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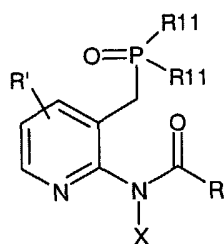
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(54) Title: PROCESS



(I-1)

(57) **Abstract:** The present application provides a process for the produc-
tion of 7-azaindole systems by reacting a compound of formula I-1 with
base

PROCESS

The present application provides a process for the production of 7-azaindole systems. The present application further provides novel compounds.

5

The 7-azaindole system occurs in natural products such as neocryptolepine and is an important core structure present in pharmaceutical agents such as dopamine D₄ ligands, p38 kinase inhibitors and corticotrophin-releasing hormone receptor antagonists. 7-Azaindole-containing structures have been
10 studied as antimalarial agents, melatonin receptor ligands, antitussive agents, 5HT_{2C} and 5HT_{2B} receptor antagonists.

15

Previous synthetic routes to 7-azaindoles can be classified based on the type of the ring formed at the final stage of synthesis i.e. formation of the pyrrole ring or the pyridine ring.

20

Methods used for the synthesis of the 7-azaindole core structure by formation of the pyrrole ring start from the properly functionalised pyridine. This group of reactions include various modifications of the Madelung synthesis, Fischer indole synthesis and the Bischler reaction

25

The Fischer, Madelung and Reissert methods do not work well for preparation of 2-substituted 7-azaindoles. The 2-substituent may be introduced into the 7-azaindole skeleton by directed ortho lithiation but the use of this method to
produce 2-substituted 7-azaindoles is limited by the number of synthetic steps involved. For the introduction of the 2-substituent by lithiation, it is necessary to have the 7-azaindole system already in place thus increasing the number of synthetic steps necessary to produce the 2-substituted 7-azaindoles. The use of

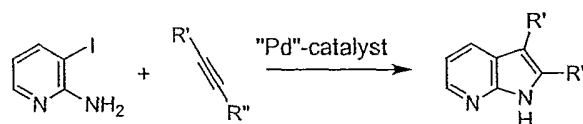
lithiation also reduces the scope of substituents that can be introduced. Furthermore, the harsh conditions involved in these methods mean that the range of 7-azaindoles which can be produced by these methods are limited.

5 Hands *et al.* (*Synthesis*, **1996**, 887) provides a method for the production of the 2-substituted 7-azaindoles utilising simple starting materials. While the yields for this method are respectable (31-84%), the final step in the synthetic scheme involves strong acidic conditions (3M HCl at 100°C over 8h or 5.5M HCl at 50°C over 2h). The range of substituents on the pyridine ring is also
10 restricted by the use of nBuLi during the formation of the intermediates.

Zhang *et al.* (*J. Org. Chem.* **2002**, 67, 2345 – 2347) has indicated that the 7-azaindole system may also be accessible via Bartoli cyclization but no experimental data has been provided in support of this assertion.

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Alternative methods of producing the 7-azaindoles include the use of a palladium catalysed cyclisation as indicated below.



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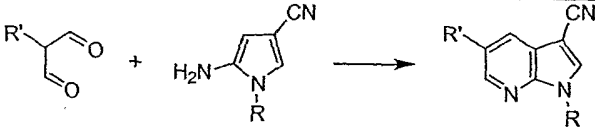
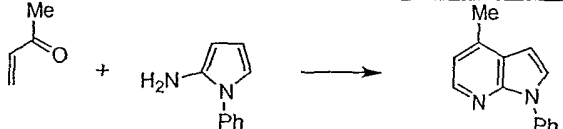
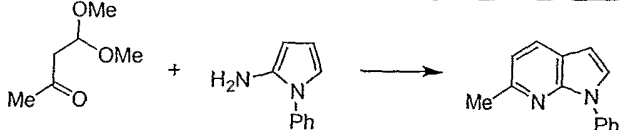
This reaction involves the use of the expensive palladium catalyst. Furthermore the starting materials illustrated are not readily available. This method is not a viable route to the production of 7-azaindole compounds.

25 Methods involving the synthesis of the pyridine ring are not commonly used due to the limited availability of properly functionalised starting materials.

Furthermore these methods require the use of pyrrole derivatives alkylated or arylated at the nitrogen atom.

Examples of such methods are summarised below.

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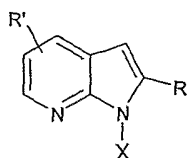
Reaction	Reference
	Brodrick, A. and Wibberley, D. G. <i>J.Chem. Soc. Perkin Trans. I</i> 1975 , 1910-1913; Zimmermann <i>et al. Arch. Pharm. (Weinheim, Ger.)</i> 1976 , 309, 597-600; Hodge <i>et al. J. Med. Chem.</i> 1999 , 42, 819-832
	Reviewed by Yakhontov and Prokopov <i>Russ. Chem. Rev.</i> 1980 , 49, 428-444
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	Zimmermann <i>et al. Arch. Pharm. (Weinheim, Ger.)</i> 1976 , 309, 597-600

10

Thus while there are a number of known processes for the production of the 7-azaindole compounds, these processes have a number of disadvantages including low yields, use of harsh conditions, use of expensive reagents and availability of starting materials. There is therefore required a new process which allows the production of the 7-azaindole derivatives in good yield and which allows the use of mild reaction conditions allowing a wide variety of potentially useful 7-azaindole and especially 2-substituted 7-azaindoles to be produced.

The first aspect of the present invention relates to a process for the production of a compound of formula I-2

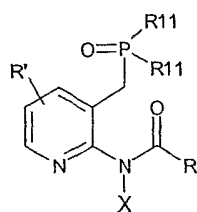
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I-2

comprising reacting a compound of formula I-1 with base

10



15

I-1

wherein X is hydrogen or a group COR;

R and R' are independently hydrogen, halogen, branched or unbranched alkyl
 20 (optionally interrupted by one or more of O-, -C(O)-, -N(R²)-, -S(O)- and -
 S(O₂)-), alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, reduced
 arylalkyl, arylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl,
 reduced aryl, reduced heterocyclyl, reduced heterocyclylalkyl or a substituted
 derivative of any of the foregoing groups, wherein the substituents are one or
 25 more independently of halogen, alkyl, halosubstituted alkyl, aryl, arylalkyl,
 heterocyclyl, reduced heterocyclyl, reduced heterocyclylalkyl, arylalkoxy,
 cyano, nitro, -C(O)R², -CO₂R², -SOR², -SO₂R², SONR³R³, NR³SO₂R²,
 NR³CO₂R², -NR³R³, -OR², -SR², -C(O)CX¹X²NR³R³, -C(O)N(OH)R³, -

$C(O)NR^3R^3$, $-NR^3C(O)R^2$, $-CR^2(NH_2)CO_2R^2$, $-NHCX^1X^2CO_2R^2$, $-N(OH)C(O)NR^3R^3$, $-N(OH)C(O)R^2$, $-NHC(O)NR^3R^3$, $-C(O)NHN^3R^3$, $-C(O)N(OR^2)R^2$,

and where:-

5

R^2 is hydrogen, C_{1-12} alkyl or aryl, optionally substituted by one or more of C_{1-4} alkyl, halogen, C_{1-4} haloalkyl, OR^4 , SR^4 , NO_2 , CN , NR^4R^4 , NR^4COR^4 , $NR^4CONR^4R^4$, NR^4COR^4 , $NR^4CO_2R^4$, CO_2R^4 , COR^4 , $CONR^4_2$, $S(O)_2R^4$, $SONH_2$, $S(O)R^4$, $SO_2NR^4R^4$, $NR^4S(O)_2R^4$, wherein the C_{1-12} alkyl group
 10 optionally incorporates one or more insertions selected from the group consisting of $-O-$, $-N(R^4)-$, $-S(O)-$ and $-S(O)_2-$, wherein each R^4 may be the same or different and is as defined below;

R^3 is C_{1-12} alkyl or aryl, optionally substituted by one or more of C_{1-4} alkyl, halogen, C_{1-4} haloalkyl, OR^4 , SR^4 , NO_2 , CN , NR^4R^4 , NR^4COR^4 , $NR^4CONR^4R^4$, NR^4COR^4 , $NR^4CO_2R^4$, CO_2R^4 , COR^4 , $CONR^4_2$, $S(O)_2R^4$, $SONH_2$, $S(O)R^4$, $SO_2NR^4R^4$, $NR^4S(O)_2R^4$, wherein the C_{1-12} alkyl group optionally incorporates one
 15 or more insertions selected from the group consisting of $-O-$, $-N(R^4)-$, $-S(O)-$ and $-S(O)_2-$, wherein each R^4 may be the same or different and is as defined below;
 20

R^4 is hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl, aryl, or heterocyclyl;

X^1 and X^2 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, arylalkyl, heterocyclylalkyl, reduced
 25 heterocyclyl or reduced heterocyclylalkyl.

