), 31.6 (C10), 24.7 (C8), 22.5 (C9); **HRMS (ESI^+):** calculated $C_{15}H_{24}N_3O$: 262.1913, found [$M+H^+$-HCl-Cl^-]: 262.1924.

Example 52 - (-)4-(N-acetyl)aminomethyl) cytisine (148)

[0419]



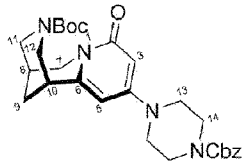
148

[0420] Amine **143** (310 mg, 1.0 mmol) was dissolved in isopropenyl acetate (0.33 mL, 3 eq.) and stirred at r.t. for 24 h. Then, the reaction was concentrated. The crude was purified by flash column chromatography on silica gel [DCM/MeOH (3% MeOH)] to give the product (330 mg, 92%) as a colourless solid. Deprotection and conversion using the general procedure A gave **148** (237 mg, 80%) as a colourless foam.

[0421] mp: >200 °C, colourless foam; **$[\alpha]_D^{23}$** = -20 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1}(neat):** 2197 (w), 1678, 1640, 1571, 1468; **^{1}H NMR (500 MHz, D_2O, δ_H):** 6.54-6.44 (m, 2H, C3-H, C5-H), 4.29 (s, 2H, C13-H), 4.17 (d, *J* = 15.0 Hz, 1H, C7-H), 4.04 (dd, *J* = 15.0, 6.0 Hz, 1H, C7-H), 3.55-3.38 (m, 5H, C10-H, C11-H, C12-H), 2.83 (s, 1H, C8-H), 2.18-2.05 (m, 5H, C9-H C16-H); **^{13}C NMR (125 MHz, D_2O, δ_C):** 174.6 (C14), 164.7 (CO), 153.3 (C4), 146.9 (C6), 112.3 (C3), 108.7 (C5), 49.5, 48.2 (C11, C12), 48.6 (C7), 41.7 (C13), 31.5 (C10), 24.8 (C8), 22.60 (C9), 21.7 (C15); **HRMS (ESI^+):** calculated $C_{14}H_{20}N_3O$: 262.1550, found [M+H-HCl]$^+$: 262.1543.

Example 53 - *N*-Boc 4-(4-((benzyloxy)carbonyl)piperazin-1-yl)cytisine (89)

[0422]



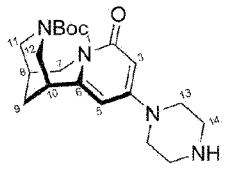
89

[0423] A solution of bromide **61** (180 mg, 0.5 mmol), Cu_2O (8 mg, 0.1 eq.) and 1-Z-piperazine (0.5 mL, 2.5 mmol) in water (1.0 mL) was stirred in a seal tube at 100 °C for 18 h. The reaction was cooled and the residue was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo.* The crude reaction mixture was purified by flash column chromatography on silica gel [DCM/MeOH (2% MeOH)] to give **89** as colourless solid (220 mg, 89%), which was used in the next step without further purification.

[0424] **^{1}H NMR (500 MHz, $CDCl_3$, δ_H):** 7.37-7.30 (m, 5H, Ar), 5.74 (d, *J* = 2.5 Hz, 1H, C3-H), 5.64 (s, 1H, C5-H), 5.16 (s, 2H, CH_2-Ph), 4.39-4.06 (m, 3H, C7-H, C11-H, C12-H), 3.77 (dd, *J* = 15.0, 6.0 Hz, 1H, C7-H), 3.60 (m, 4H, C13-H), 3.27 (m, 4H, C14-H), 3.01 (m, 2H, C11-H C12-H), 2.87 (s, 1H, C10-H), 2.35 (s, 1H, C8-H), 1.97 (d, *J* = 12.5 Hz, 1H, C9-H), 1.89 (d, *J* = 12.5 Hz, 1H, C9-H), 1.40-1.18 (s, 9H, Boc); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C):** 164.3 (CO), 156.4 (CO), 155.1 (CO), 154.6 (C4), 148.3 (C6), 136.4 (Ar), 128.5 (2C, Ar), 128.1 (Ar), 127.9 (2C, Ar), 96.4 (C3), 95.0 (C5), 80.1 (q Boc), 67.7 (CH_2-Ph), 50.6, 50.5 (C11, C12), 47.9 (C7), 46.1 (2C, C13), 43.1 (2C, C14), 35.4 (C10), 28.1 (3C, Boc), 27.7 (C8), 26.5 (C9); **HRMS (ESI^+):** calculated for $C_{28}H_{37}N_4O_5$: 509.2758, found $[M+H]^+$: 509.2733.

Example 54 - *N*-Boc 4-(piperazin-1-yl) cytisine

[0425]



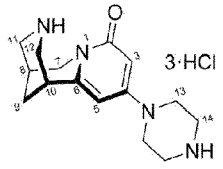
[0426] A solution of **89** (160 mg, 0.32 mmol) in methanol (5 mL) was placed under nitrogen and palladium on activated charcoal 10 wt% (5 mg, 0.1 eq.) was added. The vessel was placed under vacuum and backfilled with hydrogen for three times and stirred for 18 h. The reaction

mixture was filtered through Celite® and the solvent was concentrated, giving the piperazinyl derivative (85 mg, 71%) as a colourless solid, which was used in the next step without further purification.

[0427] **^{1}H NMR (500 MHz, $CDCl_3$, δ_H):** 5.85 (s, 1H, C3-H), 5.72 (s, 1H, C5-H), 5.49 (br, 1H, NH), 4.33-4.01 (m, 3H, C7-H, C11-H, C12-H), 3.74 (dd, *J* = 15.0, 6.0 Hz, 1H, C7-H), 3.55 (s, 4H, C13-H), 3.19 (s, 4H, C14-H), 3.07-2.94 (m, 2H, C11-H, C12-H), 2.92 (s, 1H, C10-H), 2.36 (s, 1H, C8-H), 1.96 (d, *J* = 13.5 Hz, 1H, C9-H), 1.89 (d, *J* = 13.5 Hz, 1H, C9-H); 1.38-1.19 (s, 9H, Boc); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C):** 164.6 (CO), 156.4 (CO), 154.5 (C4), 148.8 (C6), 96.9 (C3), 95.0 (C5), 80.0 (q Boc), 50.6, 50.5 (C11, C12), 48.2 (C7), 44.7 (2C, C13), 43.6 (2C, C14), 35.2 (C10), 28.1 (3C, Boc), 27.5 (C8), 26.4 (C9); **HRMS (ESI$^+$):** calculated $C_{20}H_{31}N_4O_3$: 375.2391, found $[M+H]^+$: 375.2383.

Example 55 - (+)4-(*N*-piperazinyl)cytisine trihydrochloride salt (90)

[0428]



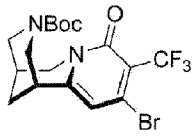
90

[0429] A solution of *N*-Boc 4-*N*-(*N*'-Cbz)-piperazine-cytisine (323 mg, 0.64 mmol) in MeOH (6.4 mL) was placed under nitrogen and Pd/C (10 wt%) (6.5 mg, 0.1 eq) was added. The vessel was placed under vacuum and backfilled with hydrogen for three times and stirred for 24 h. The mixture was filtered through Celite® and concentrated *in vacuo.* Deprotection and conversion into its HCl salt using the general procedure A gave **90** (237 mg, 96%) as a colourless solid.

[0430] mp: >200 °C, colourless powder; **$[\alpha]_D^{25}$** = +52 [c 1.0, MeOH]; **FTIR ν_{max} / cm^{-1} (neat):** 3374, 2924, 2712, 2585, 2451, 1638, 1538; **^{1}H NMR (400 MHz, D_2O, δ_H):** 6.55 (s, 1H, C3-H), 4.10 (d, *J* = 15.0 Hz, 1H, C7-H_a), 3.98 (dd, *J* = 6.5, 15.0 Hz, 1H, C7-H_b), 3.69-3.66 (m, 4H, C14-H), 3.47-3.26 (m, 9H, C10-H, C11-H, C12-H, C13-H), 2.70 (s, 1H, C8-H), 2.07-1.96 (m, 2H, C9-H), C5-H not detected due to deuterium exchange; **^{13}C NMR (100 MHz, D_2O, δ_C):**162.1 (CO), 157.2 (C4), 148.1 (C6), 102.4 (C3), 92.2-91.7 (m, C5), 49.2 (C11 or C12), 48.8 (C7), 48.1 (C11 or C12), 42.7 (2C, C13), 42.5 (2C, C14), 31.7 (C10), 24.5 (C8), 22.5 (C9); **HRMS (ESI$^+$):** calculated for $C_{15}H_{23}N_4O$: 275.1866, found $[M+H-3HCl]^+$: 275.1868.

Example 56a - N-Boc 3-(trifluoromethyl)-4-bromocytisine 161

[0431]



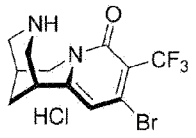
161

[0432] A solution of N-Boc 4-bromo-cytisine **61** (370 mg, 1.0 mmol) in a mixture of DMSO (3.8 mL) H_2O (1.6 mL) was cooled to 0°C and sodium trifluoromethylsulfonate (470 mg, 3.0 mmol) was added. T*ert*-butyl hydroperoxide (0.7 mL, 70% aq.sol.) was added dropwise during 5 min. and the solution was allowed to warm to r.t. and stirred for 24 h. The solvent was removed *in vacuo.* The crude was distributed between ammonia (15 mL, 15% aq. sol.) and DCM (15 mL), and the aqueous phase was extracted with DCM (3 x 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude was purified by flash column chromatography on silica gel [n-Hexane/EtOAc (1 :1)] to give **161** (130 mg, 30%) as colourless solid, together with 3% of *N*-Boc-5-CF_3-4-Bromo-cytisine. [1H NMR : 98% (C3-substituted), 2% (C5-substituted ; 87% conversion)].

