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(54) Title: DERIVATIVES OF VARIOLIN B

(57) **Abrégé/Abstract:**

The invention provides antitumour compounds of formula (I), wherein R^1 is an aromatic substituent; R^2 is hydrogen or a substituent when the dotted line is absent, or R^2 is absent when the dotted line represents a bond to give a double bond between the nitrogen which bears R^2 and the carbon which bears R^3 ; R^3 is an oxo group = O when the dotted line is absent or is a substituent when the dotted line represents a bond to give a double bond between the nitrogen bearing R^2 and the carbon bearing R^3 ; R^4 is hydrogen or a substituent; and pharmaceutically acceptable salts thereof.

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(54) Title: DERIVATIVES OF VARIOLIN B

(57) Abstract: The invention provides antitumour compounds of formula (I), wherein R¹ is an aromatic substituent; R² is hydrogen or a substituent when the dotted line is absent, or R² is absent when the dotted line represents a bond to give a double bond between the nitrogen which bears R² and the carbon which bears R³; R³ is an oxo group = O when the dotted line is absent or is a substituent when the dotted line represents a bond to give a double bond between the nitrogen bearing R² and the carbon bearing R³; R⁴ is hydrogen or a substituent; and pharmaceutically acceptable salts thereof.

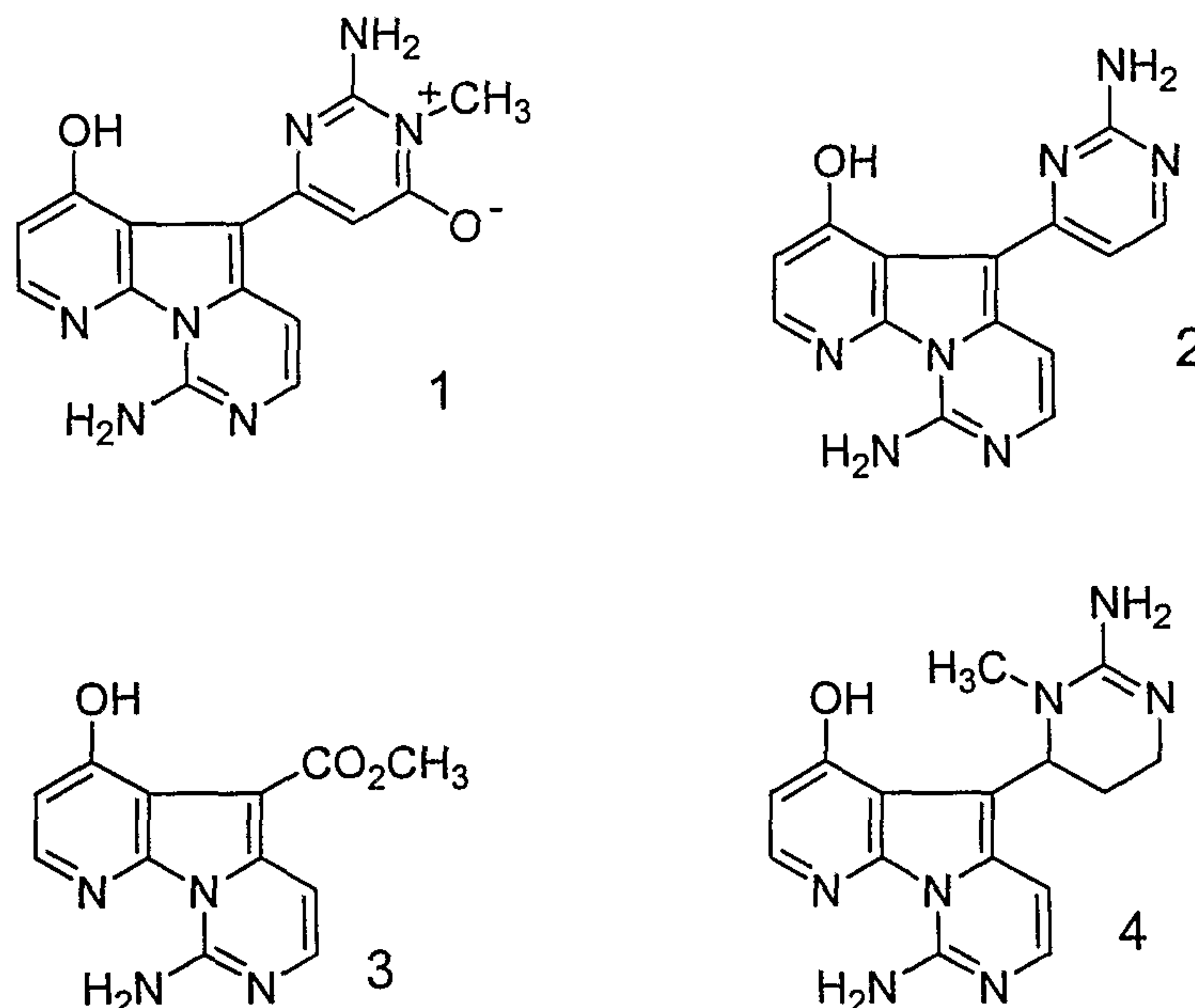


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Derivatives of variolin B

The present invention relates to derivatives of variolin B.

Variolin A (1), variolin B (2), variolin D (3) and N (3')-methyl tetrahydrovariolin B (4) are a small group of marine heterocyclic substances isolated from the Antarctic sponge *Kirkpatrickia variolosa* in 1994, see Tetrahedron 1994, 50, 3987-3992 and Tetrahedron 1994, 50, 3993-4000. They have a common tricyclic skeleton, a pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine. This structure has no precedent in either terrestrial or marine natural products. Previously only a couple of papers described synthetic related structures, see Chem. Ber. 1974, 107, 929-936 and Tetrahedron Lett. 2000, 41, 4777-4780.