R^{11} is C_{1-12} alkyl, C_{1-12} alkyloxy, aryl, or a group OR^{10} ;

R^{10} is C_{1-12} alkyl, aryl or heterocyclyl

The process of the first aspect preferably produces a compound of formula I-2
 5 wherein R is other than hydrogen. Preferably R is C_{1-12} alkyl, C_{3-12} cycloalkyl, phenyl, naphthyl, C_{1-12} alkylphenyl, pyridinyl, furanyl, pyrrolyl, thiophenyl, C_{1-12} alkylpyridinyl, optionally substituted with halogen, C_{1-6} alkyl, CF_3 , CCl_3 , CH_2CH_2Br , phenyl, benzyl, pyridyl, methoxy, ethoxy, phenoxy, benzyoxy, cyano, nitro, $C(O)R^5$, CO_2R^5 , SOR^5 , SO_2R^5 , SR^5 , NR^5R^5 , $CONR^5R^5$,
 10 $NR^5CO_2R^5$; more preferably R is C_{1-12} alkyl or C_{3-12} cycloalkyl;

Preferably R' is hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, halo, phenyl, naphthyl, C_{1-12} alkylphenyl, pyridinyl, furanyl, pyrrolyl, thiophenyl, C_{1-12} alkylpyridinyl, optionally substituted with halogen, C_{1-6} alkyl, CF_3 , CCl_3 , CH_2CH_2Br , phenyl,
 15 benzyl, pyridyl, methoxy, ethoxy, phenoxy, benzyoxy, cyano, nitro, $C(O)R^5$, CO_2R^5 , SOR^5 , SO_2R^5 , SR^5 , NR^5R^5 , $CONR^5R^5$, $NR^5CO_2R^5$; more preferably R' is hydrogen or phenyl optionally substituted with halogen, C_{1-6} alkyl, CF_3 , CCl_3 , CH_2CH_2Br , phenyl, benzyl, pyridyl, methoxy, ethoxy, phenoxy, benzyoxy, cyano, nitro, $C(O)R^5$, CO_2R^5 , SOR^5 , SO_2R^5 , SR^5 , NR^5R^5 , $CONR^5R^5$,
 20 $NR^5CO_2R^5$;

wherein R^5 is methyl, ethyl or propyl;

R^{11} is preferably, methyl, ethyl, propyl, butyl, pentyl, hexyl, phenyl, pyridyl or
 25 a group OR^{10} .

Preferably R^{10} is methyl, ethyl, propyl, butyl, pentyl, hexyl, phenyl or pyridyl;

X is preferably hydrogen or a group $\text{CO}(\text{CH}_2)_n\text{CH}_3$ or $\text{CO}(\text{CH}_2)_n\text{cycloalkyl}$ wherein n is 0, 1, 2, 3, 4 or 5, or CO-phenyl or CO-pyridyl.

5 In this text, 'reduced', in the context of 'reduced heteroaryl' and the like means fully or partially saturated.

For the purposes of this invention, "alkyl" means a straight chain or branched alkyl radical of 1 to 12 carbon atoms, preferably 1 to 6 carbon atoms and most preferably 1 to 4 carbon atoms including but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl etc. The term
10 "alkenyl" means a straight chain or branched alkyl radical of 2 to 12 carbon atoms, preferably 2 to 6 carbon atoms and most preferably 2 to 4 carbon atoms, and containing one or more carbon-carbon double bonds and includes but is not limited to ethylene, n-propyl-1-ene, n-propyl-2-ene, isopropylene, etc.. The term "alkynyl" means a straight chain or branched alkynyl radical of 2
15 to 12 carbon atoms, preferably 2 to 6 carbon atoms and most preferably 2 to 4 carbon atoms, and containing one or more carbon-carbon triple bonds and includes but is not limited to ethynyl, 2-methylethynyl etc.. The term "cycloalkyl" means a saturated or partly unsaturated 3-12 membered cyclic
20 alkyl group and includes but not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl etc. Cycloalkyl groups may be optionally substituted or fused to one or more aryl, heterocyclyl or cycloalkyl group. "Heterocycloalkyl" means a 3-12 membered saturated or partly unsaturated cycloalkyl containing one or more hetero atom selected from N, S and O.
25 "Haloalkyl" means an alkyl radical substituted with one or more halide atoms for example $\text{CH}_2\text{CH}_2\text{Br}$, CF_3 or CCl_3 .

“Aryl” means an aromatic 3-10 membered hydrocarbon containing one ring or being fused to one or more saturated or unsaturated rings including but not limited to phenyl, naphthyl, anthracenyl or phenanthracenyl; or partially saturated bicyclic rings such as tetrahydro-naphthyl. Examples of substituents which may be present on an aryl group include one or more of halogen, amino, nitro, alkyl, haloalkyl, alkoxy, phenoxy and phenoxy substituted by one or more of halo, alkyl or alkoxy.

“Heteroaryl” means an aromatic 3-10 membered aryl containing one or more heteroatoms selected from N, O or S and containing one ring or being fused to one or more saturated or unsaturated rings and.

“Heterocyclyl” means a 3-10 membered ring system containing one or more heteroatoms selected from N, O or S and includes heteroaryl. The heterocyclyl system can contain one ring or may be fused to one or more saturated or unsaturated rings; the heterocyclyl can be fully saturated, partially saturated or unsaturated and includes but is not limited heteroaryl and heterocarbocyclyl, e.g. cyclohexyl, phenyl, acridine, benzimidazole, benzofuran, benzothiophene, benzoxazole, benzoxazine, benzothiazole, carbazole, cinnoline, dioxin, dioxane, dioxolane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, naphthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyridopyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole,

thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane. A reduced heteroaryl group or moiety may be for example a fully or partially saturated derivative of the aforementioned heteroaryl groups. Examples of reduced heteroaryl groups thus include pyrrolidinyl, tetrahydrofuryl, tetrahydrothienyl and piperidinyl. Suitable substituents include one or more of halogen, oxo, amino, nitro, alkyl, haloalkyl, alkoxy, phenoxy and phenoxy substituted by one or more of halo, alkyl, haloalkyl or alkoxy.

The aryl, heteroaryl or heterocyclyl group can be optionally fused to an unsaturated, partially saturated or fully saturated five to seven membered ring containing zero to three heteroatoms, each saturated carbon in the optional fused ring is further optionally and independently substituted by =O, =S, =NNHR², NNR²R², =N-OR², =NNHCO₂R², =NNSO₂R², or =NR², wherein each R² may be the same or different and is as defined above;

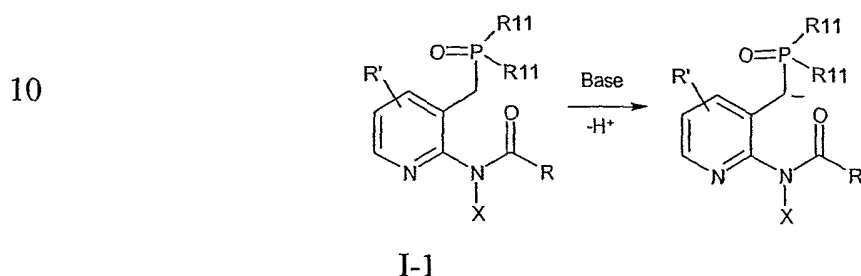
Each substitutable nitrogen atom in R is optionally substituted by R³, COR², SO₂R² or CO₂R², wherein each R² and R³ may be the same or different and is as defined above;

Halogen means F, Cl, Br or I, preferably F.

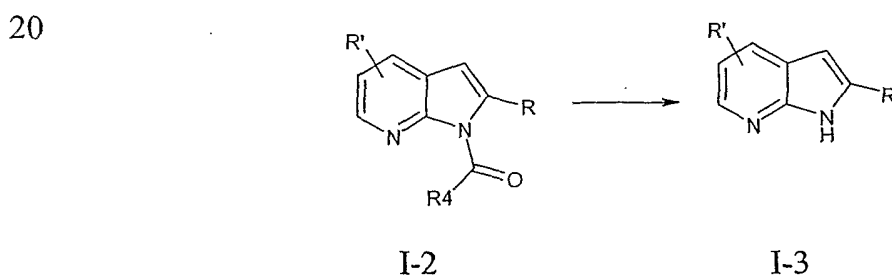
In a preferred feature of the first aspect, the compound of formula I-2 is provided wherein R and X are as defined above and R' is halide, preferably bromide or iodide, more preferably bromide. This compound can undergo a displacement reaction of the halide moiety in order to provide a different compound of formula I-2. Examples of such displacement reactions are well known in the art and usually involve the use of a palladium catalyst. Such

examples include the Suzuki coupling reaction, the Sonogashira coupling and the Stille coupling.

Compound I-1 is converted to compound I-2 by the addition of base. The base used must be sufficiently strong to convert compound I-2 into an intermediate ylide as illustrated below.



15 Examples of such bases include sodium carbonate, butyllithium, tBuOK, sodium amide, LDA, LiHMDS, sodium hydride or sodium alkoxide. For the purposes of the first aspect, the group X can be hydrogen or a group COR where R is defined as above. Where X is a group COR, the compound of formula I-2 is optionally deprotected to produce a compound of formula I-3.



25 Removal of the group COR can be carried out using conventional conditions known in the art. In particular, the acyl group is removed using neutral to basic conditions. Some acyl groups will require the use of basic conditions such as sodium hydroxide solution, preferably incubation with a 10% sodium

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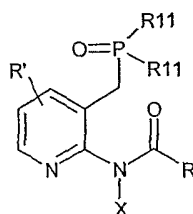
hydroxide solution at room temperature. More labile acyl groups can be removed using mild conditions. For example, where R is ethyl, the acyl group can be removed by incubation with silica at room temperature.

- 5 The process of the first aspect is carried out at temperatures less than 150°C, preferably less than 120°C, more preferably from approximately 90°C to 95°C. The use of low temperatures allows the use of temperature labile starting materials and therefore allows the production of a wider range of 7-azaindole compounds including temperature labile 7-azaindole compounds. This process
- 10 is furthermore amenable to production of the 7-azaindole compounds in quantities in excess of 1kg due to the use of reactants which are easily available or can be synthesised from easily available starting materials. The process also allows the 7-azaindoles to be produced in high purity as the starting material I-1 can be isolated and purified prior to its conversion to the compound I-2.

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The second aspect of the invention relates to a process for the production of a compound of formula I-1

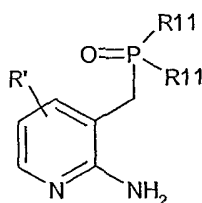
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I-1

comprising reacting a compound of formula II-5 with a group RCOY.