[0433] FTIR ν_{max} / cm^{-1} (neat): 2972, 2923, 2865,1677,1645,1543; **^{1}H NMR (500 MHz, $CDCl_3$, δ_H):** 6.41 (s, 1H, C5-H), 4.45-4.10 (m, 3H, C7-H, C11-H, C12-H), 3.88-3.76 (dd, *J* = 6.5, 15.5 Hz, 1H, C7-H), 3.23-2.91 (m, 3H, C11-H, C12-H, C10-H), 2.48 (s, 1H, C8-H), 1.99 (s, 2H, C9-H), 1.44-1.18 (m, 9H, Boc); **^{13}CNMR (125 MHz, $CDCl_3$, δ_C):** 158.7 (CO), 154.5/154.0 (CO, rotamers), 152.2/151.7 (C6), 135.0/134.7 (C4), 122.6 (q, *J* = 276 Hz, CF_3), 116.2 (q, *J* = 30 Hz, C3), 121.3/110.5 (C5, rotamers), 80.9/80.3 (q Boc, rotamers), 51.2/50.4/49.8/49.1 (C11, C12, rotamers), 49.4 (C7, rotamers), 34.7 (C10), 28.0 (3C, Boc), 27.2 (C8), 25.5 (C9); **HRMS (ESI$^+$):** calculated for $C_{17}H_{21}BrF_3N_2O_3$: 437.0682, found $[M+H]^+$: 437.0679.

Example 56b - (-)3-(Trifluoromethyl)-4-bromocytisine hydrochloride salt (162)

[0434]



162

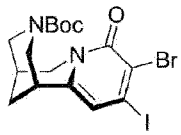
[0435] Following the general procedure A, bromide **161** (0.25 mmol) gave **162** (0.45 mg, 48%).

[0436] mp: > 200 °C, colourless powder; **$[\alpha]_D^{23}$** = -19 [c 0.20, MeOH]; **FTIR ν_{max} / cm^{-1}** (neat):

1651, 1543, 1130, 1076; **^{1}H NMR (400 MHz, D_2O, δ_H):** 6.83 (s, 1H, C5-H), 4.04 (d, *J* = 15.5 Hz, 1H, C7-H), 3.89 (dd, *J* = 6.5, 15.5 Hz, 1H, C7-H), 3.46-3.28 (m, 5H, C10-H, C11-H, C12-H), 2.76 (s, 1H, C8-H), 2.06 (d, *J* = 13.5 Hz, 1H, C9-H), 2.00 (d, *J* = 13.5 Hz, 1H, C9-H); **^{13}C NMR (100 MHz, D_2O, δ_C):** 160.7 (CO), 150.3 (C6), 136.5 (C4), 122.4 (q, *J* = 275 Hz, CF_3), 116.2 (q, *J* = 30 Hz, C3-H), 114.3 (C5-H), 48.9, 48.0 (C11, C12), 48.8 (C7), 31.4 (C10), 24.5 (C8), 22.1 (C9); **HRMS (ESI$^+$):** calculated for $C_{12}H_{13}BrF_3N_2O$: 337.0158, found $[M+H]^+$: 337.0162.

Example 57a - *N*-Boc 3-bromo-4-iodocytisine (159)

[0437]



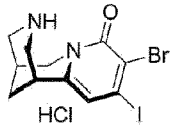
159

[0438] *N*-Boc-4-iodo-cytisine **65** (120 mg, 0.286 mmol) was dissolved in THF (6 mL, 0.05 M) and *N*-bromosuccinimide (51 mg, 0.286 mmol) was added. The reaction mixture was stirred at r.t. for 24 h. The reaction was diluted with water (15 mL), and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude was purified by flash column chromatography on silica gel [n-Hexane/EtOAc (1 :1)] to give **159** (91 mg, 65%), contaminated with *N*-Boc-5-bromo-4-iodo-cytisine (in a ratio 22:3).

[0439] FTIR ν_{max} / cm^{-1} (neat): 2925, 2865, 1669, 1634, 1569; **^{1}H NMR (500 MHz, $CDCl_3$, δ_H):** 6.58 (s, 1H, C5-H), 4.43-4.06 (m, 3H, C7-H, C11-H, C12-H), 3.78 (dd, *J* = 6.5, 15.5 Hz, 1H, C7-H), 3.16-2.86 (m, 3H, C10-H, C11-H, C12-H), 2.42 (s, 1H, C8-H), 1.96 (m, 2H, C9-H), 1.40-1.15 (m, 9H, Boc); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C):** 157.7 (CO), 156.5 (CO), 154.6/154.1 (C6, rotamers), 147.7/147.2 (C4, rotamers), 121.4 (C3), 115.5/114.9 (C5, rotamers), 80.6/80.1 (q Boc, rotamers), 51.8/51.5/50.0/49.4 (C11, C12, rotamers), 50.4 (C7, rotamers), 34.3 (C10), 28.1 (3C, Boc), 27.4 (C8), 25.9 (C9), **HRMS (ESI$^+$):** calculated for $C_{16}H_{21}BrIN_2O_3$: 494.9774, found $[M+H]^+$: 494.9761.

Example 57b - (+)3-Bromo-4-iodocytisine hydrochloride salt (160)

[0440]



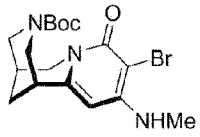
160

[0441] Following the general procedure A, iodide **159** (0.16 mmol) gave **160** (57 mg, 81%); contaminated with 5-bromo-4-iodo-cytisine (ratio 22:3).

[0442] $[\alpha]_D^{23}$ = +7 [c 0.3, water]; **FTIR ν_{max} / cm^{-1} (neat):** 2985, 1606, 1566, 1096; **^{1}H NMR (500 MHz, DMSO, δ_H):** 6.83 (s, 1H, C5-H), 3.92 (d, *J* = 15.5 Hz, 1H, C7-H), 3.79 (dd, *J* = 6.5, 15.5 Hz, 1H, C7-H), 3.33-3.12 (m, 5H, C11-H, C12-H, C10-H), 2.62 (s, 1H, C8-H), 1.99 (d, *J* = 13.5 Hz, 1H, C9-H), 1.87 (d, *J* = 13.5 Hz, 1H, C9-H); **^{13}C NMR (125 MHz, DMSO, δ_C):** 157.7 (CO), 147.7 (C6), 121.0 (C4), 116.4 (C3), 115.6 (C5), 49.8 (C7), 48.8, 48.0 (C11, C12), 30.9 (C10), 14.9 (C8), 22.9 (C9); **HRMS (ESI$^+$):** calculated for $C_{11}H_{13}BrIN_2O$: 394.9250, found $[M+H-HCl]^+$: 394.9249.

Example 58a - *N*-Boc 3-Bromo-4-methylaminocytisine (157)

[0443]



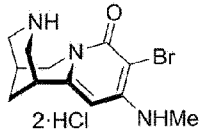
157

[0444] To a solution of *N*-methyl amine **83** (96 mg, 0.30 mmol) in THF (6.0 mL) was added *N*-bromosuccinimide (54 mg, 0.30 mmol) and the reaction was stirred at r.t. for 24 h. The reaction was diluted with water (15 mL) and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude was purified by flash column chromatography on silica gel [DCM/MeOH (2% MeOH)] to give **157** (*N*-Boc-3-bromo-4-methylamino-cytisine) (84 mg, 70%), and *N*-Boc-5-bromo-4-methylamino (27 mg, 22%), which was used in the next step without further purification.

[0445] Data for 157: FTIR ν_{max} / cm^{-1} (neat): 3290, 2946, 2761, 2623, 1633, 1493, 1206, 1100, 1025, 567, 521 ; **^{1}H NMR (500 MHz, $CDCl_3$, δ_H):** 5.68 (s, 1H, C5-H), 4.84 (s, 1H, NH), 4.36-4.05 (m, 3H, C11-H, C12-H, C7-H), 3.79 (dd, *J* = 6.5, 15.5 Hz, 1H, C7-H), 3.13-2.85 (m, 6H, C11-H, C12-H, C10-H, NHMe), 2.33 (s, 1H, C8-H), 1.91 (m, 2H, C9-H), 1.36-1.13 (m, 9H, Boc); **^{13}C NMR (125 MHz, $CDCl_3$, δ_C):** 159.2 (CO), 154.7, 154.2 (C6, rotamers), 152.4 (CO), 148.0, 147.7 (C4, rotamers), 93.0, 92.5 (C5-H), 90.4 (C3), 80.3, 79.7 (q Boc, rotamers), 51.6, 50.6, 50.2, 49.3 (C11, C12), 49.1 (C7), 35.0 (C10), 29.8 (C8), 28.0, 27.7 (Boc, rotamers), 26.2 (C9).

Example 58b - (+)3-Bromo-4-N-methylaminocytisine hydrochloride salt (158)

[0446]



158

[0447] Following the general procedure A, *N*-Methyl amine **157** (0.21 mmol) gave **158** (45 mg, 73%) as a colourless solid, contaminated with 9% of 5-Bromo-4-methylamino-cytisine. **$[\alpha]_D^{23}$** = +38 [c 0.5, MeOH]; **FTIR ν_{max} / cm^{-1} (neat):** 3291, 2949, 2761, 2624, 1634, 1583; **^{1}H NMR (500 MHz, D_2O, δ_H):** 6.14 (s, 1H, C5-H), 4.13 (d, *J* = 15.5 Hz, 1H, C7-H), 3.88 (dd, J= 6.5, 15.5 Hz, 1H, C7-H), 3.52-3.32 (m, 5H, C11-H, C12-H, C10-H), 2.84 (s, 3H, NHMe), 2.70 (s, 1H, C8-H), 2.04 (m, 2H, C9-H); **^{13}C NMR (125 MHz, D_2O, δ_C):** 160.5 (CO), 154.3 (C6), 145.6 (C4), 97.0 (C3), 89.6 (C5), 49.3, 48.5 (C11, C12), 48.9 (C7), 31.6 (C10), 28.9 (NHMe), 24.9 (C8), 22.9 (C9); **HRMS (ESI^+):** calculated for $C_{12}H_{17}BrN_3O$: 298.0549, found $[M+H]^+$: 298.0549

Example 59 - Iridium-catalyzed C-H borylation of (-)-cytisine

[0448] Synthesis of 4-Bpincytisine.

[0449] A Schlenk tube was charged with (-)-cytisine (190 mg, 1.0 mmol), $[Ir(COD)(OMe)]_2$ (6.6 mg, 0.01 eq), 4,4'-2,2'-di-tert-butylbispyridine (5.4 mg, 0.02 eq) and bis(pinacolato)diboron (380 mg, 1.50 eq). After purging with nitrogen, THF (1.4 mL) was added and the reaction mixture was heated at reflux for 24 h. After this time, the volatile materials were removed under reduced pressure and 4-Bpincytisine was partially characterized without further purification and obtained as a brown foam.