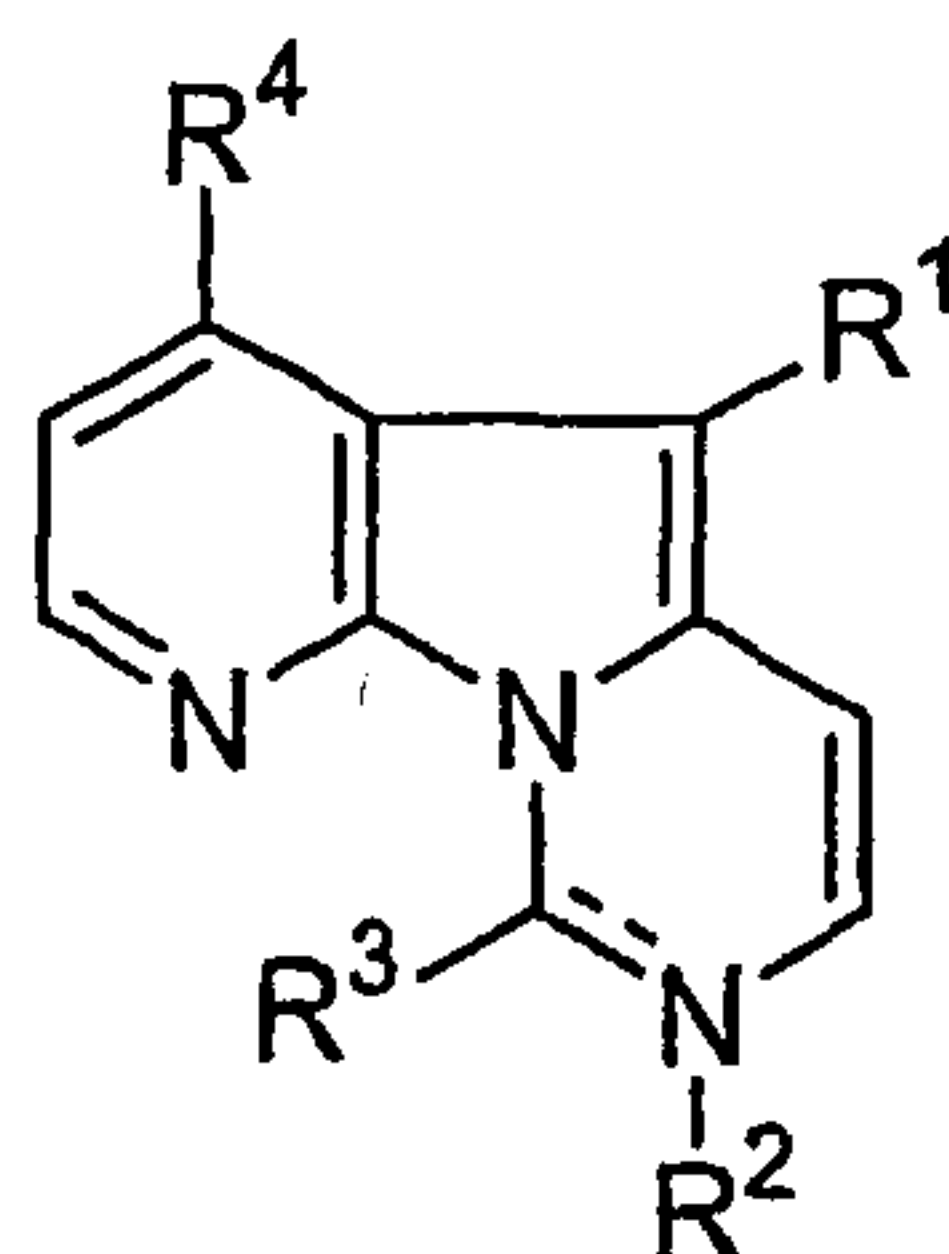
An important feature of these compounds is their bioactivity: variolin B is the most active, having cytotoxic activity against the P388 cell line, and also being effective against *Herpes simplex*; it was inactive against a range of other microorganisms, see Tetrahedron 1994, 50, 3987-3992. Variolin A also showed important cytotoxic activity against the P388 cell line. N(3')-methyltetrahydrovariolin B inhibited the growth of *Sacharomyces cerevisiae* and showed *in vitro* activity against the HCT 116 cell line. Variolin D was inactive in all the

assays. The differential activity of these alkaloids is believed to show the biological importance of the aminopyrimidine ring in (2), the oxidised form in (1) and the reduced pyrimidine in (4), as opposed to the methoxycarbonyl substituent in variolin D (3).

With this invention we provide deoxyvariolin compounds which possess cytotoxic activity and are expected to be useful as antitumour agents.

Summary of the Invention

According to one embodiment, the present invention provides a compound of the formula (I):



wherein:

R^1 is an aromatic substituent;

R^2 is hydrogen or a substituent when the dotted line is absent, or R^2 is absent when the dotted line represents a bond to give a double bond between the nitrogen which bears R^2 and the carbon which bears R^3 ;