25



II-5

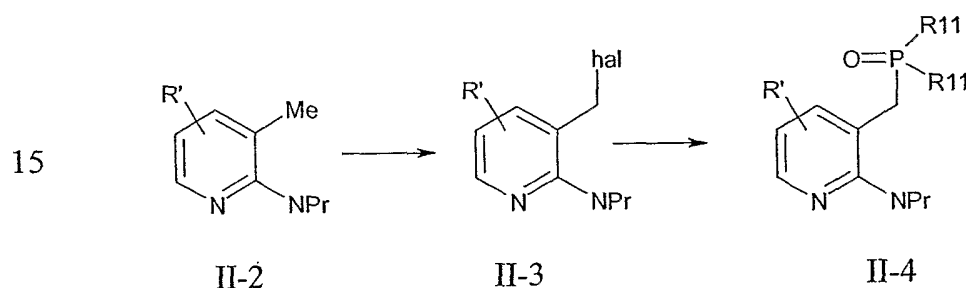
Wherein the groups R', R and R¹¹ are as defined as for the first aspect of the invention,
and the group Y is OH, halide or OCOR.

- 5 When the group Y is OH, the compound RCOY is activated prior to reaction with the compound of formula II-5 to form the amide of compound I-1. Activation of the acid group can be carried out by methods known in the art. Preferably the acid group is reacted with a coupling agent to form an active intermediate which then reacts with the amine of compound II-5 to form
- 10 compound I-1. Examples of such coupling agents include dicyclohexylcarbodiimide, water soluble carbodiimide, N,N'-carbonyldimimidazole, molecular sieves, N,N,N',N-tetramethyl(succinimido)uronium tetrafluoroborate, CBMIT, benzotriazol-1-yl diethyl phosphate, BOP, and PyBOP. Alternatively the acid can be converted
- 15 into an active ester. Examples of such esters include para-nitrophenyl esters, pentafluorophenyl esters, 2, 4,5-trichlorophenyl esters and succinimide esters. Such esters can be prepared by the DCC-mediated coupling of an acid RCO₂H and an appropriate ester moiety. The active esters are preferably crystalline stable materials which can be isolated and purified prior to the amide coupling
- 20 reaction. In addition, the free acid RCOOH may be converted into the acid chloride by the action of thionyl chloride or oxalyl chloride.

- The second aspect may alternatively utilise a compound of formula RCOY where Y is a halide preferably chloride. Such acid halides can be produced
- 25 from the corresponding acid by reaction with thionyl chloride, oxalyl chloride, phosphorus pentachloride etc.

When Y is OCOR, the compound RCOY is an acid anhydride. Such acid anhydrides can be symmetrical anhydrides (i.e. where both R groups are the same) or mixed anhydrides (where the R groups are different). Symmetrical anhydrides can be produced from a variety of reagents including
 5 dicyclohexylcarbodiimide. Mixed anhydrides can be produced using acids and symmetrical anhydrides or by using reagents such as 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline or diphenylphosphinic acid.

The third aspect of the invention relates to a process for the production of a
 10 compound of formula II-4



comprising halogenating the methyl group to form a halomethyl derivative II-3
 20 and reacting the compound of formula II-3 with a P(III) compound $(R^{10}O)(R^{11})_2P$ to form a compound of formula II-4. The groups R^1 , R^{10} and R^{11} are as defined for the first aspect.

The primary amine of compound II-1 is protected with an amino protecting
 25 group (Pr), allowing halogenation of the methyl group to form the halomethyl derivative II-3. The protecting group can be any group routinely used in the art to protect amine functionalities provided such protecting group does not require deprotection under strongly basic conditions. The protecting group must

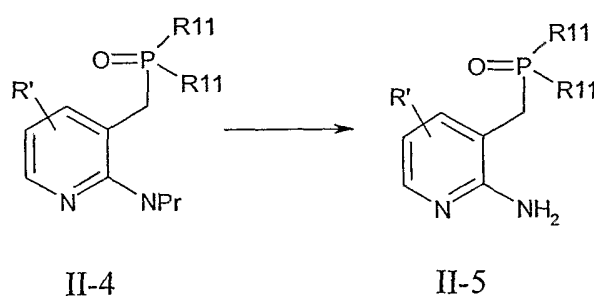
withstand the conditions of bromination. Examples of such acceptable protecting groups include benzyloxycarbonyl, t-butyloxycarbonyl, 2-(4-biphenyl)-isopropoxycarbonyl, 9-fluorenylmethoxycarbonyl, triphenylmethyl, 2-nitrophenylsulphenyl groups. Preferably the amine group is
 5 reacted with phthalic anhydride to form an isoindole-dione derivative.

The methyl group can be halogenated with for example, NBS or Br_2 .

Halogenation may occur at reflux, preferably using a catalytic amount of a free radical promoter such as AIBN or benzoyl peroxide. Reaction with a group
 10 $(\text{R}^{10}\text{O})(\text{R}^{11})_2\text{P}$ displaces the halide to form the phosphonate of formula II-4.

The halide may be refluxed with the phosphite, preferably one equivalent of phosphite or above. The halide is preferably refluxed in a neutral solvent such as toluene, benzene or xylene.

15 The fourth aspect of the invention provides a process for the production of a compound of formula II-5



comprising deprotecting the amino group of compound II-4. The groups R^1 , R^{10} and R^{11} and Pr are as defined for the first to third aspects.

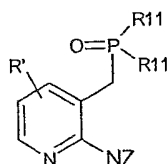
25 The conditions for the amine deprotection will depend on the protecting group used. As discussed above, any conditions can be used to deprotect the amine

group with the exception of strong base which will result in the formation of the ylide and potentially in the intramolecular reaction of II-4.

The amine group is preferably protected with phthalimide. Removal of the phthalimide protection can be achieved by the action of hydrazine in alcoholic medium at room (or elevated) temperatures.

The fifth aspect of the invention provides a compound of formula I-4

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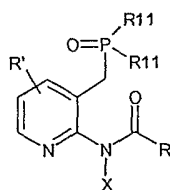


I-4

Wherein the groups R', and R¹¹ are as defined for the first aspect and the group Z is hydrogen or a protecting group selected from benzyloxycarbonyl, t-butyloxycarbonyl, 2-(4-biphenyl)-isopropoxycarbonyl, 9-fluorenylmethoxycarbonyl, triphenylmethyl, and 2-nitrophenylsulphenyl groups. Preferably Z with the nitrogen atom is an isoindole-dione derivative.

The sixth aspect of the invention provides a compound of formula I-1

25



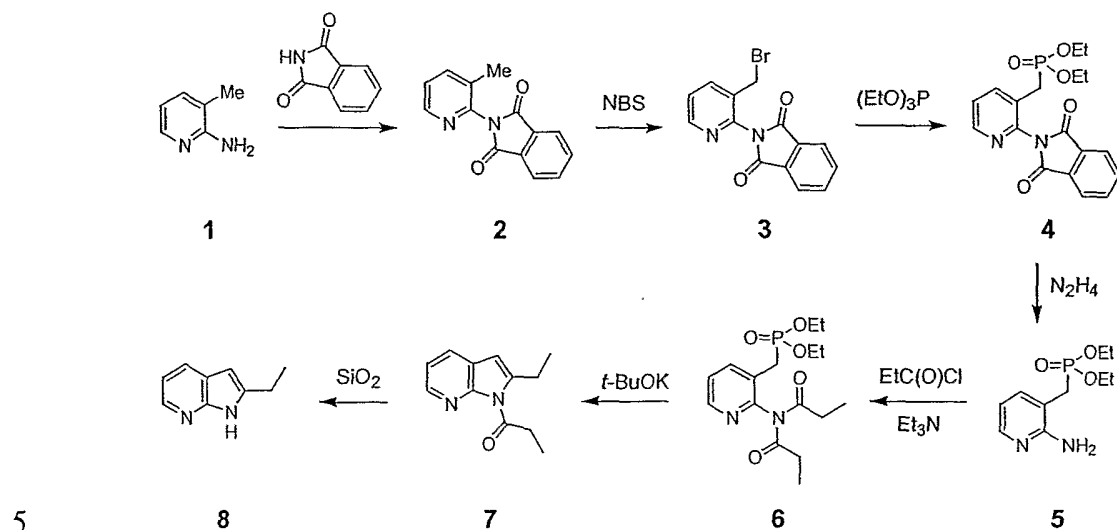
I-1

Wherein the groups R, R', R¹¹ and X are as defined for the first aspect.

The invention will now be illustrated by the following non-limiting examples.

Examples

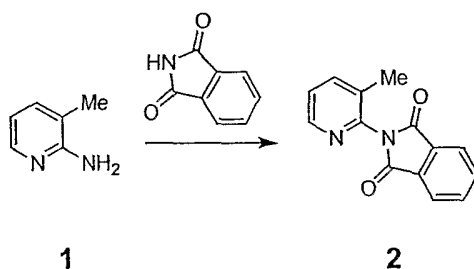
Synthesis of example 2-substituted 7-azaindole derivative **8** is presented in Scheme 3.



Scheme 3

2-(3-Methyl-pyridin-2-yl)-isoindole-1,3-dione (**2**)

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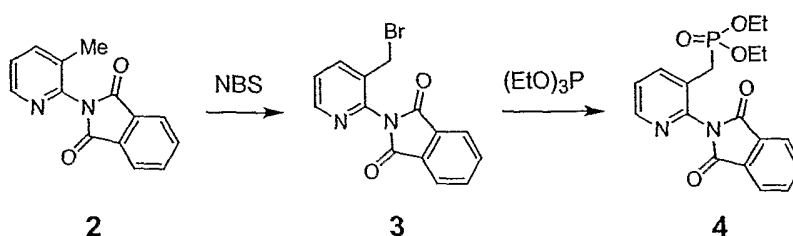


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Following the method of Moorman *et al.* (*Synth. Commun.* **1987**, *17*, 1695-1699) 2-amino-3-picoline (32.44 g, 0.30 mol) and phthalic anhydride (44.44 g, 0.30 mol) were heated at 190 °C for 5 h. The product was dissolved in CH₂Cl₂ (600 mL), and the solution was washed with water (200 mL), dried MgSO₄,

and concentrated. The semisolid residue was triturated with ether. Solid product was filtered off and dried in vacuum to afford 2 (66.66 g, 93%) as white powder. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 2.19 (s, 3H), 7.49 (dd, $J = 7.6$, 4.6 Hz, 1H), 7.90 (d, $J = 7.6$ Hz, 1H), 7.91-7.97 (m, 2H), 7.98-8.03 (m, 2H), 8.46 (d, $J = 4.6$ Hz, 1H).