[0450] 1H NMR (500 MHz, $CDCl_3$): δ = 6.88 (d, 1 H, J = 1.0 Hz), 6.27 (s, 1H), 4.11 (d, 1 H, J = 15.5 Hz), 3.86 (dd, 1 H, J = 6.5, 15.5 Hz), 3.15-2.78 (m, 5 H), 3.21 (s, 1 H), 1.94-1.91 (m, 2 H), 1.23 (s, 12 H).

[0451] 13C NMR (125 MHz, CDCl3): δ = 163.1, 149.2, 124.1, 108.8, 84.4, 82.7, 53.3, 52.3, 49.6, 35.1, 27.5, 25.5, 14.5.

[0452] To confirm the identity of 4-Bpincytisine, that compound was further converted to 4-bromocytisine by treatment with an aqueous solution of $CuBr_2$ in MeOH. The spectroscopic properties of 4-bromocytisine were consistent with the data available in literature.

Example 60 - Iridium-catalyzed C-H borylation of (-)-cytisine

[0453] Synthesis of 4-Bpincytisine.

[0454] The process of Example 59 was carried out, using the same apparatus and solvents, catalysts and ligands in the same molar amounts as outlined above, except that Me4phen was used as a ligand and the borylating agent B_2Pin_2 was present at 3.00 eq. The process resulted in 100% conversion of cytisine to 4-Bpincytisine.

Example 61 - Iridium-catalyzed C-H borylation of (-)-cytisine

[0455] Synthesis of 4-Bpincytisine.

[0456] The process of Example 59 was carried out, using the same apparatus and solvents, catalysts and ligands in the same molar amounts as outlined above, except that neocuproine was used as a ligand. The process resulted in 100% conversion of cytisine to 4-Bpincytisine.

Example 62 - Iridium-catalyzed C-H borylation of N-Boc cytisine (56)

[0457] Synthesis of N-Boc 4-Bpincytisine (58).

[0458] A Schlenk tube was charged with N-Boc cytisine (56) (290 mg, 1.0 mmol), $[Ir(COD)(OMe)]_2$ (6.6 mg, 0.01 eq), 4,4'-2,2'-di-tert-butylbispyridine (5.4 mg, 0.02 eq) and bis(pinacolato)diboron (178 mg, 0.70 eq). After purging with nitrogen, THF (1.4 mL) was added and the reaction mixture was heated at reflux for 18 h. After this time, 1H NMR showed essentially 100% conversion, the volatile materials were removed under reduced pressure.

[0459] The crude product N-Boc 4-Bpincytisine (58) was shown to be essentially pure by 1H NMR and although further purification is possible, this is unnecessary prior to using N-Boc 4-Bpincytisine (58) as a reactant.

[0460] Further purification of crude N-Boc 4-Bpincytisine (58) was achieved using chromatography (DCM-MeOH, 95:5) to give pure N-Boc 4-Bpincytisine (58) (180 mg, 43%) as a pale yellow foam;

[0461] Rf = 0.23 (DCM-MeOH, 95:5).

[0462] IR (neat): 3433, 2977, 1688, 1657, 1563, 1423 cm^{-1}.

[0463] 1H NMR (400 MHz, CDCl3): δ = 6.85 (s, 1 H), 6.31 (s, 1 H), 4.34-4.10 (m, 3 H), 3.80 (dd, 1 H, J = 6.5, 15.5 Hz), 3.07-2.91 (m, 3 H), 2.41 (s, 1 H), 1.95-1.88 (m, 2 H), 1.41-1.09 (m, 21 H).

[0464] 13C NMR (100 MHz, CDCl3): δ = 162.9, 154.6/154.3 (rotamers), 147.9/147.5 (rotamers), 124.4, 109.3/108.8 (rotamers), 84.4, 82.6/80.3, 79.7/75.0 (2 C, rotamers), 51.7/50.6/50.3/49.2 (2 C, rotamers), 48.9, 34.7, 28.0 (4 C), 27.5, 26.1, 24.8/24.6 (3 C, rotamers); C-Bpin was not observed.

[0465] 11B NMR (96.4 MHz, CDCl3): δ = 28.94 (br s).

[0466] HRMS-ESI: m/z [M + H]+ calcd for C22H33BN2NaO5: 439.2379; found: 439.2373.

Example 63 - Iridium-catalyzed C-H borylation of N-Boc cytisine (56)

[0467] Synthesis of N-Boc 4-Bpincytisine (58).

[0468] The process of Example 62 was carried out, using the same apparatus and solvents, catalysts and ligands in the same molar amounts as outlined above, except that N-methyl cytisine was used as a starting material of Formula IIa. The process resulted in 98% conversion of cytisine to 4-Bpincytisine.

Example 64 - Iridium-catalyzed C-H borylation of N-Boc cytisine (56)

[0469] Synthesis of N-Boc 4-Bpincytisine (58).

[0470] The process of Example 62 was carried out, using the same apparatus and solvents, catalysts and ligands in the same molar amounts as outlined above, except that N-Cbz cytisine was used as a starting material of Formula IIa. The process resulted in 88% conversion of cytisine to 4-Bpincytisine.

Example 65 - N-Boc 4-p-tolylcytisine (72)

[0471] N-Boc 4-Bpincytisine 58 was made following the general procedure discussed above on a 0.5 mmol scale. To crude N-Boc 4-Bpincytisine was added potassium carbonate (124 mg, 0.90 mmol), tetrakis (triphenylphosphine) palladium(0) (28 mg, 0.05 eq) and 4-bromotoluene (0.25 mL, 1.0 mmol) and a mixture of DME/water (5:1) (5 mL, 0.1 M) was added. The mixture was heated at 80 °C for 24 h, then cooled to room temperature and diluted with water (15 mL). The aqueous phase was extracted with DCM (3 x 15 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography [DCM/MeOH (1.5% MeOH)] afforded N-Boc 4-(p tolyl)cytisine (104 mg, 55%) as a colourless solid.

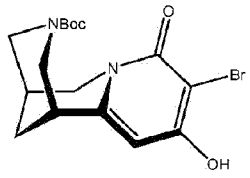
Example 66 - *N*-Boc 4-methylcytisine (109)

[0472] N-Boc 4-Bpincytisine 58 was made following the general procedure discussed above for the borylation of cytisine on a 0.5 mmol scale.

[0473] Using a modification of a related procedure, to crude N-Boc 4-Bpincytisine 58 were added Pd_2dba_3 (11 mg, 0.025 eq), tri(p tolyl)phosphine (7.6 mg, 0.05 eq), potassium carbonate (138 mg, 2.0 eq), iodomethane (0.03 mL, 1.0 eq) and the vessel was placed under vacuum and backfilled with nitrogen three times. A mixture of DMF/water (9:1,5 mL) was added and the reaction mixture was stirred at 60°C for 18 h. The mixture was cooled to r.t. and the solvent removed in vacuo. The residue was partitioned between EtOAc (15 mL) and water (15 mL) and the aqueous phase was extracted with EtOAc (3 x 15mL). The combined organic phases were dried over $MgSO_4$, filtered, concentrated and purified by flash column chromatography on silica gel [DCM/MeOH (3% MeOH)] to give N-Boc 4-methylcytisine (98 mg, 64%) as a pale yellow solid.

Example 67a - *N*-Boc (3-bromo-4-hydroxy)cytisine

[0474]

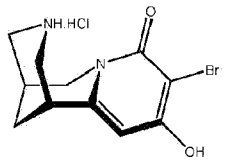


[0475] A solution of *N*-Boc 4-aminocytisine (512 mg, 1.67 mmol) in THF (32 mL) was cooled to 0 °C, *N*-bromosuccinimide (312 mg, 1.76 mmol) was added, and the reaction mixture was stirred at 0°C for 18 hours. Water (25 mL) was added and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification of the crude reaction mixture by flash column chromatography [EtOAc/MeOH (1% MeOH)] afforded *N*-Boc (3-bromo-4-hydroxy)cytisine (350 mg, 55%) as a colourless solid.

[0476] R_f: 0.37 [DCM/MeOH (5% MeOH)]; **FTIR vmax /cm^{-1} (neat):** 2864, 1698, 1581, 1408, 1245, 1129; **^{1}H NMR (500 MHz, DMSO, δ_H):** 11.00 (s, 1H), 5.94 (s, 1H), 4.18-3.81 (m, 3H), 3.58 (dd, *J* = 15.0, 6.5 Hz, 1H), 3.14-2.85 (m, 3H), 2.30 (s, 1H), 1.85 (s, 2H), 1.29-1.02 (m, 9H); **^{13}C NMR (500 MHz, DMSO, δ_C):** 162.6, 160.4, 154.1, 149.0, 98.0, 93.2, 79.1, 51.7, 50.5, 49.6, 34.3, 28.0, 27.4, 25.7; **HRMS (ESI$^+$):** calculated for $C_{16}H_{22}{}^{79}BrN_2O_4$: 385.0757, found $[M+H]^+$: 385.0764.

Example 67b - (-)-(3-bromo-4-hydroxy)cytisine hydrochloride salt (BS70)

[0477]

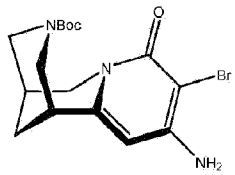


[0478] Following the general procedure A, N-Boc (3-bromo-4-hydroxy)cytisine (0.83 mmol) gave BS70 (236 mg, quantitative) as a colourless solid.

[0479] mp: ≥200 °C; **$[\alpha]_D^{24}$** = -0.12 [c 1.0, water]; **FTIR vmax /cm^{-1} (neat):** 2573, 1646, 1550, 1408, 1310, 1097, 854; **^{1}H NMR (500 MHz, D_2O, δ_H):** 6.34 (s, 1H), 4.26 (d, *J* = 15.5 Hz, 1H), 4.00 (dd, *J* = 15.5, 7.0 Hz, 1H), 3.60 (d, *J* = 13.5 Hz, 1H), 3.50-3.40 (m, 4H), 2.82 (s, 1H), 2.13 (m, 2H); **^{13}C NMR (500 MHz, D_2O, δ_C):** 163.3, 162.3, 146.4, 101.5, 94.8, 49.3, 49.2, 48.3, 31.4, 24.8, 22.7; **HRMS (ESI$^+$):** calculated for $C_{11}H_{14}{}^{79}BrN_2O_2$: 285.0160, found $[M+H]^+$: 285.0230.