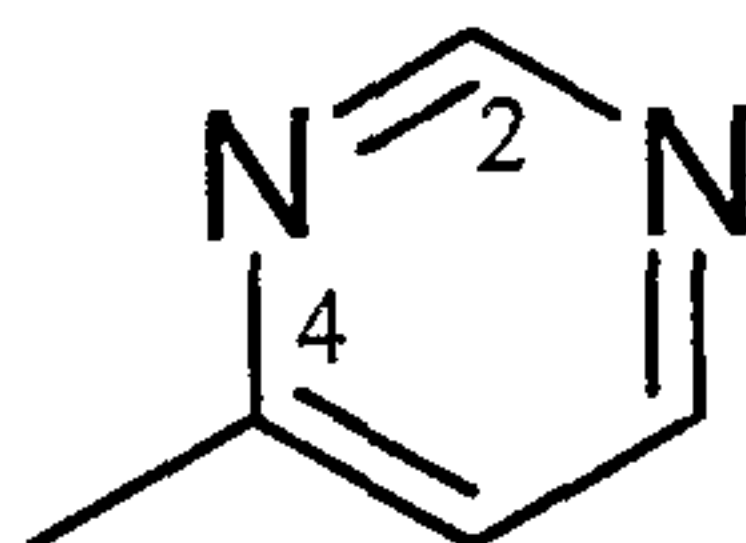
R^3 is an oxo group $=O$ when the dotted line is absent or is a substituent when the dotted line represents a bond to give a double bond between the nitrogen bearing R^2 and the carbon bearing R^3 ;

R^4 is hydrogen or a substituent; or

a pharmaceutically acceptable salt thereof.

The group R^1 is typically an aromatic ring of 4 to 10 ring atoms, more preferably 5, 6 or in ring atoms, and most preferably 6 ring atoms. Fused ring systems are permitted by the present invention. The ring can have one or more heteroatoms, and suitably then has 1 to 3 ring heteroatoms chosen from nitrogen, oxygen or sulphur, especially 2 heteroatoms. Particularly

preferred are nitrogen heteroatoms, and R^1 is for example a pyrimidine ring, especially a 4-pyrimidyl substituent, that is a group of formula:



The aromatic ring can be substituted, as for example with one or more groups chosen from alkyl, alkoxy, thioalkyl, halo, amino, substituted amino, haloalkyl, alkoxyalkyl, aryl, hydroxy, carboxy, alkoxycarbonyl or other conventional groups including mesyl groups. Other groups are given later in this text which may be used as substituents.

R^2 when present is preferably hydrogen, a nitrogen protecting group, or some other substituent. Examples of nitrogen protecting groups such as methoxymethyl or tosyl are well known and do not need to be given in detail. Examples of other substituents include any group which can be substituted at this position by reaction of the compound where R^1 is hydrogen. More generally, reference is made to the other groups given later in this text.

R^3 is an oxo group or can be a substituent such as might be introduced by reaction of the oxo compound, including amino, substituted amino including protected amino, thioalkyl. More generally, reference is made to the other groups given later in this text.

R^4 is hydrogen or a substituent such as alkoxy especially methoxy, hydroxy, halo especially chloro, or other group which might be introduced by nucleophilic substitution or by other derivatisation, including thioalkyl or mesyl. When R^4 is hydrogen, the compounds are deoxyvariolin B derivatives. When R^4 is hydroxy, the compounds are variolin B derivatives. More generally, reference is made to the other groups given later in this text.

R^1 is preferably a 4-pyrimidyl group substituted at the 2-position. Suitable substituents include an amino group and derivatives thereof such as N-acyl, especially N-acetyl. Other nucleophilic substituents are envisaged, such as alkoxy or alkylthio substituents, especially a methylthio group.

R^2 is preferably absent.

R^3 is preferably an amino group and derivatives thereof such as N-acyl, especially N-acetyl.

R^4 is preferably hydrogen.

The dotted line preferably represents a bond.

A particularly preferred class of compounds includes those compounds of the formula (I) wherein:

R^1 is a 4-pyrimidyl group substituted at the 2-position with amino, N-acyl especially N-acetyl, alkylthio especially a methylthio group, alkyl- or aryl-sulphinyl especially methanesulphinyl, or alkyl- or aryl-sulphonyl especially methanesulphonyl;

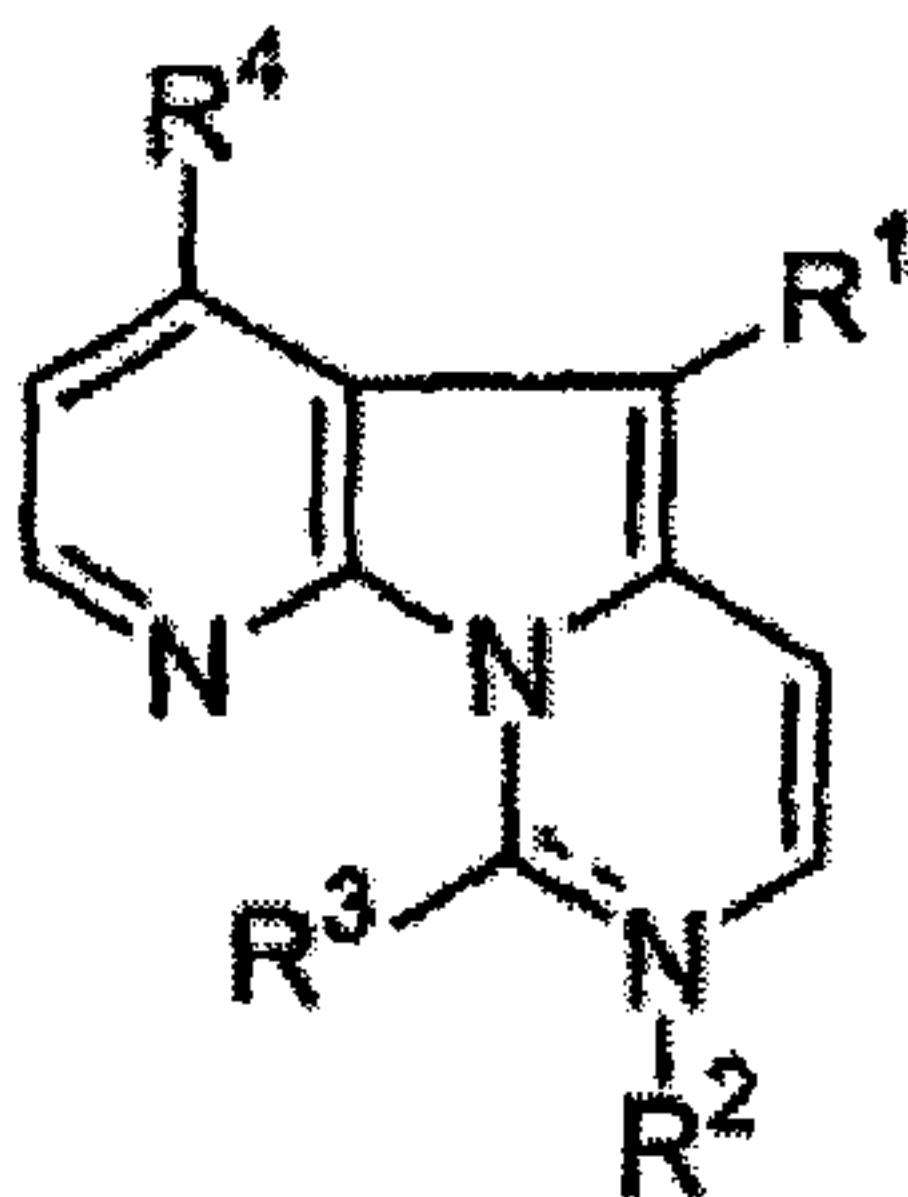
R^2 is absent;