[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-pyridin-3-ylmethyl]-phosphonic acid diethyl ester (4)

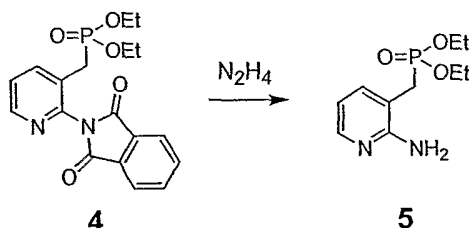


A mixture of 2 (23.81 g, 0.1 mol) and NBS (19.58 g, 0.11 mol) in CCl_4 (270 mL) was refluxed by heating with two sun lamps (250 W each). The bromination reaction was initiated by addition of AIBN in 50 mg portions. Progress of the reaction was followed by TLC. Total of 200 mg of AIBN was added over 2 h. After this period the reflux was discontinued and the mixture allowed to cool to r.t. overnight. Solid, which formed, was filtered off, and the filtrate was concentrated to dryness in vacuum to afford crude 3 (30.19 g, containing also unreacted 2 and the relevant dibromide) as tan solid. A mixture of this solid (28.48 g) and triethyl phosphite (15.4 mL, 89.8 mmol) in toluene (120 mL) was refluxed under N_2 for 17 h. The crude reaction mixture was applied on a column (40 mm o.d., length 30 cm) loaded with silicagel (Kieselgel 60, 230-400 mesh) in CH_2Cl_2 , and the product was isolated by gradient elution with CH_2Cl_2 :AcOEt followed by crystallization from benzene:hexane. Obtained 4 (16.21 g, 46% from 2) as white crystalline solid. ^1H NMR (400 MHz, CDCl_3) δ 1.16 (t, $J = 7.1$ Hz, 6H), 3.17 (d, $J = 21.7$ Hz,

2H), 3.88-4.01 (m, 4H), 7.40 (dd, $J = 7.8, 4.7$ Hz, 1H), 7.78-7.83 (m, 2H), 7.93-7.99 (m, 3H), 8.58 (dt, $J = 4.7, 1.9$ Hz, 1H).

(2-Amino-pyridin-3-ylmethyl)-phosphonic acid diethyl ester (5)

5

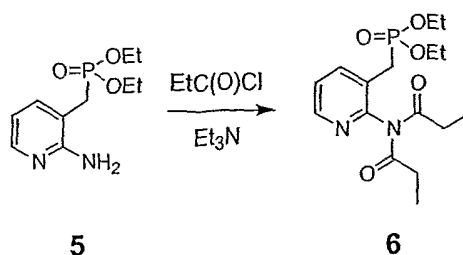


Hydrazine hydrate (3.26 mL, 57.7 mmol) was added to a solution of **4** (14.40 g, 38.5 mmol) in absolute EtOH (300 mL). The white suspension, which formed, was stirred at r.t. overnight. The solid was filtered off and the filtrate was concentrated in vacuum. The semisolid residue was extracted with CH₂Cl₂ (4x100 mL). Combined organic solutions were extracted with 5% HCl (3x40 mL). The combined acidic extracts were basified to pH 10 with 50% aqueous NaOH (about 9.0 mL; external ice bath cooling) and the product was extracted with CH₂Cl₂ (4x50 mL). The extracts were dried (MgSO₄) and concentrated in vacuum to afford **5** (9.03 g, 96%) as colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 1.26 (t, $J = 7.1$ Hz, 6H), 3.04 (d, $J = 21.0$ Hz, 2H), 3.98-4.12 (m, 4H), 5.08 (bs, 2H), 6.66 (ddd, $J = 7.3, 5.0, 1.0$ Hz, 1H), 7.28 (dt, $J = 7.3, 2.3$ Hz, 1H), 8.02 (dt, $J = 5.0, 2.1$ Hz, 1H).

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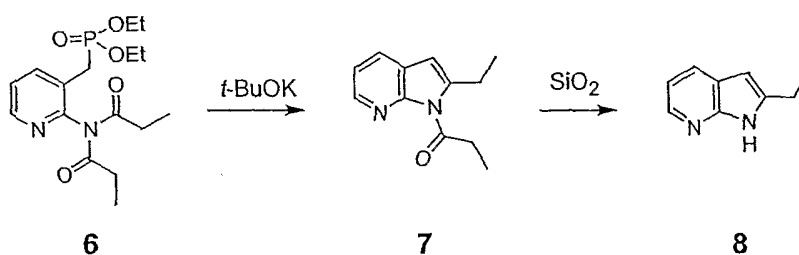
(2-Dipropionylamino-pyridin-3-ylmethyl)-phosphonic acid diethyl ester (6)

19



Propionyl chloride (352 μ L, 4.05 mmol) was added dropwise to a stirred and cooled (0 $^{\circ}$ C) solution of **5** (329.5 mg, 1.35 mmol) and Et₃N (753 μ L, 5.40 mmol) in CH₂Cl₂ (10 mL). After overnight stirring the mixture was diluted with AcOEt (100 mL) and washed with saturated NaHCO₃ solution (2x10 mL). The organic layer was dried (MgSO₄), concentrated and separated by silicagel chromatography (SGC) with AcOEt as eluent to afford **6** (370.2 mg, 77%) as colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 1.12 (t, J = 7.2 Hz, 6H), 1.29 (t, J = 7.1 Hz, 6H), 2.57 (dq, J = 17.9, 7.1 Hz, 2H), 2.69 (dq, J = 17.9, 7.2 Hz, 2H), 2.98 (d, J = 21.8 Hz, 2H), 4.02-4.15 (m, 4H), 7.36 (dd, J = 7.8, 4.6 Hz, 1H), 8.02 (dt, J = 7.8, 2.1 Hz, 1H), 8.49 (dt, J = 4.7, 1.8 Hz, 1H).

2-Ethyl-1H-pyrrolo[2,3-b]pyridine (**8**)

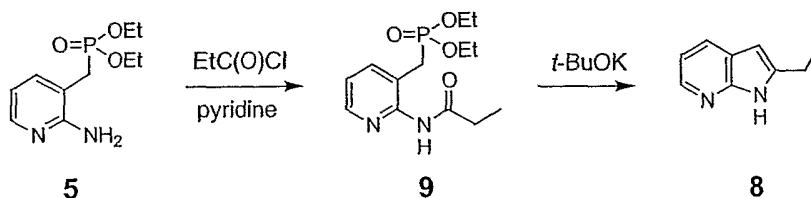


1.0 M solution of *t*-BuOK in THF (205 μ L, 0.205 mmol) was added to a solution of **6** (61.0 mg, 0.171 mmol) in toluene (1.0 mL). Then the mixture was stirred at 105 $^{\circ}$ C for 80 min, when TLC showed that the reaction was completed. The mixture was cooled to r.t.. Silicagel (192 mg; Kieselgel 60,

230-400 mesh) and 10% aqueous HCl (72 μ L, 0.2 mmol) were added, and the mixture was stirred at r.t. for 4 days. Acid was neutralised with Et₃N (28 μ L, 0.2 mmol) and the mixture was separated by means of SGC with CH₂Cl₂:MeOH (19:1, v/v) as eluent to afford **8** (18.2 mg, 73% from **6**). ¹H NMR (400 MHz, CDCl₃) δ 1.40 (t, J = 7.6 Hz, 3H), 2.88 (qd, J = 7.6, 0.8 Hz, 2H), 6.20 (t, J = 0.8 Hz, 1H), 7.04 (dd, J = 7.8, 4.9 Hz, 1H), 7.83 (dd, J = 7.8, 1.5 Hz, 1H), 8.19 (dd, J = 4.9, 1.5 Hz, 1H), 10.39 (bs, 1H).

The intermediate 1-(2-ethyl-pyrrolo[2,3-b]pyridin-1-yl)-propan-1-one (**7**) can be isolated by rapid SGC using hexane:AcOEt=1:1 (v/v) as eluent. ¹H NMR (400 MHz, CDCl₃) δ 1.31 (t, J = 7.3 Hz, 6H), 3.14 (qd, J = 7.4, 0.9 Hz, 2H), 3.63 (q, J = 7.3 Hz, 2H), 6.35 (t, J = 0.9 Hz, 1H), 7.14 (dd, J = 7.8, 4.8 Hz, 1H), 7.76 (dd, J = 7.8, 1.6 Hz, 1H), 8.27 (dd, J = 4.8, 1.6 Hz, 1H).

Synthesis of example 2-substituted 7-azaindole derivative **8** via monoamide **9** (Scheme 4).