Example 68a - N-Boc (3-bromo-4-amino)cytisine

[0480]



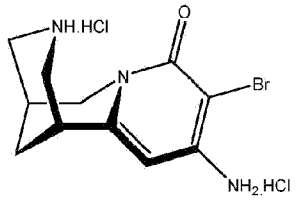
[0481] A solution of 4-aminocytisine (250 mg, 0.82 mmol) in THF (16 mL) was cooled to 0 °C, *N*-bromosuccinimide (153 mg, 0.86 mmol) was added, and the reaction mixture was stirred at 0°C for 18 hours. Water (25 mL) was added and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification of the crude reaction mixture by flash column chromatography [EtOAc] afforded N-Boc (3-bromo-4-amino)cytisine (95 mg, 30%) as a colourless solid.

[0482] ***R_f*:** 0.43 [DCM/MeOH (6% MeOH)]; **mp:** ≤200 °C (toluene); **FTIR vmax /cm^{-1} (neat):** 3441, 3178, 2917, 1682, 1633, 1591, 1427, 1124, 820, 751; **^{1}H NMR (500 MHz, $CDCl_3$, δ_H):** 5.67 (s, 1H), 4.59 (s, 2H), 4.43-4.00 (m, 3H), 3.82 (dd, *J* = 15.5, 6.5 Hz, 1H), 3.13-2.87 (m, 3H), 2.36 (s, 1H), 1.95 (d, *J* = 12.5 Hz, 1H), 1.91 (d, *J* = 12.5 Hz, 1H), 1.39-1.18 (m, 9H); **^{13}C**

NMR (500 MHz, $CDCl_3$, δ_C): 159.8, 154.4, 151.5, 146.9, 96.1, 91.4, 80.3, 51.5, 50.4, 49.3, 34.7, 28.0, 27.4, 26.3; **HRMS (ESI^+):** calculated for $C_{16}H_{22}{}^{81}BrN_3NaO_3$: 408.0737, found $[M+Na]^+$: 408.0713.

Example 68b - (+)-(3-bromo-4-amino)cytisine hydrochloride salt (BS71)

[0483]

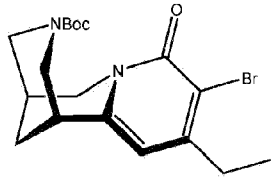


[0484] Following the general procedure A, *N*-Boc (3-bromo-4-amino)cytisine gave BS71 (62 mg, 64%) as a colourless solid.

[0485] mp: ≥200 °C (toluene); **$[\alpha]_D^{24}$** = +0.08 [c 1.0, water]; **FTIR vmax /cm^{-1} (neat):** 3313, 3132, 2934, 2756, 1641, 1532, 1454, 1163; **^{1}H NMR (500 MHz, MeOD, δ_H):** 6.15 (s, 1H), 4.37 (d, *J* = 15.5 Hz, 1H), 3.92 (dd, *J* = 15.5, 6.5 Hz, 1H), 3.54 (d, *J* = 13.0 Hz, 1H), 3.49-3.36 (m, 3H), 3.31 (s, 1H), 2.70 (s, 1H), 2.15 (d, *J* = 13.5 Hz, 1H), 2.07 (d, *J* = 13.5 Hz, 1H); **^{13}C NMR (500 MHz, MeOD, δ_C):** 159.9, 154.7, 144.9, 100.2, 89.3, 49.2, 48.9, 48.3, 31.6, 25.4, 23.2; **HRMS (ESI^+):** calculated for $C_{11}H_{15}{}^{79}BrN_3O$: 284.0393, found $[M+H]^+$: 284.0390.

Example 69a - *N*-Boc (3-bromo-4-ethyl)cytisine

[0486]



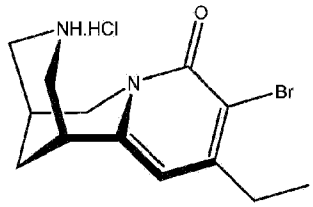
[0487] A solution of *N*-Boc 4-ethyl-cytisine (341 mg, 1.07 mmol) in THF (20 mL) was cooled to 0 °C, *N*-bromosuccinimide (190 mg, 1.07 mmol) was added, and the reaction mixture was stirred at 0 °C for 18 hours. Water (25 mL) was added and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification of the crude reaction mixture by flask column chromatography [DCM/MeOH (2% MeOH)] afforded N-Boc (3-bromo-4-ethyl)cytisine (296 mg, 70%) as a

colourless solid.

[0488] R_f: 0.22 [DCM/MeOH (2% MeOH)]; **^{1}H NMR (500 MHz, $CDCl_3$, δ_H):** 5.99 (s, 1H), 4.45-4.02 (m, 3H), 3.86 (dd, *J* = 15.5, 6.5 Hz, 1H), 3.16-2.86 (m, 3H), 2.66 (m, 2H), 2.40 (s, 1H), 2.00-1.88 (m, 2H), 1.44-1.03 (m, 12H); **^{13}C NMR (500 MHz, $CDCl_3$, δ_C):** 159.5, 154.5, 146.8, 112.9, 106.3, 80.3, 51.5, 50.4, 50.0, 29.8, 29.6, 28.0, 27.4, 26.2, 12.7, (C9 has not been found); **HRMS (ESI$^+$):** calculated for $C_{18}H_{26}{}^{79}BrN_2O_3$: 397.1121, found $[M+H]^+$: 397.1121.

Example 69b - (-)-(3-bromo-4-ethyl)cytisine (BS74)

[0489]



[0490] Following the general procedure A, N-Boc (3-bromo-4-ethyl)cytisine (296 mg, 0.75 mmol) gave BS74 (80 mg, 37%) as a colourless solid.

[0491] mp: ≥200 °C; **$[\alpha]_D^{24}$** = -0.21 [c 1.0, water]; **FTIR vmax /cm^{-1} (neat):** 2935, 2544, 1635, 1572, 1450, 1101, 705; **^{1}H NMR (500 MHz, MeOD, δ_H):** 6.50 (s, 1H), 4.45 (d, *J* = 15.5 Hz, 1H), 4.02 (dd, *J* = 15.5, 6.5 Hz, 1H), 3.63 (d, *J* = 13.5 Hz, 1H), 3.54-3.42 (m, 4H), 2.81 (s, 1H), 2.72 (m, 2H), 2.22 (d, *J* = 13.5 Hz, 1H), 2.12 (d, *J* = 13.5 Hz, 1H), 1.25 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (500 MHz, MeOD , δ_C):** 159.9, 156.0, 144.9, 112.9, 108.8, 49.6, 49.3, 48.4, 31.6, 29.4, 25.4, 22.9, 11.5; **HRMS (ESI$^+$):** calculated for $C_{13}H_{18}{}^{79}BrN_2O$: 297.0597, found [M+H]+: 297.0591.

[0492] The following examples illustrate the activity of compounds prepared in accordance with the present invention.

Example 70 Binding to Nicotinic Receptor Subtypes

[0493] The binding of a group of compounds mentioned above were tested for their affinity at different nAChR subtypes, specifically the α4β2, the α3β4 and α7. The protocol for these tests is set out below, and the results are provided at Table 1 below.

Binding to heterologously expressed_α4β2 and α3β4 human subtypes

[0494] HEK 293 cells were grown in Dulbecco's modified Eagle medium supplemented with 10% fetal bovine serum, 1% L-Glutamine, 100 units/ml penicillin G, and 100 µg/streptomycin in a humidified atmosphere containing 10% CO_2. The cDNAs encoding α3 and β4 or α4 and β2 (were transfected into the HEK 293 cells at 30% confluency). The cell transfections were carried out in 100 mm Petri dishes using 30 µL of JetPEI™ (Polypus, France) (1 mg/ml, pH 7.2) and 3 µg of each cDNA. After 24 h transfection, the cells were collected, washed with PBS by centrifugation, and used for binding analysis.

[0495] [^{3}H]-epibatidine saturation binding experiments to HEK transfected α3β4 or α4β2 receptors were performed by means of overnight incubation at 4°C at concentrations ranging from 0.005 to 1 nM in a buffer containing 50 mM Tris-HCl, pH 7, 150 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 2.5 mM $CaCl_2$ and 2 mg/ml BSA, in the presence (aspecific binding) or absence (total binding) of 100 nM cold epibatidine. Specific ligand binding was defined as total binding minus the binding in the presence of 100 nM cold epibatidine.

[0496] The inhibition of [^{3}H]-epibatidine binding induced by the compounds or nicotinic ligands was measured by incubating increasing concentrations (10 pM - 10 mM) of the test compounds for 30 min at room temperature (r. t.), followed by overnight incubation at 4°C with a final concentration of 0.25 nM [^{3}H]-epibatidine (in the case of the α4β2* subtype) or 0.5 nM (in the case of the α3β4 subtype). After incubation, the membranes of HEK cells transfected with α4β2* or α3β4 subtypes were washed by filtration on GFC filters with ice-cold PBS. The GFC filters were pre-soaked in polyethylenimine and filtered through a harvester apparatus. [^{3}H]-epibatidine binding was determined by means of liquid scintillation counting in a beta counter.

Binding to heterologously expressed_α7 subtype

[0497] The human α7 cDNA was transfected into SH-SY5Y human neuroblastoma cells. The cell transfections were carried out in 100 mm Petri dishes using 30 µL of JetPEI™ (Polypus, France) (1 mg/ml, pH 7.2) and 6 µg of α7 cDNA. After 24 h transfection, the cells were collected, washed with PBS by centrifugation, and used for binding analysis.