R^3 is an optionally protected amino group or N-acyl, especially N-acetyl; and

R^4 is hydrogen, hydroxy or methoxy.

The invention also extends to pharmaceutically acceptable salts.

According to another embodiment of the present invention there is provided a compound of the formula (I):



wherein:

R^1 is an aromatic substituent of 4 to 10 ring atoms, which is optionally substituted with one or more groups chosen from alkyl, alkoxy, thioalkyl, halo, amino, N-acylamino, haloalkyl, alkoxyalkyl, aryl, hydroxy, carboxy, or alkoxycarbonyl;

4a

R^2 is hydrogen or a nitrogen protecting group when the dotted line is absent, or R^2 is absent when the dotted line represents a bond to give a double bond between the nitrogen which bears R^2 and the carbon which bears R^3 ;

R^3 is an oxo group $=O$ when the dotted line is absent, or is an amino group or a N-acylamino group when the dotted line represents a bond to give a double bond between the nitrogen bearing R^2 and the carbon bearing R^3 ;

R^4 is hydrogen;

or a pharmaceutically acceptable salt thereof.

According to another embodiment, a pharmaceutical composition comprising a compound of the present invention is provided.

According to a further embodiment, the use of a compound of the present invention in the treatment of cancer is also provided. Preferably, the present invention provides for the use of variolin B or a pharmaceutically acceptable salt thereof for the treatment of non-small cell lung cancer.

Examples of substituents which may be employed in the present invention include OH, OR', SH, SR', SOR', SO₂R', NH₂, NHR', N(R')₂, NHCOR', N(COR')₂, NHSO₂R', C(=O)R', CO₂H, CO₂R', C₁-C₁₂ alkyl and C₁-C₁₂ haloalkyl, the or each group R' being independently selected from the group consisting of OH, C₁-C₁₂ alkyl, C₁-C₁₂ haloalkyl, aryl (which may optionally be substituted with a group selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, NH₂, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, NO₂, CN and halogen), aralkyl or arylalkenyl (the aryl moiety of which may optionally be substituted with a group selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, NH₂, C₁-C₆ alkylamino, di(C₁-C₆ alkyl)amino, NO₂, CN and halogen), and wherein the group R₁ is a group of formula N(R')₂ or N(COR')₂, each of the R' groups may be the same or different, or the two R' groups, together with the nitrogen atom to which they are attached, form a 5-12 membered heterocyclic ring.

In the definitions used in the present specification, alkyl groups may be straight or branched chain groups and preferably have from 1 to about 12 carbon atoms, more preferably 1 to about 8 carbon atoms, still more preferably 1 to about 6 carbon atoms, and most preferably 1, 2, 3 or 4 carbon atoms. Methyl, ethyl and propyl including isopropyl are particularly preferred alkyl groups in the compounds of the present invention. As used herein, the term alkyl, unless otherwise modified, refers to both cyclic and noncyclic groups, although cyclic groups will comprise at least three carbon ring members.

Haloalkyl groups are alkyl groups (including cycloalkyl groups) as defined above which are substituted with one or more halogen atoms (preferably fluorine, chlorine, bromine or iodine) and preferably have from 1 to about 12 carbon atoms, more preferably 1 to about 8 carbon atoms, still more preferably 1 to about 6 carbon atoms, and most preferably 1, 2, 3 or 4 carbon atoms. Methyl, ethyl and propyl including isopropyl groups which are substituted with 1, 2 or 3 halogen atoms which may be the same or different, especially fluoromethyl, fluorochloromethyl, trifluoromethyl and trichloromethyl, are particularly preferred haloalkyl groups in the compounds of the present invention.

Preferred alkenyl and alkynyl groups in the compounds of the present invention have one or more unsaturated linkages and from 2 to about 12 carbon atoms, more preferably 2 to about 8 carbon atoms, still more preferably 2 to about 6 carbon atoms, even more preferably 2, 3 or 4 carbon atoms. The terms alkenyl and alkynyl as used herein refer to both cyclic and noncyclic groups, although straight or branched noncyclic groups are generally more preferred.

Preferred alkoxy groups in the compounds of the present invention include groups having one or more (but preferably only one) oxygen linkages and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms, and most preferably 1, 2, 3 or 4 carbon atoms.