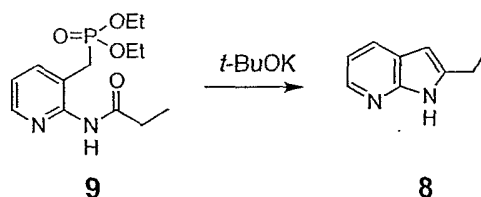
Scheme 4

(2-Propionylamino-pyridin-3-ylmethyl)-phosphonic acid diethyl ester (9)

Propionyl chloride (518 mL, 6.0 mmol) was added dropwise to a cooled (0 °C) and stirred solution of **5** (1.1662 g, 4.78 mmol) in pyridine (10 mL). Cooling bath was then removed and the mixture was stirred at r.t. overnight. Solvent

was evaporated in vacuum and the residue was separated between AcOEt-saturated aqueous NaHCO₃. The aqueous layer was extracted with AcOEt (3x4 mL). Combined organic solutions were washed with saturated aqueous NaHCO₃, dried (MgSO₄), concentrated and evaporated with *p*-xylene to remove residual pyridine. The crude product was separated by SGC with AcOEt:MeOH as eluent (in gradient, up to 5% MeOH) to afford diamide **6** (124.9 mg, 7%) and the desired monoamide **9** (996.6 mg, 69%) as colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 1.24 (t, *J* = 7.0 Hz, 6H), 1.26 (t, *J* = 7.6 Hz, 3H), 2.49 (q, *J* = 7.6 Hz, 2H), 3.12 (d, *J* = 21.2 Hz, 2H), 3.96-4.02 (m, 4H), 7.09 (ddd, *J* = 7.6, 4.8, 0.9 Hz, 1H), 7.54 (dt, *J* = 7.6, 2.2 Hz, 1H), 8.44 (dt, *J* = 4.8, 2.1 Hz, 1H), 9.33 (bs, 1H).

2-Ethyl-1H-pyrrolo[2,3-b]pyridine (**8**)



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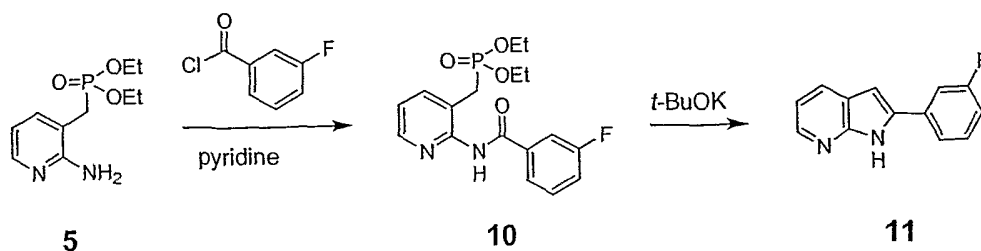
1.0 M solution of *t*-BuOK in THF (1.27 mL, 1.27 mmol) was added to a solution of **9** (158.9 mg, 0.529 mmol) in toluene (3.0 mL). The mixture turned into a gel, which was stirred at 93 °C for 1 h, when TLC showed that the reaction was completed. The mixture was cooled to r.t., and separated by means of SGC with CH₂Cl₂:MeOH (19:1, v/v) as eluent to afford **8** (52.2 mg, 68%), indistinguishable (¹H NMR, TLC) from the product obtained from **6** (see above).

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Synthesis of example 2-aryl-substituted 7-azaindole derivative **11** (Scheme 5).

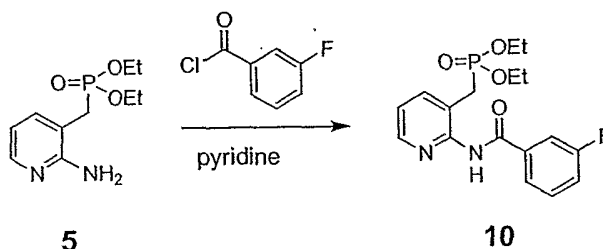
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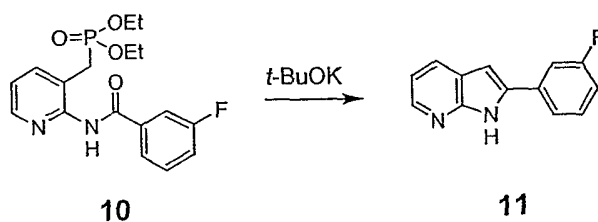
Scheme 5

[2-(3-Fluoro-benzoylamino)-pyridin-3-ylmethyl]-phosphonic acid diethyl ester (10)



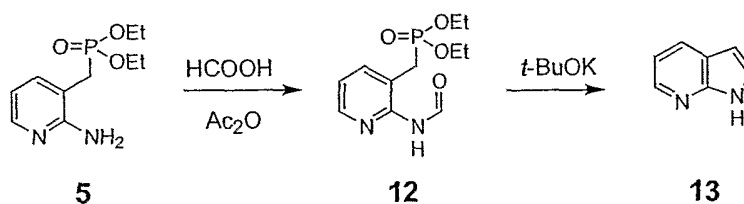
Compound **10** was obtained from **5** (244.1 mg, 1.0 mmol) and the relevant acid chloride following the method used for the synthesis of **9**. Yield 304.0 mg (83%) of colourless oil. ^1H NMR (400 MHz, CDCl_3) δ 1.25 (t, $J = 7.1$ Hz, 6H), 3.18 (d, $J = 21.1$ Hz, 2H), 3.97-4.14 (m, 4H), 7.17 (ddd, $J = 7.5, 4.8, 0.8$ Hz, 1H), 7.24 (tdd, $J = 8.3, 2.6, 0.8$ Hz, 1H), 7.46 (td, $J = 8.0, 5.7$ Hz, 1H), 7.59 (dt, $J = 7.6, 2.1$ Hz, 1H), 7.87 (ddd, $J = 9.6, 2.4, 1.6$ Hz, 1H), 7.92 (ddd, $J = 7.7, 1.2, 0.9$ Hz, 1H), 8.55 (dt, $J = 4.8, 2.1$ Hz, 1H), 10.45 (bs, 1H).

2-(3-Fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine (11)



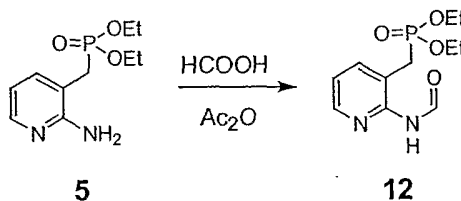
1.0 M solution of *t*-BuOK in THF (1.09 mL, 1.09 mmol) was added to a solution of **10** (133.4 mg, 0.364 mmol) in toluene (2.0 mL). The mixture was stirred at 90 °C overnight. The mixture was cooled to r.t., and separated by means of SGC with CH₂Cl₂:MeOH (19:1, v/v) and then with AcOEt as eluent to afford recovered starting **10** (61.7 mg, 46%) and desired **11** (14.0 mg, 18%);
¹H NMR (400 MHz, CDCl₃) δ 6.82 (s, 1H), 7.10 (tdd, *J* = 8.4, 2.5, 0.9 Hz, 1H), 7.14 (dd, *J* = 7.8, 4.9 Hz, 1H), 7.48 (ddd, *J* = 9.9, 8.4, 5.9 Hz, 1H), 7.58 (ddd, *J* = 9.9, 2.4, 1.7 Hz, 1H), 7.64 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1H), 7.99 (dd, *J* = 7.8, 1.5 Hz, 1H), 8.34 (dd, *J* = 4.8, 1.5 Hz, 1H), 12.07 (bs, 1H).

Synthesis of example 2-unsubstituted 7-azaindole **13** (Scheme 6).



Scheme 6

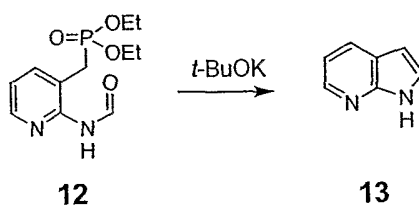
(2-Formylamino-pyridin-3-ylmethyl)-phosphonic acid diethyl ester (**12**)



98% Formic acid (0.22 mL, 5.71 mmol) was added to a solution of acetic anhydride (0.54 mL, 5.72 mmol) in dry ether (5.0 mL). The solution was stirred at r.t. for 15 min. Then a solution of **5** (1.1349 g, 4.65 mmol) in ether (5.7 mL) was added over a period of 1 min. After overnight stirring at r.t., the mixture was separated between saturated aqueous NaHCO₃ – AcOEt (50 mL). The

aqueous layer was extracted with AcOEt (30 mL). Combined organic solutions were washed with saturated aqueous NaHCO₃, dried MgSO₄ and concentrated to afford **12** (789 mg, 62%) as white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.26 (t, *J* = 7.1 Hz, 6H), 3.09 (d, *J* = 21.3 Hz, 2H), 3.98-4.13 (m, 4H), 7.06 (dd, *J* = 7.0, 5.1 Hz, 1H), 7.27 (dt, *J* = 7.6, 2.1 Hz, 1H), 8.25 (bs, 1H), 9.27 (bs, 2H).