[0498] The [^{115}I]-α-Bungarotoxin (purchased from Perkin Elmer, Boston MA) saturation binding was performed by incubating SH-SY5Y membranes overnight with 0.1-10 nM concentrations of [^{125}I]-α-bungarotoxin at r. t. Non-specific binding was determined in parallel by means of incubation in the presence of 1 µM unlabelled α-bungarotoxin. After incubation, the samples were filtered as described above and the bound radioactivity directly counted in a γ counter. The inhibition of [^{125}I]-α-Bungarotoxin binding by the test compounds was measured by preincubating SH-SY5Y membranes with increasing concentrations (10 M-1 mM) of the drug to

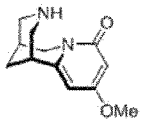
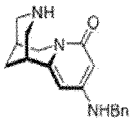
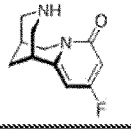
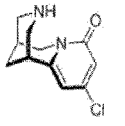
be tested for 30 min at r. t., followed by overnight incubation with a final concentration of 2-3 nM [^{125}I]-α-bungarotoxin at room temperature.

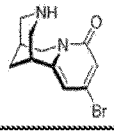
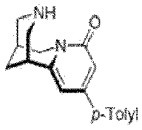
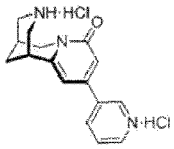
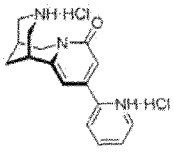
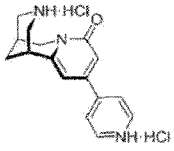
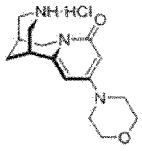
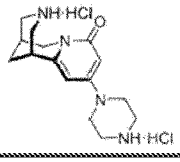
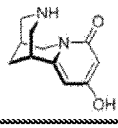
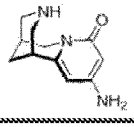
[0499] After overnight incubation, the membranes of SH-SY5Y cells transfected with α7 were washed by filtration on GFC filters with ice-cold PBS. The GFC filters were pre-soaked in polyethylenimine and filtered through an harvester apparatus. and [^{125}I]-α-Bungarotoxin binding was determined by directly counting in a gamma counter.

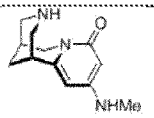
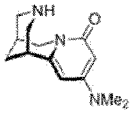
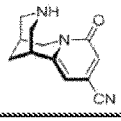
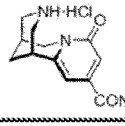
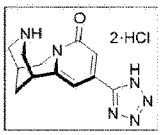
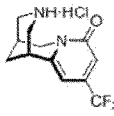
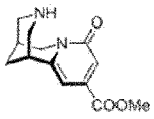
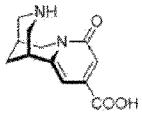
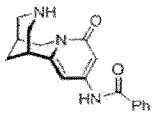
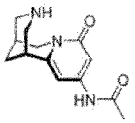
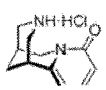
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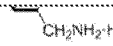
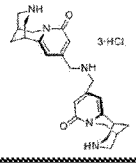
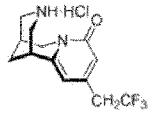
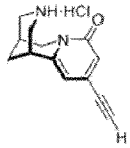
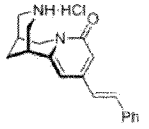
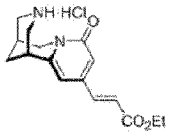
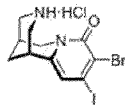
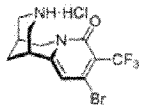
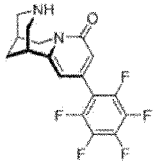
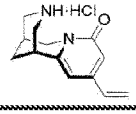
[0500] The ligand binding data were analyzed by means of nonlinear regression using Prism version 5 (GraphPad Software, Inc., La Jolla, CA). The K_i values were calculated from the experimental IC_{50} values using the Cheng-Prusoff equation for a single population of competitive sites: $K_i = IC_{50}/[1 + (L/K_d)]$, where L is the concentration of radioligand used in each experiment and the K_d values were determined by saturation binding experiment All of the assays were performed in duplicate and repeated at least two-three times.

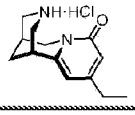
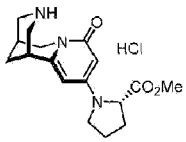
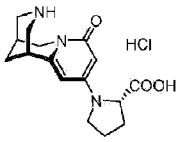
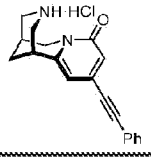
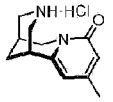
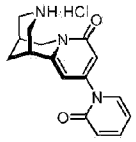
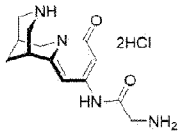
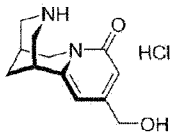
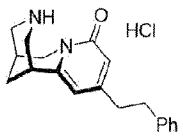
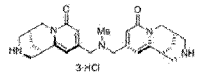
Table 1 - Binding Results

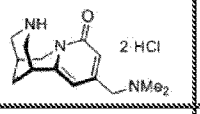
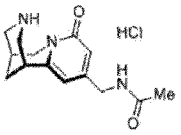
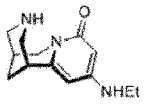
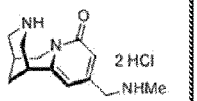
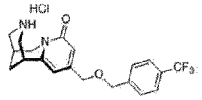
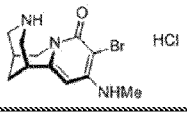
CODE	COMPOUND	Mw	α4β2 **nM**	α3β4 **nM**	**Ratio** α3β4/ α4β2	Rat α7 (Ki) **nM**	Human α7 K(i) **nM**
Cytisine		**190.24**	**1.27** 0,89-1,8	**103** 70,2-152	**81.1**	**661.7 363-1206nM**	**690.7 362-1318nM**
Nicotine		**162.23**	**8.6** 4,8-15,6	**172** 109-274	**20.0**		
68		220.27	**41** 27,5-61,2	**8452** 4011-17810	**206.1**	21300 5347-84810	
70		295.39	**12.5** 6,8-22,9	**1563** 832-2933	**125.0**	29000 8887-94320	
82		208.23	**2.87** 1,98-4,1	**1921** 1018-3626	**669.3**	9760 4689-20340	
60		224.69	**2.31** 1,17-4,6	**759** 486-1186	**328.6**	223 94.04-527.5	

CODE	COMPOUND	Mw	α4β2 **nM**	α3β4 **nM**	**Ratio** α3β4/ α4β2	Rat α7 (Ki) **nM**	Human α7 K(i) **nM**
62		269.14	**1.77** 0,98-3,2	**537** 275-1049	**303.4**	323 69.02-1510	
73		280.37	**14.1** 5,822-34,2	**2280** 759-6840	**161.7**	5630 2136-14830	
104		340.25	**13.4** 5,8-31,1	**2260** 1223-4182	**168.7**	11900 4432-31870	
101		340.25	**1.24** 0,66-2,43	**1953** 1018-3746	**1575.0**	5780 3302-10130	**4930** 1956-12410
103		340.25	**3.24** 1,32-7,94	**2785** 1590-4881	**859.6**	3090 2161-4419	
92		311.81	**18.5** 8,74-39,4	**1306** 582-2928	**70.6**	7773 732.3-82500 (query?)	
90		347.28	**430** 153-1209	**6080** 1116-33110	**14.1**	7879 2910-21330	
66		242.7	**22.5** 5,0-100,8	**8951** 4083-19620	**397.8**	12400 5329-28900	
81		278.18	**6.36** 5,37-20,4	**9928** 4005-24610	**1561.0**	9680 4992-13090	**10270** 5163-20420
		292.2					**24550**

CODE	COMPOUND	Mw	α4β2 **nM**	α3β4 **nM**	**Ratio** α3β4/ α4β2	Rat α7 (Ki) **nM**	Human α7 K(i) **nM**
84			**10.8** 5,37-20,4	**27500** 11170-66270	**2546.3**	15600 7638-32170	5634-106900 (query)
86		306.23	**573** 264-1245	**3329** 1769-6264	**5.8**	12400 6463-24050	
140		215.26	**1.84** 1,18-2,87	**367** 196-687	**199.5**	25600 9971-65750	
142		269.73	**69** 46,7-102,2	**2497** 739-8434	**36.2**	21900 9400-51230	
149		331.2	**92.6** 55,3-157	**13820** 2974-64230	**149.2**	10400 4684-23140	
77		294.7	**30.9** 6,09-156	**399** 214-745	**12.9**	1820 762.5-4328	
119		248.28	**7.29** 3,97-13,3	**2672** 1076-6631	**366.5**	77500 22320-268800	
120		270.71	**39.5** 15,3-102,4	**2281** 691-7525	**57.7**	8890 3617-21860	
96		345.83	**11.9** 3,64-39,4	**1066** 560-2028	**89.6**	5610 1391-22620	
94		283.76	**10.5** 5,63-19,5	**7886** 2796-22240	**751.0**	14500 3731-57010	
144		292.2	**90.3** 46-	**7046** 2178-	**78.0**	1030 164.4-	

CODE	COMPOUND	Mw	α4β2 **nM**	α3β4 **nM**	**Ratio** α3β4/ α4β2	Rat α7 (Ki) **nM**	Human α7 K(i) **nM**
			177,2	22800		6456	
154		256.73	**3.5** 2,28-5,38	**26000** 4031-167600	**7428.0**	8080 4992-13090	**10600** 1739-64410
79		308.73	**5.21** 0,8-33,6	**143** 74,6-275	**27.4**	1040 314.2-3462	
127		250.73	**0.86** 0,52-1,43	**611** 136-2733	**710.5**	8970 2302-34950	
114		328.84	**2.9** 1,66-5,19	422 159-1124	**145.5**	5400 1577-18500	
112		324.81	**8.1** 4,8-13,5	**1238** 547-2801	**152.8**	3060 591.9-15780	
160		431.5	**0.238** 0.166-0.341	**11.9** 5-27,8	**50.0**		**26** 19.4-35
162		373.6	**0.88** 0,69-1,18	**120** 43,8-328	**136.4**	5450 1676-17740	
74		356.3	**19.1** 7.57-48.4	**154** 89-268	**8.1**		**10890** 1919-61830
116		252.74	**14.2** 6.9-29.5	**1422** 419-4820	100.1		**40600** 10090-163800