Preferred alkylthio groups in the compounds of the present invention have one or more (but preferably only one) thioether linkages and from 1 to about 12 carbon atoms, more preferably

from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms.

Alkylthio groups having 1, 2, 3 or 4 carbon atoms are particularly preferred.

Preferred alkylsulfinyl groups in the compounds of the present invention include those groups having one or more sulfoxide (SO) groups and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Alkylsulfinyl groups having 1, 2, 3 or 4 carbon atoms are particularly preferred.

Preferred alkylsulfonyl groups in the compounds of the present invention include those groups having one or more sulfonyl (SO₂) groups and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Alkylsulfonyl groups having 1, 2, 3 or 4 carbon atoms are particularly preferred.

Preferred alkanoyl groups in the compounds of the present invention include those groups having one or more carbonyl (CO) groups and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms (including the carbonyl carbon). Alkanoyl groups having 1, 2, 3 or 4 carbon atoms, especially the formyl, acetyl, propionyl, butyryl and isobutyryl groups, are particularly preferred.

Preferred alkylamino groups in the compounds of the present invention have one or more (but preferably only one) NH linkages and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Alkylamino groups having 1, 2, 3 or 4 carbon atoms, especially the methylamino, ethylamino, propylamino and butylamino groups, are particularly preferred.

Preferred dialkylamino groups in the compounds of the present invention have one or more (but preferably only one) nitrogen atom bonded to two alkyl groups, each of which may from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. The alkyl groups may be the same or different. Dialkylamino groups wherein each alkyl group has 1, 2, 3 or 4 carbon atoms, especially the dimethylamino, diethylamino, N-methylethylamino, N-ethylpropylamino, dipropylamino,

dibutylamino and N-methylbutylamino groups, are particularly preferred.

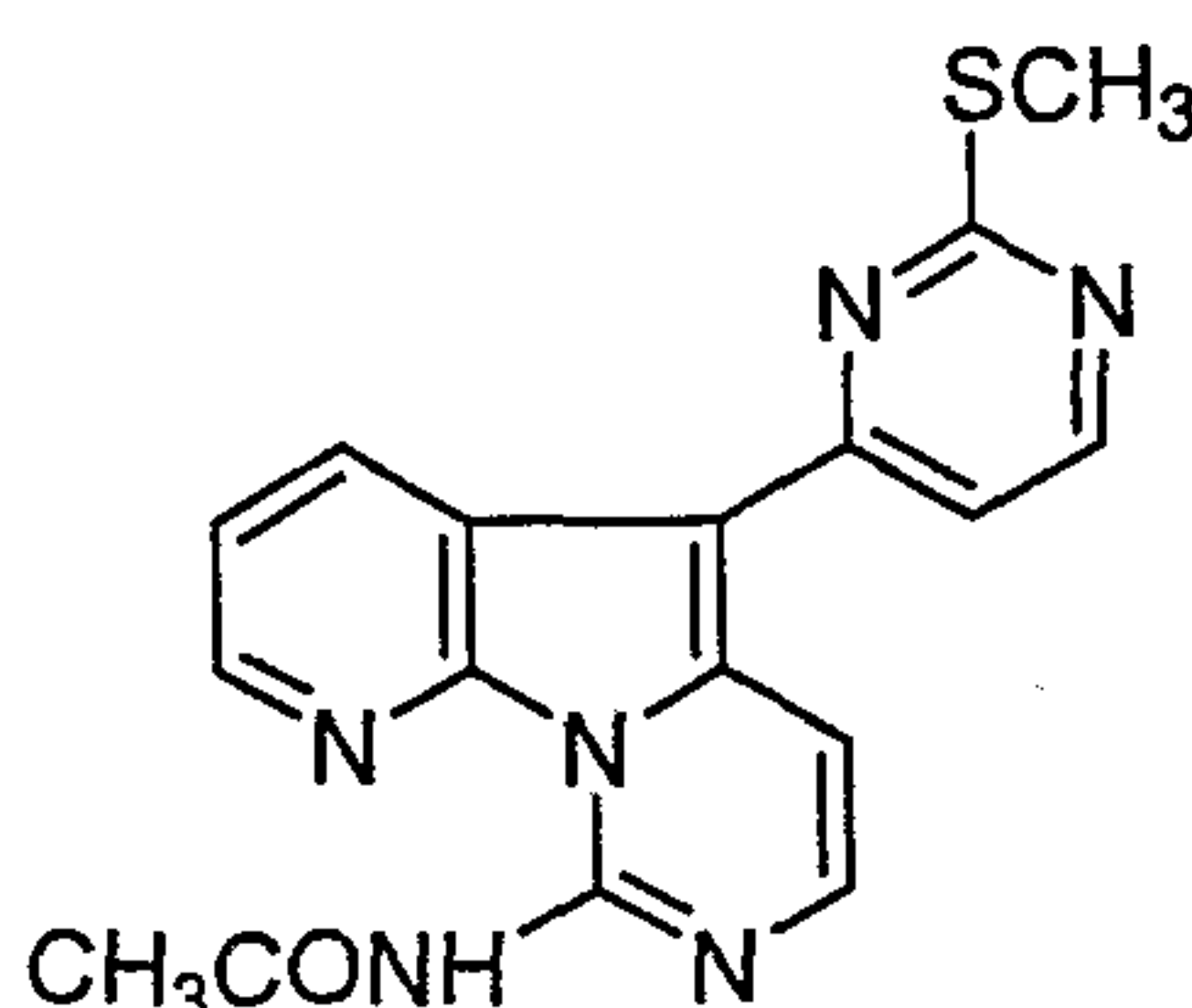
Preferred alkanoylamino groups in the compounds of the present invention have one NH-CO-linkage bonded to an alkyl group having from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms.