1H-Pyrrolo[2,3-b]pyridine (7-azaindole, 13)

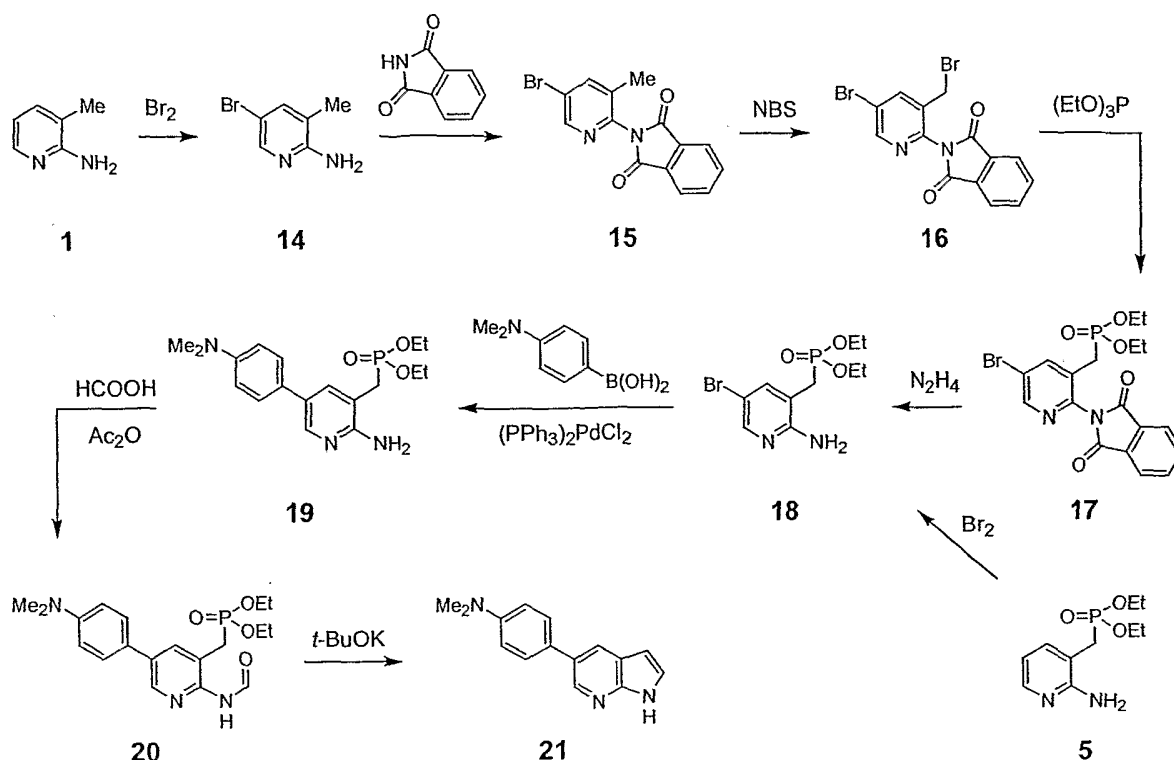


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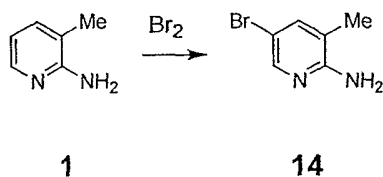
1.0 M solution of *t*-BuOK in THF (1.08 mL, 1.08 mmol) was added to a solution of **12** (122.4 mg, 0.450 mmol) in toluene (2.6 mL). The mixture was stirred for 30 min. at 90 °C, after which TLC showed that the reaction was completed. The mixture was cooled to r.t., and separated between water-AcOEt. The aqueous layer was extracted with AcOEt (3x). Combined organic solutions were dried (MgSO₄), concentrated, and the product was isolated by means of SGC with AcOEt as eluent to afford **13** (13.4 mg, 25%), indistinguishable (¹H NMR, TLC) from the commercially available material.

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Synthesis of example 5-substituted 7-azaindole **21** (Scheme 7).



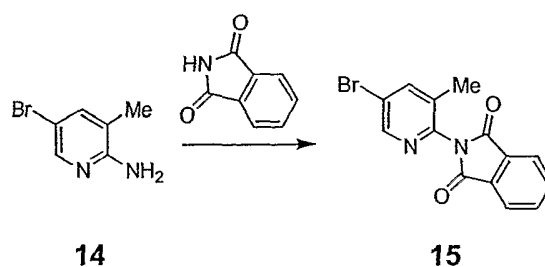
5 5-Bromo-3-methyl-pyridin-2-ylamine (14)



Bromine (15.4 mL, 0.30 mol) was added dropwise to a stirred and cooled (0-2 °C) solution of 2-amino-3-picoline (**1**; 32.44 g, 0.30 mol) in dry CH_2Cl_2 (1000 mL) over a period of 1 h. The cooling bath was then removed, and the yellowish suspension was stirred at r.t. for 3 h 40 min. The mixture was basified to pH 9 with 2N NaOH (145 mL) followed by a mixture of saturated aqueous NaHCO_3 (100 mL) – saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL). The organic

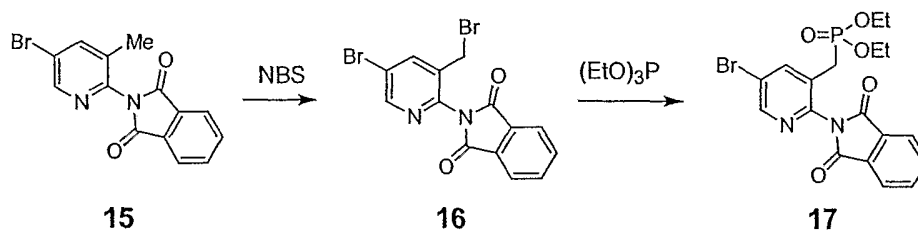
layer was separated and washed with brine, dried MgSO_4 and concentrated to afford **14** (56.83 g, 102%) as brown solid, which was used in the next step without purification.

5 **2-(5-Bromo-3-methyl-pyridin-2-yl)-isoindole-1,3-dione (15)**



Compound **14** (55.64 g, 0.299 mol) was converted into **15** following the
10 protocol used for the preparation of **2**. Yield 83.77 g (87%) of brownish
powder. ¹H NMR (400 MHz, CDCl₃) δ 2.27 (s, 3H), 7.78-7.83 (m, 2H), 7.88
(dd, *J* = 2.3, 0.7 Hz, 1H), 7.93-7.99 (m, 2H), 8.56 (dd, *J* = 2.3, 0.4 Hz, 1H).

[5-Bromo-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pyridin-3-ylmethyl]-
phosphonic acid diethyl ester (17)

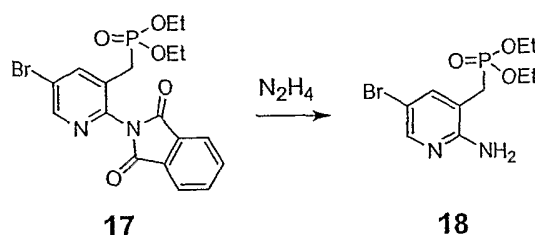


A mixture of **15** (79.42 g, 0.251 mol) and NBS (49.2 g, 0.251 mol) in CCl₄ (700 mL) was refluxed by heating with two sun lamps (250 W each). The bromination reaction was initiated by addition of AIBN in 100 mg portions.

Progress of the reaction was followed by ^1H NMR spectra of small aliquots dissolved in CDCl_3 . Total of 1.05 g of AIBN was added over 7 h. The reaction mixture was concentrated to dryness in vacuum and redissolved in CH_2Cl_2 (1 L). This solution was washed with 1N HCl (5x400 mL). The aqueous layers were discarded and the organic layer was washed with saturated aqueous NaHCO_3 (50 mL), dried MgSO_4 and concentrated in vacuum to afford crude **16** (101.77 g; containing also unreacted **15** and the relevant dibromide) as tan solid.

A mixture of the crude **16** (100.63 g) and triethyl phosphite (28 mL, 0.163 mol) in toluene (350 mL) was refluxed for 40 h. The crude reaction mixture was applied on a column (90 mm o.d., length 24 cm) loaded with silicagel (Kieselgel 60, 230-400 mesh) in CH_2Cl_2 , and the product was isolated by gradient elution with CH_2Cl_2 :AcOEt. Obtained **17** (51.94 g, 46% from **15**) as white crystalline solid. ^1H NMR (400 MHz, CDCl_3) δ 1.18 (t, $J = 7.1$ Hz, 6H), 3.14 (d, $J = 21.8$ Hz, 2H), 3.93-4.02 (m, 4H), 7.78-7.83 (m, 2H), 7.94-7.98 (m, 2H), 8.09 (t, $J = 2.3$ Hz, 1H), 8.62 (t, $J = 2.3$ Hz, 1H).

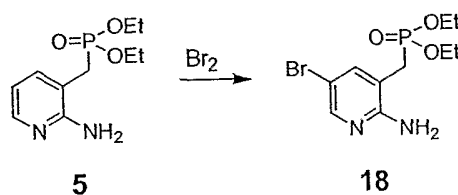
(2-Amino-5-bromo-pyridin-3-ylmethyl)-phosphonic acid diethyl ester (18)



Hydrazine hydrate (4.2 mL, 74 mmol) was added to a warm (65 °C) solution of **17** (22.60 g, 50.0 mmol) in absolute EtOH (390 mL). The white suspension, which formed, was allowed to cool to r.t. and was stirred at r.t. overnight. The

solid was filtered off and the filtrate was concentrated in vacuum. The semisolid residue was extracted with CH_2Cl_2 (4x100 mL). Combined organic solutions were extracted with 5% aqueous HCl (3x45 mL). The combined acidic extracts were basified to pH 10 with 50% aqueous NaOH (about 10 mL; external ice bath cooling) and the product was extracted with CH_2Cl_2 (3x100 mL). The extracts were dried (MgSO_4) and concentrated in vacuum to afford **18** (15.72 g, 98%) as yellowish oil. ^1H NMR (400 MHz, CDCl_3) δ 1.28 (t, $J = 7.1$ Hz, 6H), 2.99 (d, $J = 21.1$ Hz, 2H), 4.01-4.13 (m, 4H), 5.15 (bs, 2H), 7.39 (t, $J = 2.5$ Hz, 1H), 8.04 (t, $J = 2.5$ Hz, 1H).