CODE	COMPOUND	Mw	α4β2 **nM**	α3β4 **nM**	**Ratio** α3β4/ α4β2	Rat α7 (Ki) **nM**	Human α7 K(i) **nM**
118		254.76	**3.01** 2.06-4.39	**5723** 2403-13630	**1901.3**		**6928** 2276-21080
137		353.85	**No data**				
138		339.82	**671.8** 194-2326	**1785** 472-6746	**2.7**		**39810** 12990-122000
129		326.82	**2.94** 1.67-5.18	**95** 45-198	**32.2**		**3946** 1856-8389
110		240.73	**2.63** 1.59-4.36	**2273** 536-9633	**864.3**		**5027** 1071-23590
108		319.79	**35.8** 20.5-23.8	**3233.00** 1458-7171	**90.3**		**17080** 1972-147900
98*		335.23	**160** 41.9-627	**267200.00** 13130-543700	**1670.0**		**54660** 10480-285000
122		256.73	**36.8** 18-75	**2685.00** 864-8345	**73.0**		**116000** 18400-731500
?		330.86	**7.15** 4.16-12.2	**155.00** 70.4-340	**21.7**		**22470** 8590-58780
156		544.95	**30.2** 18.8-48.4	**6278.00** 1023-38510	**207.9**		**29270** 6790-126200

CODE	COMPOUND	Mw	α4β2 **nM**	α3β4 **nM**	**Ratio** α3β4/ α4β2	Rat α7 (Ki) **nM**	Human α7 K(i) **nM**
151		320.25	**226** 81.3-630	**23890.00** 6020-94800	**105.7**		**250900** 5517-1141000
148		297.78	**94.1** 23.4-378	**19270.00** 6908-53760	**204.8**		**34150** 5669-205700
87		233.32	**17.9** 4.3-74.2	**14950.00** 7611-29370	**835.2**		**9804** 1255-76600
152		306.23	**124.9** 35.4-439	**100800.00** 14770-687400	**807.0**		**89600** 19560-410500
124		414.85	**22.8** 16.7-31.1	**1402** 322-6097	**61.5**		**56190** 21780-144900
158		334.64	**27.2** 5.6-132	**2908.00** 973-8689	**106.9**		**6593** 2235-19450

[0501] As can be seen from this data, the compounds of the present invention exhibit high selectivity at the human α4β2 receptor subtypes as compared to both α3β4 subtype subtype and α7 (in both rat cells and human cells, where tested), minimising the likelihood of 'off-target' effects.

Example 71 - Relative Efficacy at Nicotinic Receptor Subtypes

[0502] Compounds of the invention were tested for effects on the function of human α4β2, α3β4 and α7 nicotinic acetylcholine receptors (nAChRs) expressed heterologously in *Xenopus* oocytes. Human α4β2 nACh receptors were expressed as either $(\alpha4)_3(\beta2)_2$ (low sensitivity for ACh) or $(\alpha4)_2(\beta2)_3$ receptors (high sensitivity for ACh) (Moroni et al., 2006). Expression in oocytes was obtained as follows: pCI (Promega, UK) plasmid containing human α4, β2, β4 or α7 complementary DNA were injected as previously described (Moroni et al., 2006). To express $(\alpha4)_3(\beta2)_2$ nACh receptors, a mixture of 10α4:1β2 cDNAs was injected into the nucleus of oocytes, whereas for $(\alpha4)_2(\beta2)_3$ receptors the cDNA ratio injected was 1α4:10β2.

[0503] Functional studies: Recordings were performed manually using a Geneclamp amplifier (Molecular Devices, USA) or using an automated HiClamp system. In both cases the oocytes were impaled with two electrodes filled with 3 M KCl and the cells were held at -60 mV throughout the experiments.

[0504] Oocyte isolation and two-electrode voltage-clamp recordings on oocytes were carried out as previously described (Moroni et al., 2006; Carbone et al., 2009). Concentration-response curves for agonists were obtained by normalizing the compounds-induced responses to the responses elicited by 1 mM ACh, a concentration of ACh that maximally activates all the receptors tested (Abin-Carriquiry et al., 2006; Moroni et al., 2006; Carbone et al., 2009). A minimum interval of 5 min was allowed between agonist applications to ensure reproducible recordings. Oocytes were exposed to increasing concentrations of the compounds until no further increases in the response amplitude were obtained. This concentration was taken as the concentration that causes maximal responses on the receptors tested. The data summarised in Tables 1-4 were obtained from at least 5 experiments carried out on oocytes obtained from at least three different donors.

a) Effects of compounds on $(\alpha4)_3(\beta2)_2$ nAChRs (low sensitivity stoichiometry)

[0505] Maximal gating efficacy of the compounds: The concentration of the compounds of the invention causing maximal activation of the $(\alpha4)_3(\beta2)_2$ nAChRs expressed heterologously in *Xenopus* oocytes was determined using two electrode voltage clamping. The maximal currents elicited by the compounds was relativized to the maximal concentration elicited by 1 mM ACh (which induces maximal responses for $(\alpha4)_3(\beta2)_2$ receptors.

Table 2.

Compound	Relative efficacy (ACh)
ACh	1
Cytisine	0.19±0.07
Varenicline	0.40±0.09
Nicotine	0.48±0.3
69	0.071±0.009
82	0.12±0.02
60	0.110±0.08
62	0.057±0.007
73	0.017±0.019
101	0.009±0.008
103	0.023±0.006
67	0.07±0.009
81	0.007±0.01061

Compound	Relative efficacy (ACh)
84	0.048±0.040
140	0.050±0.027
119	0.021±0.007
94	0.153±0.006
154	0.013±0.008
127	0.071±0.009
162	0.072±0.026
75	0.011±0.010
118	0.036±0.055
110	0.014±0.007
122	0.058±0.057
156	0.052±0.007
148	0.041±0.057
87	0.011± 0.001
152	0.031±0.043
158	0.049±0.012
BS70	0.114±0.113
BS71	0.152±0.1223
BS74	0.126±0.067

b) Effects on $(\alpha4)_2(\beta2)_3$ nAChRS

[0506] Maximal gating efficacy of compounds on $(\alpha4)_2(\beta2)_3$ receptors (high sensitivity receptors): The concentration of the compounds causing maximal activation of the $(\alpha4)_2(\beta2)_3$ nAChRs expressed heterologously in *Xenopus* oocytes was determined using two electrode voltage clamping. The maximal current elicited by the compounds was then relativized to the maximal concentration elicited by 1 mM ACh (which induces maximal responses on $(\alpha4)_2(\beta2)_3$ receptors.

Table 3.

Compound	Relative efficacy (ACh)
ACh	1.0
Cytisine	0.02±0.001
Varenicline	0.14±0.03
Nicotine	0.31±0.07

Compound	Relative efficacy (ACh)
69	0.009±0.0008
82	0.01±0.001
60	0.01±0.007
62	0.009±0.0001
73	0.030±0.013
101	0.0001±0.00008
103	0.0067±0.0006
67	0.005±0.0001
81	0.024±0.034
84	0.042±0.059
140	0.026±0.036
119	0.0065±0.0005
94	0.001±0.0006
154	0.0001±0.00001
127	0.009±0.0009
162	0.042±0.060
75	0.050±0.071
118	0.062±0.025
110	0.041±0.004
122	0.025±0.000
156	No response
148	0.015±0.021
87	0.023±0.032
158	0.038±0.054
BS74	0.121±0.171

c) Effects of the compounds on α3β4 nAChRs

[0507] Maximal gating efficacy of the compounds on α3β4 nAChRs: The concentration of the compounds causing maximal activation of α3β4 nAChRs expressed heterologously in *Xenopus* oocytes was determined using two electrode voltage clamping. The maximal currents elicited by the compounds were then relativized to the maximal concentration elicited by 1 mM ACh (which induces maximal responses on α3β4 receptors).

Table 4.

Compound	Relative efficacy (ACh)
ACh	1.0
Cytisine	0.54±0.01
Varenicline	0.51±0.09
Nicotine	0.71±0.07
69	0.044±0.059
82	0.073±0.06
60	0.133±0.017
62	0.184±0.046
73	0.076±0.093
101	0.066±0.056
103	0.016±0.010
67	0.047±0.036
81	0.0210±0.008
84	0.0233±0.005
140	0.172±0.064
119	0.040±0.049
94	0.055±0.047
154	0.093±0.091
127	0.165±0.064
162	0.250±0.077
75	0.120±0.039
118	0.086±0.106
110	0.0708± 0.059
122	0.015±0.020
156	0.012±0.007
148	0.034± 0.038
87	0.010±0.009
158	0.057±0.016
BS70	0.108±0.149
BS71	0.632±0.067
BS74	1.75±0.56

d) Effects of the compounds on α7 nAChRs

[0508] Relative efficacy of the compounds on α7 nAChRs: The amplitude of currents elicited by the compounds at 100 μM was measured and then relativized to the amplitudes of the responses to 1 mM ACh, the concentration of ACh that causes maximal activation of α7 nAChRs.

Table 5

Compound	Relative efficacy (ACh)
ACh	1.0
Cytisine	1±0.0.08
Varenicline	0.96±0.03
Nicotine	0.96±0.1
69	0.061±0.09
82	0.18±0.04
60	0.38±0.09
62	0.28±0.01
73	0.0027±0.0021
101	0.16±0.03
103	0.07±0.009
67	No response at 100 μM
94	0.0001 ±0.00001
154	No response at 100 μM
127	0.17±0.03
75	0.0007±0.0006
118	0.0057±0.0028
110	0.0017±0.0024
122	0.0067±0.0015

[0509] The data in Table 5 show that the compounds exhibit lower relative efficacy on the α7 receptor compared to cytisine and varenicline.