Alkanoylamino groups having 1, 2, 3 or 4 carbon atoms, especially the formylamino, acetylamino, propionylamino and butyrylamino groups, are particularly preferred. The acetylamino group is especially preferred.

Preferred dialkanoylamino groups in the compounds of the present invention have one nitrogen atom bonded to two alkanoyl groups as defined above, each of which may be the same or different and has from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Dialkanoylamino groups wherein each alkanoyl group has 1, 2, 3 or 4 carbon atoms, especially the diformylamino, formylacetylamino, diacetylamino, dipropionylamino and dibutyrylamino groups, are particularly preferred. The diacetylamino group is especially preferred.

Preferred alkylsulfonylamino groups in the compounds of the present invention have one NH-SO₂- linkage bonded to an alkyl group having from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Alkylsulfonylamino groups having 1, 2, 3 or 4 carbon atoms, especially the methanesulfonylamino, ethanesulfonylamino, propanesulfonylamino and butanesulfonylamino groups, are particularly preferred.

Examples of particular compounds of this invention include the compounds (1), (2), (5), (16), (18) and (21) in the following pages, as well the compound we now designate (20a) which in Scheme 4 is intermediate between compound (20) and (21), where R² is absent, R³ is acetamido, R⁴ is hydrogen and R¹ is 2-methylthiopyrimidin-4-yl, being a compound of formula:



The present invention further provides pharmaceutical compositions comprising a compound of this invention with a pharmaceutically acceptable carrier, and the use of the compounds of this invention in the preparation of a medicament. Methods of treatment are also provided.

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules, etc.) or liquid (solutions, suspensions or emulsions) with suitable composition or oral, topical or parenteral administration, and they may contain the pure compound or in combination with any carrier or other pharmacologically active compounds. These compositions may need to be sterile when administered parenterally.

Administration of the compounds or compositions of the present invention may be by any suitable method, such as intravenous infusion, oral preparations, intraperitoneal and intravenous administration. We prefer that infusion times of up to 24 hours are used, more preferably 2-12 hours, with 2-6 hours most preferred. Short infusion times which allow treatment to be carried out without an overnight stay in hospital are especially desirable. However, infusion may be 12 to 24 hours or even longer if required. Infusion may be carried out at suitable intervals of say 2 to 4 weeks. Pharmaceutical compositions containing compounds of the invention may be delivered by liposome or nanosphere encapsulation, in sustained release formulations or by other standard delivery means.

The correct dosage of the compounds will vary according to the particular formulation, the mode of application, and the particular situs, host and tumour being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

The present invention further provides pharmaceutical formulations for combination therapy, comprising a compound of this invention and at least one other therapeutically active compound. The other compound can have antitumour activity, or can have some other activity of use in conjunction with the antitumour activity of the compounds of this invention.

The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or a different time. The identity of the other drug is not particularly limited, and suitable candidates include:

- a) drugs with antimetabolic effects, especially those which target cytoskeletal elements, including microtubule modulators such as taxane drugs (such as taxol, paclitaxel, taxotere, docetaxel), podophylotoxins or vinca alkaloids (vincristine, vinblastine);
- b) antimetabolite drugs such as 5-fluorouracil, cytarabine, gemcitabine, purine analogues such as pentostatin, methotrexate);
- c) alkylating agents such as nitrogen mustards (such as cyclophosphamide or ifosfamide);
- d) drugs which target DNA such as the anthracycline drugs adriamycin, doxorubicin, pharmorubicin or epirubicin;
- e) drugs which target topoisomerases such as etoposide;
- f) hormones and hormone agonists or antagonists such as estrogens, antiestrogens (tamoxifen and related compounds) and androgens, flutamide, leuprorelin, goserelin, cyprotrone or octreotide;
- g) drugs which target signal transduction in tumour cells including antibody derivatives such as herceptin;
- h) alkylating drugs such as platinum drugs (cis-platin, carbonplatin, oxaliplatin, paraplatin) or nitrosoureas;
- i) drugs potentially affecting metastasis of tumours such as matrix metalloproteinase inhibitors;
- j) gene therapy and antisense agents;
- k) antibody therapeutics;
- l) other bioactive compounds of marine origin, notably the didemnins such as aplidine or the ecteinascidins such as Et 743;
- m) anti-emetic drugs, in particular dexamethasone.

The cytotoxicity of the compounds of scheme 4 of this invention is illustrated by the following IC₅₀ μ M data:

compound	P-388	A-549	HT-29
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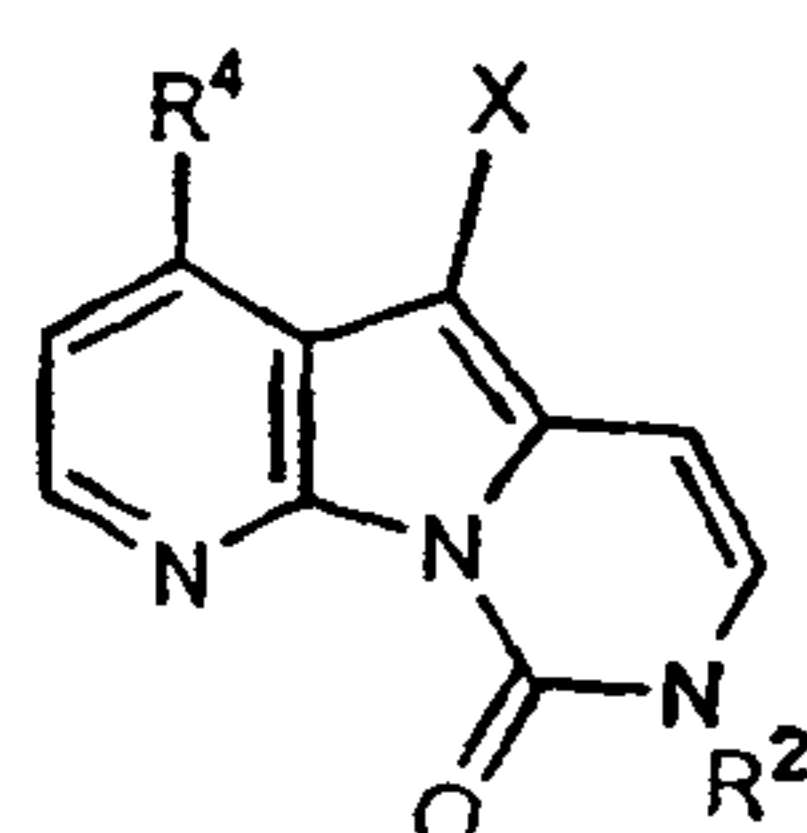
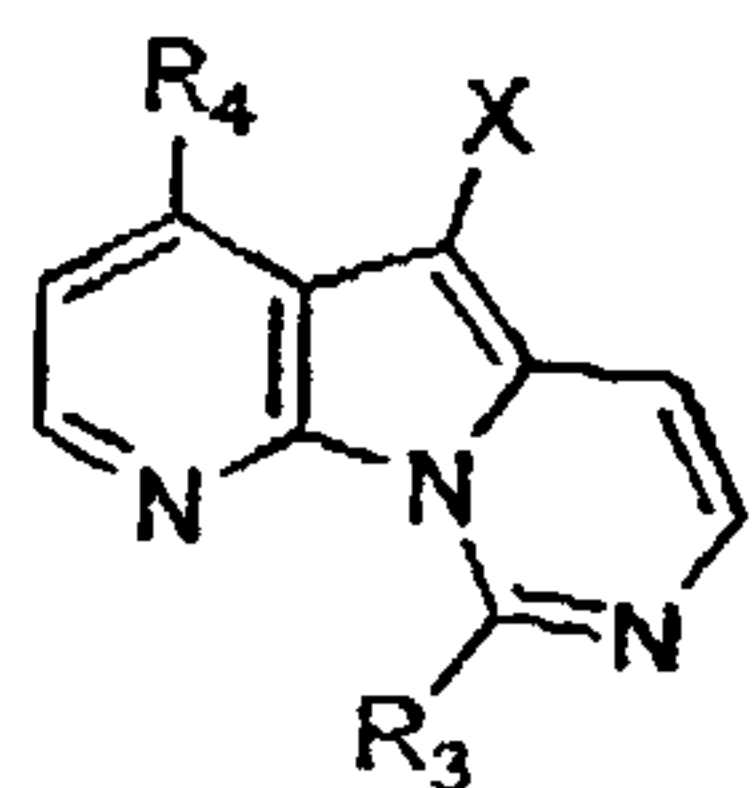
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5	0.36	0.04	0.04
21	>3	0.16	0.16
20a	>3	0.29	0.29
variolin B	0.85	0.17	0.09

The invention also extends to a synthesis of the compounds, starting from a 7-azaindole or at a later stage. Preparation of the tricyclic pyridopyrrolopyrimidones (11) was achieved starting from a 7-azaindole by lithiation at carbon 2, introduction of a C₂-side chain, then cyclization. A heteroaryl coupling reaction was used for the introduction of the fourth aromatic ring.

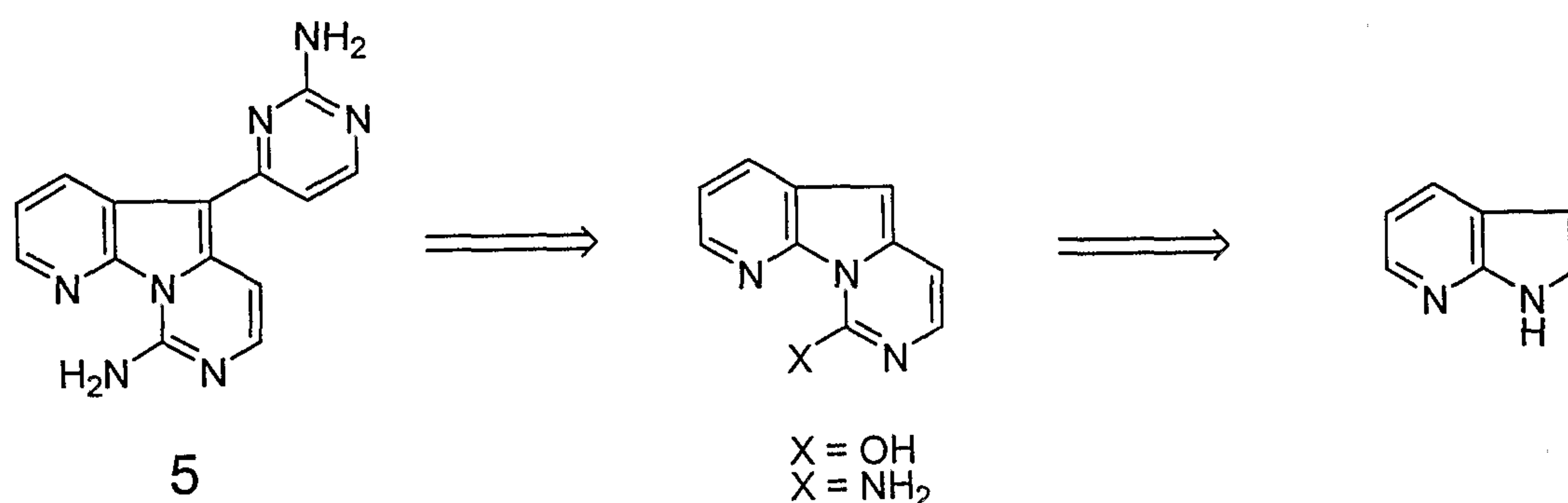
Thus, according to the present invention, there is provided a method for preparing the compounds of this invention which involves reaction of an optionally substituted 5-halopyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine or 8,9-dihydro-5-halopyrido[3',2':4,5]-pyrrolo[1,2-c]pyrimid-9-one with a derivatised aromatic compound such as a stannylaryl compound, notably a trimethylstannylaryl compound, especially a trimethylstannylpyrimidine derivative. The resultant product can be further reacted to change substituent groups. Amino or other reactive substituents in the starting compound can be protected and thereafter deprotected.