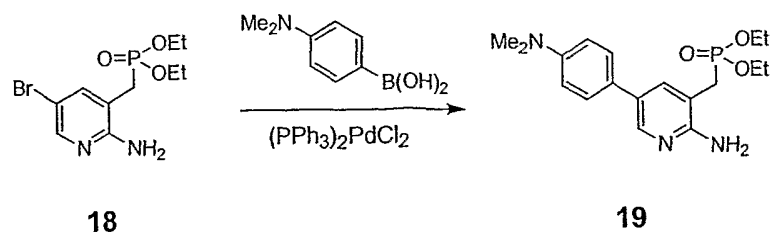
Compound **18** may also be synthesized from **5** as shown below



Bromine (24 μL , 0.46 mmol) was added dropwise to a stirred solution of aminopyridine **5** (112.0 mg, 0.459 mmol) in dry CHCl_3 (2.0 mL). The mixture was then stirred for 2 h at r.t., and treated with a mixture of saturated aqueous NaHCO_3 (2.0 mL) – saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (0.2 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x2 mL). Combined organic solutions were dried MgSO_4 and concentrated to afford **18** (144.4 mg, 98%) as brown oil.

[2-Amino-5-(4-dimethylamino-phenyl)-pyridin-3-yl-methyl]-phosphonic acid diethyl ester (19)

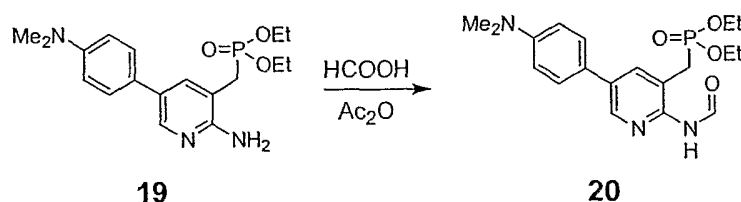
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A mixture of **18** (5.47 g, 17.0 mmol), 4-(N,N-dimethylamino)phenylboronic acid (4.21 g, 25.5 mmol), LiCl (2.17 g, 51.7 mmol), (PPh₃)₂PdCl₂ (0.55 g, 0.78 mmol) and 1.0 M aqueous Na₂CO₃ (42.3 mL, 42.3 mmol) in ethanol (100 mL) – toluene (100 mL) was refluxed under N₂ for 2 h 30 min. The mixture was cooled to r.t., water (100 mL) was added, the organic layer was separated and washed with brine (100 mL). Combined aqueous solutions were extracted with AcOEt (3x100 mL). The organic extracts were washed with brine, combined with the main organic layer, dried (MgSO₄), and separated by means of SGC with CH₂Cl₂:MeOH (19:1, v/v) as eluent to afford **19** (5.34 g, 87%). ¹H NMR (400 MHz, CDCl₃) δ 1.27 (t, *J* = 7.1 Hz, 6H), 2.98 (s, 6H), 3.10 (d, *J* = 21.0 Hz, 2H), 4.00-4.13 (m, 4H), 5.10 (bs, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.48 (t, *J* = 2.5 Hz, 1H), 8.23 (t, *J* = 2.5 Hz, 1H).

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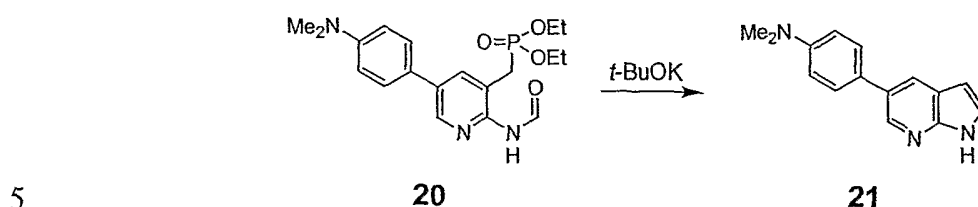
[5-(4-Dimethylamino-phenyl)-2-formylamino-pyridin-3-ylmethyl]-phosphonic acid diethyl ester (20)



Compound **19** (124.4 mg, 0.342 mmol) was converted into **20** following the protocol used for the preparation of **12**. Yield 99.5 mg (74%) of white solid. ¹H NMR (400 MHz, CDCl₃) δ 1.28 (t, *J* = 7.1 Hz, 6H), 3.01 (s, 6H), 3.14 (d, *J* =

21.2 Hz, 2H), 4.03-4.17 (m, 4H), 6.81 (d, $J = 8.9$ Hz, 2H), 7.44 (d, $J = 8.9$ Hz, 2H), 7.65 (t, $J = 2.5$ Hz, 1H), 8.45 (bs, 1H), 9.20-9.30 (m, 2H).

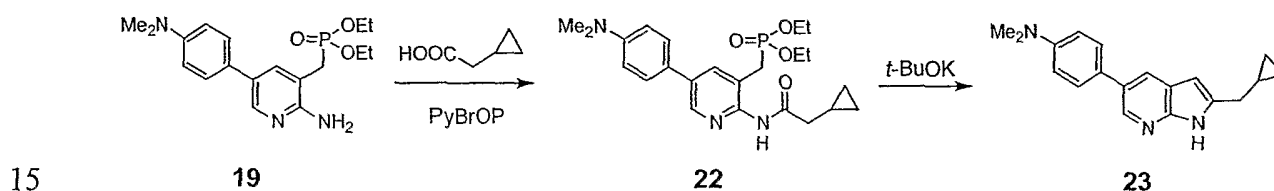
Dimethyl-[4-(1H-pyrrolo[2,3-b]pyridin-5-yl)-phenyl]-amine (21)



Compound **20** (95.3 mg, 0.244 mmol) was converted into **21** following the protocol used for the preparation of **13**. Yield 12.3 mg (21%) of white solid. ^1H NMR (400 MHz, CDCl_3) δ 3.01 (s, 6H), 6.54 (dd, $J = 3.4, 0.9$ Hz, 1H), 6.86 (d, $J = 8.8$ Hz, 2H), 7.36 (dd, $J = 3.4, 1.5$ Hz, 1H), 7.54 (d, $J = 8.8$ Hz, 2H), 8.09 (d, $J = 2.1$ Hz, 1H), 8.54 (d, $J = 2.1$ Hz, 1H), 9.87 (bs, 1H).

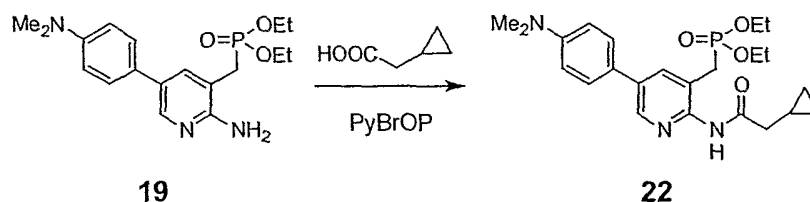
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Synthesis of 2,5-disubstituted 7-azaindole **23**



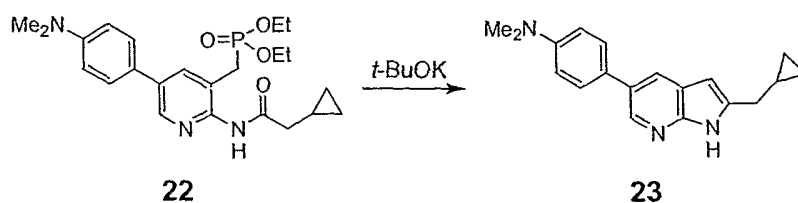
[2-(2-Cyclopropyl-acetylamino)-5-(4-dimethylamino-phenyl)-pyridin-3-ylmethyl]-phosphonic acid diethyl ester (22)

31



5 *i*-Pr₂NEt (348 μ L, 2.0 mmol) was added to a solution of **19** (363.2 mg, 1.0 mmol), PyBrOP (466 mg, 1 mmol), and cyclopropylacetic acid (100 mg, 1 mmol) in CH₂Cl₂ (1.0 mL). The mixture was stirred at r.t. overnight and separated by means of SGC with AcOEt:MeOH (in gradient, up to 19:1, v/v) as eluent to afford **22** (210.4 mg, 47%). ¹H NMR (400 MHz, CDCl₃) δ 0.29-0.34 (m, 2H), 0.64-0.70 (m, 2H), 1.16-1.24 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 6H), 2.41 (d, *J* = 7.2 Hz, 2H), 3.01 (s, 6H), 3.19 (d, *J* = 21.1 Hz, 2H), 3.98-4.12 (m, 4H),
 10 6.81 (d, *J* = 8.9 Hz, 2H), 7.46 (d, *J* = 8.9 Hz, 2H), 7.70 (t, *J* = 2.5 Hz, 1H), 8.67 (t, *J* = 2.3 Hz, 1H), 9.34 (bs, 1H).

15 [4-(2-Cyclopropylmethyl-1H-pyrrolo[2,3-b] pyridin-5-yl)-phenyl]-dimethyl-amine (**23**).

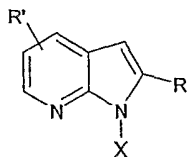


20 1.0 M solution of *t*-BuOK in THF (0.70 mL, 0.70 mmol) was added to a suspension of **22** (130.3 mg, 0.293 mmol) in toluene (1.7 mL). The mixture turned into a gel, which was stirred at 110 °C for 20 h. The mixture was cooled to r.t., and separated by means of SGC with CH₂Cl₂:MeOH (19:1, v/v) as eluent to afford **23** (35.5 mg, 42%) of white solid. ¹H NMR (400 MHz, CDCl₃) δ 0.29-0.33 (m, 2H), 0.62-0.67 (m, 2H), 1.08-1.17 (m, 1H), 2.75 (d, *J* = 6.9 Hz,

2H), 3.01 (s, 6H), 6.28 (dt, $J=2.1, 0.9$ Hz, 1H), 6.85 (d, $J=8.9$ Hz, 2H), 7.52 (d, $J=8.9$ Hz, 2H), 7.95 (d, $J=1.9$ Hz, 1H), 8.41 (d, $J=1.9$ Hz, 1H), 9.34 (bs, 1H).