REFERENCES CITED IN THE DESCRIPTION

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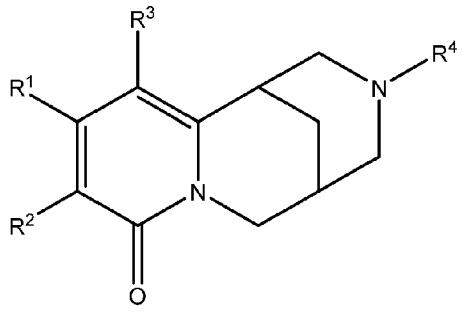
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PATENTKRAV

1. Fremgangsmåde til fremstilling af en 4-substitueret cytisinanalog med formlen (I):



(I)

eller et farmaceutisk acceptabelt salt, et solvat og/eller en ester deraf, hvor:

R^1 er

- hydroxyl;
- halogen;
- eventuelt substitueret alifatisk forbindelse;
- eventuelt substitueret cycloalifatisk forbindelse;
- eventuelt substitueret heterocycloalifatisk forbindelse;
- eventuelt substitueret aryl;
- eventuelt substitueret heteroaryl;
- $-(CH_2)_m-NR^6R^7R^8$, hvor

∘ R^6 og R^7 hver uafhængigt vælges fra gruppen bestående af hydrogen, halo, hydroxy, oxo, amino, amido, nitro, cyano, alkoxy, N-alkylamino, N,N-dialkylamino, phospho, carbonyl, carboxy, sulfoxy, sulfinyl, sulfonyl, sulfanyl, sulfamid, sulfo, mercapto, carbamoyl, methylpivalat, trimethylsilyl, urea, thiourea, eventuelt substitueret aryl, eventuelt substitueret heteroaryl, eventuelt substitueret alkyl, eventuelt substitueret cycloalifatisk forbindelse, eventuelt substitueret heterocycloalifatisk forbindelse, eventuelt substitueret heteroaryl, eventuelt substitueret haloalkyl, eventuelt substitueret aroyl, eventuelt substitueret heteroaroyl, eventuelt substitueret acyl, eventuelt substitueret alkenyl, eventuelt substitueret alkynyl, eventuelt substitueret aralkyl, eventuelt substitueret cycloalkyl, eventuelt substitueret cycloalkenyl, eventuelt substitueret heterocycloalkyl eller eventuelt substitueret heterocycloalkenyl eller

∘ én af R^6 eller R^7 er $-CO-R^9$, og den anden af R^6 eller R^7 er som defineret ovenfor,

∘ R^8 vælges fra gruppen bestående af hydrogen, halo, hydroxy, oxo, amino, amido, nitro, cyano, alkoxy, N-alkylamino, N,N-dialkylamino, phospho, carbonyl, carboxy, sulfoxy, sulfinyl, sulfonyl, sulfanyl, sulfamid, sulfo, mercapto, carbamoyl, methylpivalat, trimethylsilyl, urea,

thiourea, eventuelt substitueret aryl, eventuelt substitueret heteroaryl, eventuelt substitueret alkyl, eventuelt substitueret cycloalifatisk forbindelse, eventuelt substitueret heterocycloalifatisk forbindelse, eventuelt substitueret heteroaryl, eventuelt substitueret haloalkyl, eventuelt substitueret aroyl, eventuelt substitueret heteroaroyl, eventuelt substitueret acyl, eventuelt substitueret alkenyl, eventuelt substitueret alkynyl, eventuelt substitueret aralkyl, eventuelt substitueret cycloalkyl, eventuelt substitueret cycloalkenyl, eventuelt substitueret heterocycloalkyl eller eventuelt substitueret heterocycloalkenyl eller er fraværende,

- R^9 vælges fra gruppen bestående af hydrogen, halo, hydroxy, oxo, amino, amido, nitro, cyano, alkoxy, N-alkylamino, N,N-dialkylamino, phospho, carbonyl, carboxy, sulfoxy, sulfinyl, sulfonyl, sulfanyl, sulfamid, sulfo, mercapto, carbamoyl, methylpivalat, trimethylsilyl, urea, thiourea, eventuelt substitueret aryl, eventuelt substitueret heteroaryl, eventuelt substitueret alkyl, eventuelt substitueret cycloalifatisk forbindelse, eventuelt substitueret heterocycloalifatisk forbindelse, eventuelt substitueret heteroaryl, eventuelt substitueret haloalkyl, eventuelt substitueret aroyl, eventuelt substitueret heteroaroyl, eventuelt substitueret acyl, eventuelt substitueret alkenyl, eventuelt substitueret alkynyl, eventuelt substitueret aralkyl, eventuelt substitueret cycloalkyl, eventuelt substitueret cycloalkenyl, eventuelt substitueret heterocycloalkyl eller eventuelt substitueret heterocycloalkenyl,
- og m er 0, 1, 2, 3, 4 eller 5,

• $-(CH_2)_m-O-(CH_2)_n-R^{10}$, hvor

- R^{10} vælges fra gruppen bestående af hydrogen, halo, hydroxy, oxo, amino, amido, nitro, cyano, alkoxy, N-alkylamino, N,N-dialkylamino, phospho, carbonyl, carboxy, sulfoxy, sulfinyl, sulfonyl, sulfanyl, sulfamid, sulfo, mercapto, carbamoyl, methylpivalat, trimethylsilyl, urea, thiourea, eventuelt substitueret aryl, eventuelt substitueret heteroaryl, eventuelt substitueret alkyl, eventuelt substitueret cycloalifatisk forbindelse, eventuelt substitueret heterocycloalifatisk forbindelse, eventuelt substitueret heteroaryl, eventuelt substitueret haloalkyl, eventuelt substitueret aroyl, eventuelt substitueret heteroaroyl, eventuelt substitueret acyl, eventuelt substitueret alkenyl, eventuelt substitueret alkynyl, eventuelt substitueret aralkyl, eventuelt substitueret cycloalkyl, eventuelt substitueret cycloalkenyl, eventuelt substitueret heterocycloalkyl eller eventuelt substitueret heterocycloalkenyl, og
- m og n hver uafhængigt er 0, 1, 2, 3, 4 eller 5,

• -CN

• $-COOR^{12}$, hvor R^{12} vælges fra gruppen bestående af hydrogen, halo, hydroxy, oxo, amino, amido, nitro, cyano, alkoxy, N-alkylamino, N,N-dialkylamino, phospho, carbonyl, carboxy, sulfoxy, sulfinyl, sulfonyl, sulfanyl, sulfamid, sulfo, mercapto, carbamoyl,

methylpivalat, trimethylsilyl, urea, thiourea, eventuelt substitueret aryl, eventuelt substitueret heteroaryl, eventuelt substitueret alkyl, eventuelt substitueret cycloalifatisk forbindelse, eventuelt substitueret heterocycloalifatisk forbindelse, eventuelt substitueret heteroaryl, eventuelt substitueret haloalkyl, eventuelt substitueret aroyl, eventuelt substitueret heteroaroyl, eventuelt substitueret acyl, eventuelt substitueret alkenyl, eventuelt substitueret alkynyl, eventuelt substitueret aralkyl, eventuelt substitueret cycloalkyl, eventuelt substitueret cycloalkenyl, eventuelt substitueret heterocycloalkyl eller eventuelt substitueret heterocycloalkenyl,

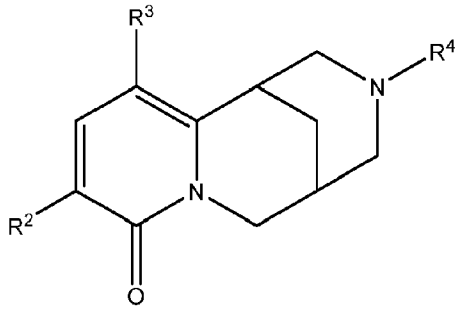
- $-(CH_2)_o-CO-(CH_2)_p-R^{13}$, hvor
  - R^{13} vælges fra gruppen bestående af hydrogen, halo, hydroxy, oxo, amino, amido, nitro, cyano, alkoxy, N-alkylamino, N,N-dialkylamino, phospho, carbonyl, carboxy, sulfoxy, sulfinyl, sulfonyl, sulfanyl, sulfamid, sulfo, mercapto, carbamoyl, methylpivalat, trimethylsilyl, urea, thiourea, eventuelt substitueret aryl, eventuelt substitueret heteroaryl, eventuelt substitueret alkyl, eventuelt substitueret cycloalifatisk forbindelse, eventuelt substitueret heterocycloalifatisk forbindelse, eventuelt substitueret heteroaryl, eventuelt substitueret haloalkyl, eventuelt substitueret aroyl, eventuelt substitueret heteroaroyl, eventuelt substitueret acyl, eventuelt substitueret alkenyl, eventuelt substitueret alkynyl, eventuelt substitueret aralkyl, eventuelt substitueret cycloalkyl, eventuelt substitueret cycloalkenyl, eventuelt substitueret heterocycloalkyl eller eventuelt substitueret heterocycloalkenyl, og
  - o og p hver uafhængigt er 0, 1, 2, 3, 4 eller 5,
- en aminosyre eller ester deraf,
- acylchlorid,
- en beskyttelsesgruppe eller
- cytisinyl,

R^2, R^3 og R^4 hver uafhængigt vælges fra gruppen bestående af hydrogen, halo, hydroxy, oxo, amino, amido, nitro, cyano, alkoxy, N-alkylamino, N,N-dialkylamino, phospho, carbonyl, carboxy, sulfoxy, sulfinyl, sulfonyl, sulfanyl, sulfamid, sulfo, mercapto, carbamoyl, methylpivalat, trimethylsilyl, urea, thiourea, eventuelt substitueret aryl, eventuelt substitueret heteroaryl, eventuelt substitueret alkyl, eventuelt substitueret cycloalifatisk forbindelse, eventuelt substitueret heterocycloalifatisk forbindelse, eventuelt substitueret heteroaryl, eventuelt substitueret haloalkyl, eventuelt substitueret aroyl, eventuelt substitueret heteroaroyl, eventuelt substitueret acyl, eventuelt substitueret alkenyl, eventuelt substitueret alkynyl, eventuelt substitueret aralkyl, eventuelt substitueret cycloalkyl, eventuelt substitueret cycloalkenyl, eventuelt substitueret heterocycloalkyl eller eventuelt substitueret

heterocycloalkenyl, aminosyre eller cytisin, eller R^4 kan være en beskyttelsesgruppe, eller en gruppe med strukturen -(CH_2)v-FORMEL 1, hvor v er 0, 1, 2, 3, 4, 5 eller 6 og FORMEL 1 er en forbindelse med formlen (I) som beskrevet heri,

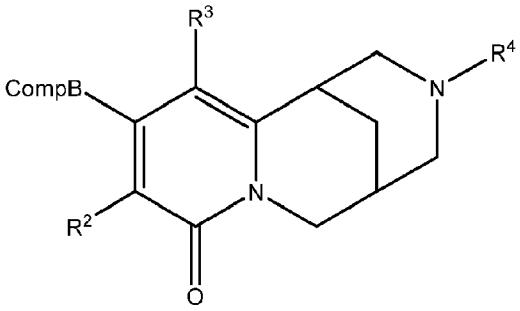
hvilken fremgangsmåde omfatter:

i) tilvejebringelse af en forbindelse med formlen IIa



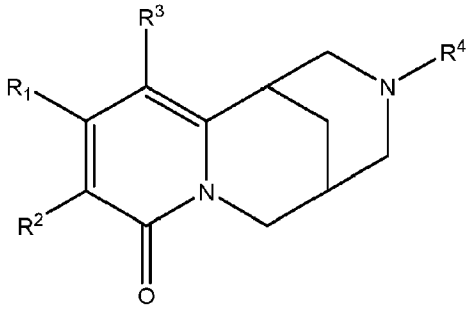
hvor R^2, R^3 og R^4 er som defineret ovenfor;

ii) frembringelse af en forbindelse med formlen IIb



hvor R^2, R^3 og R^4 er som defineret ovenfor, og BComp er et boryleret kompleks, ved at bringe forbindelsen med formlen IIa i kontakt med et boryleringsmiddel;

iii) erstatning af BComp med R^1 for at frembringe forbindelse med formlen I:



.

2. Fremgangsmåde ifølge krav 1, hvor forbindelsen med formlen IIa tilvejebragt i trin i) omfatter et hydrogenatom ved R^4-positionen, hvor trinnet endvidere omfatter substitution af hydrogenatomet ved R^4-positionen med en beskyttelsesgruppe.

3. Fremgangsmåde ifølge krav 2, hvor beskyttelsesgruppen er Boc.

4. Fremgangsmåde ifølge krav 2 eller krav 3, hvor forbindelsen med formlen IIa er cytisin.

5. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 4, hvor boryleringsmidlet vælges fra:

ét med formlen $(RO)_2$-B-B-$(OR)_2$ eller $HB(OR)_2$ og

B_2Pin_2 eller B_2Cat_2.

6. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 5, hvor molforholdet mellem boryleringsmiddel og udgangsmateriale for formlen IIa er mindst ca. 0,5:1, mindst ca. 0,75:1, mindst ca. 1:1, mindst ca. 1,5:1 eller mindst ca. 2:1.

7. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 6, hvor reaktionen i trin ii) udføres i tilstedeværelse af en overgangsmetalkatalysator omfatter iridium, palladium, zink, nikkel og/eller rhodium.

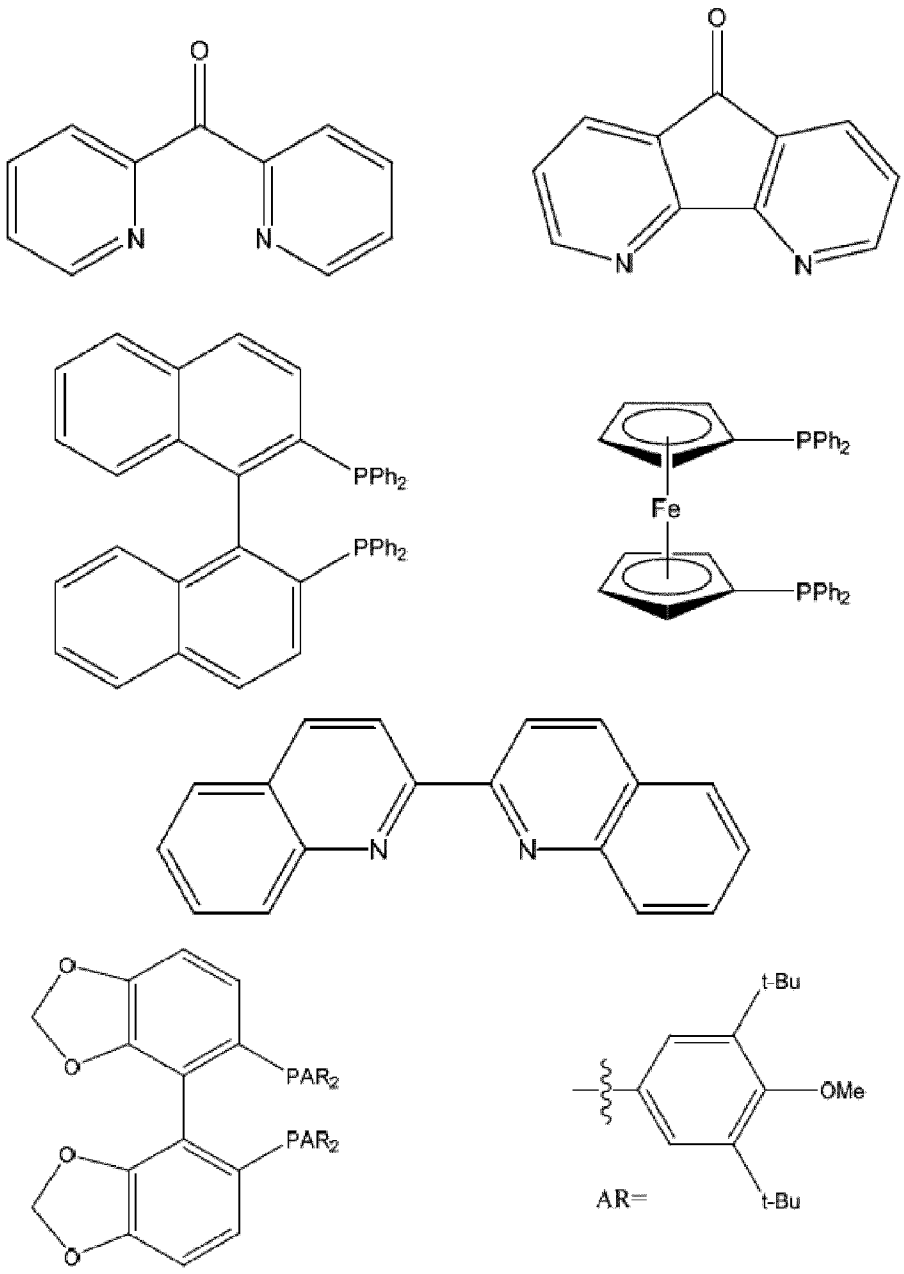
8. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 7, hvor reaktionen i trin ii) udføres i et opløsningsmiddel valgt blandt et esteropløsningsmiddel, et etheropløsningsmiddel, et ketonopløsningsmiddel, et sulfoxidopløsningsmiddel, et aromatisk opløsningsmiddel, et fluorineret, aromatisk opløsningsmiddel, et alkanopløsningsmiddel eller blandinger deraf.

9. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 8, hvor trin ii) udføres i tilstedeværelse af en ligand valgt blandt:

tetramethyl-1,10-phenanthrolin (Me4phen), di-tert-butyl-2,2'-bipyridyl (dtbpy), 2,2'-bipyridin (bpy), 1,1'-bis(diphenylphosphino)ferrocen (dppf), bis(2-di-tert-butylphosphinophenyl)ether, 1,3-bis(diphenylphosphino)propan, (dppp) 1,2-bis(diphenylphosphino)ethan (dppe), hexamethylbenzene (C6Me6), xantphos eller 1,2-bis(dimethylphosphino)ethan (dmpe) og

phenanthrolin (phen), dimethylphenanthrolin (me2phen) tetramethyl-1,10-phenanthrolin (me4phen), bathophenanthrolin (bathophen), di-tert-butyl-2,2'-bipyridyl (dtbpy), 2,2'-bipyridin (bpy), dimethoxy-2,2'-bipyridyl (MeO-bpy), 1,1'-bis(diphenylphosphino)ferrocen (dppf), bis(2-di-tert-butylphosphinophenyl)ether, 1,3-bis(diphenylphosphino)propan (dppp), 1,2-

bis(diphenylphosphino)ethan (dppe), hexamethylbenzen (C6Me6), neocuproin, xantphos, 1,2-is(dimethylphosphino)ethan (dmpe), eller én af:



.

10. Fremgangsmåde ifølge krav 9, hvor molforholdet mellem boryleringsudgangsmateriale for formlen IIa er mindre end ca. 2:1, mindre end ca. 1,5:1, mindre end ca. 1:1, mindre end ca. 0,75:1, mindre end ca. 0,5:1, mindre end ca. 0,1:1, mindre end ca. 0,05:1 til mindst ca. 0,001:1.

11. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 10, hvor boryleringen i trin ii) udføres ved en temperatur på ca. 50 °C til ca. 100 °C.

12. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 11, hvor, før starten på trin iii), forbindelsen med formlen IIb ikke isoleres fra produktblandingen dannet i trin ii), og/eller der ikke udføres et oprensningstrin mellem trin ii) og iii).

13. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 12, hvor trin iii) startes i den samme reaktionszone, hvori trin ii) blev udført.

14. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 13, hvor i trin iii) BComp erstattes af en første R^1-mellemsubstituent.

15. Fremgangsmåde ifølge krav 14, hvor den første mellemsubstituent erstattes med en anden R^1-mellemsubstituent, eller med en substituent R^1 for at tilvejebringe forbindelsen med formlen I;

eller den første mellemsubstituent erstattes af en anden R^1-mellemsubstituent, og den anden mellemsubstituent erstattes af en tredje R^1-mellemsubstituent eller af en substituent R^1 for at tilvejebringe forbindelsen med formlen I.

16. Fremgangsmåde ifølge et hvilket som helst af kravene 13 til 15, hvor den første, anden eller tredje R^1-mellemsubstituent uafhængigt vælges fra brom, chlor, iod, benzyloxypyridin, alkylester, f.eks. methylester, alkenyl, f.eks. vinyl, alkynyl, f.eks. acetylenyl, trimethylsilylacetylen, 1,2,3-triazol-1-ylmethylpivalat, cyan, aminomethyl, N-Boc-aminomethyl og (benzyloxy)carbonyl)piperazin-1-yl.

17. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 16, hvor forbindelsen med formlen IIb eller formlen I omfatter en beskyttelsesgruppe ved R^4-position, hvilken fremgangsmåde endvidere omfatter afbeskyttelse af forbindelsens R^4-gruppe med formlen IIb eller formlen I og afbeskyttelse af forbindelsens R^4-gruppe med formlen IIb, eller formlen I finder sted efter afslutning af trin ii), før starten på trin iii), under trin iii) eller efter afslutning af trin iii).