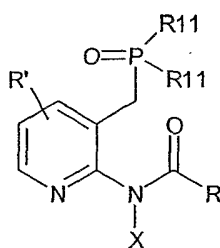
CLAIMS

1. A process for the production of a compound of formula I-2



I-2

comprising reacting a compound of formula I-1 with base



I-1

wherein X is hydrogen or a group COR;

R and R' are independently hydrogen, branched or unbranched alkyl (optionally interrupted by one or more of O-, -C(O)-, -N(R²)-, -S(O)- and -S(O₂)-), alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, reduced arylalkyl, arylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, reduced aryl, reduced heterocyclyl, reduced heterocyclylalkyl or a substituted derivative of any of the foregoing groups, wherein the substituents are one or more independently of halogen, alkyl, halosubstituted alkyl, aryl, arylalkyl, heterocyclyl, reduced heterocyclyl, reduced heterocyclylalkyl, arylalkoxy, cyano, nitro, -C(O)R², -CO₂R², -SOR², -SO₂R², SONR³R³, NR³SO₂R², NR³CO₂R², -NR³R³, -OR², -SR², -C(O)CX¹X²NR³R³, -C(O)N(OH)R³, -C(O)NR³R³, -NR³C(O)R², -CR²(NH₂)CO₂R², -NHCX¹X²CO₂R², -

$\text{N(OH)C(O)NR}^3\text{R}^3$, $-\text{N(OH)C(O)R}^2$, $-\text{NHC(O)NR}^3\text{R}^3$, $-\text{C(O)NHN}^3\text{R}^3$, $-\text{C(O)N(OR}^2\text{)R}^2$,

and where:-

- 5 R^2 is hydrogen, C_{1-12} alkyl or aryl, optionally substituted by one or more of C_{1-4} alkyl, halogen, C_{1-4} haloalkyl, OR^4 , SR^4 , NO_2 , CN , NR^4R^4 , NR^4COR^4 , $\text{NR}^4\text{CONR}^4\text{R}^4$, NR^4COR^4 , $\text{NR}^4\text{CO}_2\text{R}^4$, CO_2R^4 , COR^4 , CONR^4_2 , $\text{S(O)}_2\text{R}^4$, SONH_2 , S(O)R^4 , SO_2 NR^4R^4 , $\text{NR}^4\text{S(O)}_2\text{R}^4$, wherein the C_{1-12} alkyl group optionally incorporates one or more insertions selected from the group
- 10 consisting of $-\text{O}-$, $-\text{N(R}^4\text{)}-$, $-\text{S(O)}-$ and $-\text{S(O)}_2-$, wherein each R^4 may be the same or different and is as defined below;

- R^3 is C_{1-12} alkyl or aryl, optionally substituted by one or more of C_{1-4} alkyl, halogen, C_{1-4} haloalkyl, OR^4 , SR^4 , NO_2 , CN , NR^4R^4 , NR^4COR^4 , $\text{NR}^4\text{CONR}^4\text{R}^4$,
- 15 NR^4COR^4 , $\text{NR}^4\text{CO}_2\text{R}^4$, CO_2R^4 , COR^4 , CONR^4_2 , $\text{S(O)}_2\text{R}^4$, SONH_2 , S(O)R^4 , SO_2 NR^4R^4 , $\text{NR}^4\text{S(O)}_2\text{R}^4$, wherein the C_{1-12} alkyl group optionally incorporates one or more insertions selected from the group consisting of $-\text{O}-$, $-\text{N(R}^4\text{)}-$, $-\text{S(O)}-$ and $-\text{S(O)}_2-$, wherein each R^4 may be the same or different and is as defined below;

20

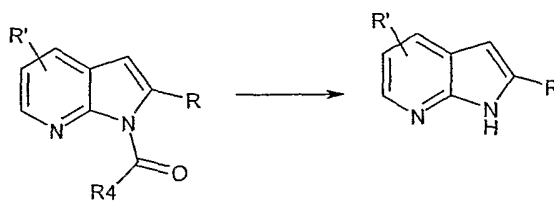
R^4 is hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl, aryl, or heterocyclyl;

- X^1 and X^2 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, arylalkyl, heterocyclylalkyl, reduced
- 25 heterocyclyl or reduced heterocyclylalkyl;

R^{11} is C_{1-12} alkyl, aryl, heterocyclyl or OR^{10} and R^{10} is C_{1-12} alkyl, aryl, or heterocyclyl.

2. A process as claimed in claim 1 wherein R is C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, phenyl, naphthyl, C₁₋₁₂ alkylphenyl, pyridinyl, furanyl, pyrrolyl, thiophenyl, C₁₋₁₂ alkylpyridinyl, optionally substituted with halogen, C₁₋₆ alkyl, CF₃, CCl₃, CH₂CH₂Br, phenyl, benzyl, pyridyl, methoxy, ethoxy, phenoxy, benzyoxy, cyano, nitro, C(O)R⁵, CO₂R⁵, SOR⁵, SO₂R⁵, SR⁵, NR⁵R⁵, CONR⁵R⁵ or NR⁵CO₂R⁵; wherein R⁵ is methyl, ethyl or propyl.
3. A process as claimed in claim 1 or claim 2 wherein R' is hydrogen, C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, halo, phenyl, naphthyl, C₁₋₁₂ alkylphenyl, pyridinyl, furanyl, pyrrolyl, thiophenyl, C₁₋₁₂ alkylpyridinyl, optionally substituted with halogen, C₁₋₆ alkyl, CF₃, CCl₃, CH₂CH₂Br, phenyl, benzyl, pyridyl, methoxy, ethoxy, phenoxy, benzyoxy, cyano, nitro, C(O)R⁵, CO₂R⁵, SOR⁵, SO₂R⁵, SR⁵, NR⁵R⁵, CONR⁵R⁵ or NR⁵CO₂R⁵ wherein R⁵ is methyl, ethyl or propyl.
4. A process as claimed in any one of claims 1 to 3 wherein R¹¹ is methyl, ethyl, propyl, butyl, pentyl, hexyl, phenyl, pyridyl or a group OR¹⁰, wherein R¹⁰ is methyl, ethyl, propyl, butyl, pentyl, hexyl, phenyl or pyridyl.
5. A process as claimed in any one of claims 1 to 4 wherein X is hydrogen or a group CO(CH₂)_nCH₃ or CO(CH₂)_ncycloalkyl wherein n is 0, 1, 2, 3, 4 or 5, or CO-phenyl or CO-pyridyl.
6. A process for the production of a compound of formula I-3 comprising deprotecting a compound of formula I-2 to produce a compound of formula I-3.

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5

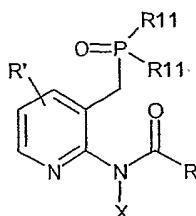
I-2

I-3

wherein R^1 and R are as defined in any one of claims 1 to 5.

7. A process for the production of a compound of formula I-1

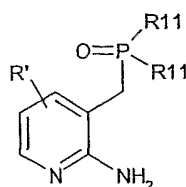
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15

I-1

comprising reacting a compound of formula II-5 with a group RCOY.



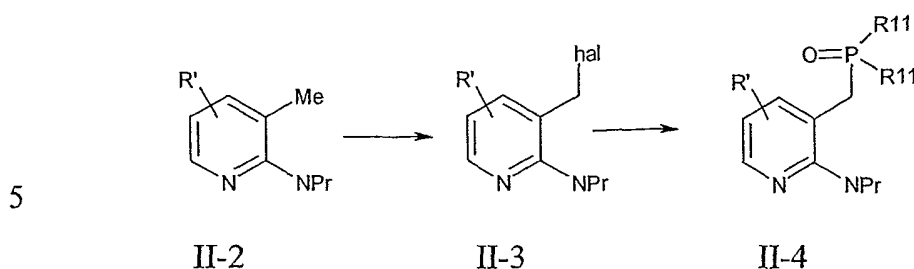
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II-5

wherein the groups R' , R and R^{11} are as defined in any one of claims 1 to 5,
and the group Y is OH, halide or OCOR.

25

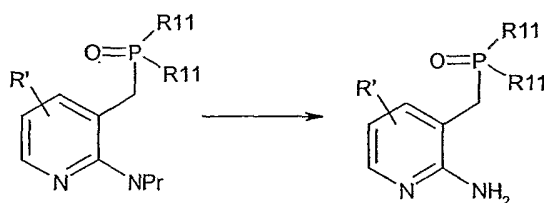
8. A process for the production of a compound of formula II-4



- 10 comprising halogenating a compound of formula II-2, to form a methyl-halo derivative II-3 and reacting the compound of formula II-3 with a phosphite $(R^{10}O)(R^{11})_2P$ to form a compound of formula II-4, wherein R^{11} is C_{1-12} alkyl, aryl or heterocyclyl or OR^{10} , R^{10} is C_{1-12} alkyl, aryl or heterocyclyl R^1 is as defined in any one of claims 1 to 5 and Pr is a protecting group.

9. A process for the production of a compound of formula II-5

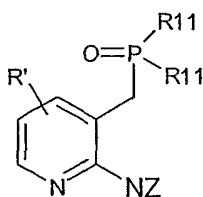
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- 20 comprising deprotecting the amino group of compound II-4, wherein R^{11} , Pv and R^1 are as defined in claim 8.

10. A compound of formula I-4,

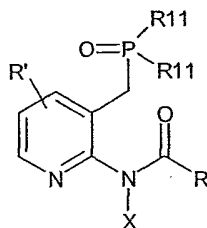
25



wherein the groups R' , and R^{11} are as defined in any one of claims 1 to 5 and the group Z is hydrogen or a protecting group selected from enzyloxycarbonyl, t-butyloxycarbonyl, 2-(4-biphenyl)-isopropoxycarbonyl, 9-fluorenylmethoxycarbonyl, triphenylmethyl, 2-nitrophenylsulphenyl or isoindole-dione.

11. A compound of formula I-1

10



wherein the groups R , R' , R^{11} and X are as defined in any one of claims 1 to 5.