Preferred intermediate compounds of this invention are thus of formula:



X is halo and R^2 , R^3 and R^4 are as defined, particularly wherein X is iodo, R^2 is a protecting group, R^3 is a protected amino group, and R^4 is hydrogen, hydroxy or methoxy.

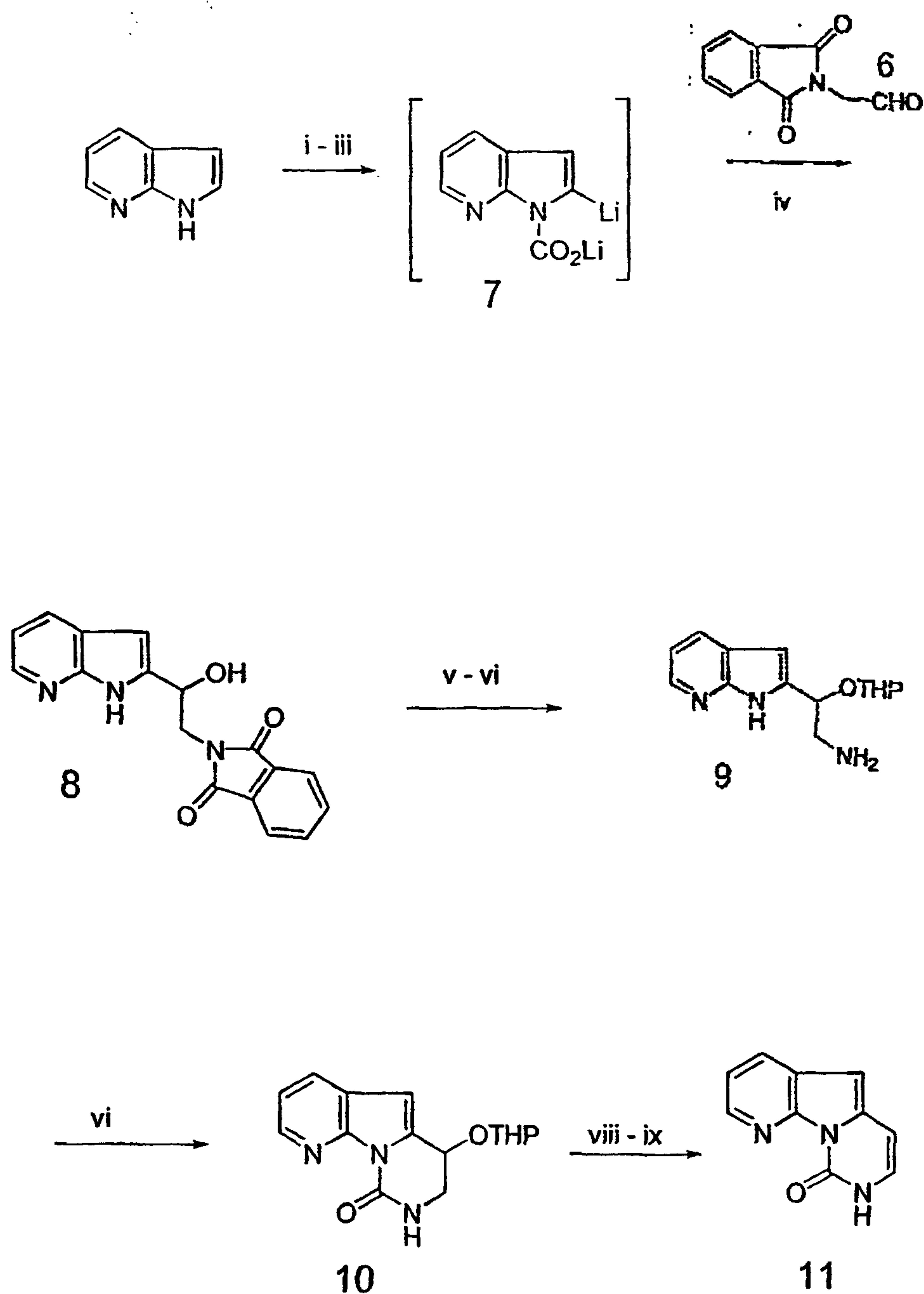
Our synthetic approach to variolin B has been developed using deoxyvariolin B (5) as a target. We show our retrosynthesis which is based on the preparation of the common pyridopyrrolopyrimidine tricyclic system from a 7-azaindole. The key step is a heteroaryl coupling catalysed by Pd(0) for the introduction of the pyrimidine substituent.



The introduction of a functionalised two-carbon chain at the 2-position of 7-azaindole, see J. Org. Chem. 1965, 30, 2531-2533, was achieved by reaction of a 2-lithio-derivative with 2-phthalimidoacetaldehyde (6), itself obtained in 75% yield from 2-aminoacetaldehyde dimethylacetal by protection of the amino group by reaction with phthalic anhydride in CH₂Cl₂ at 140°C for 15 minutes followed by hydrolysis of the acetal group with 10% HCl at reflux. Lithiation of a 7-azaindole had previously been described only for its N-phenylsulphonyl derivative, see Tetrahedron, 1997, 53, 3637-3648. We used the method described by Katritzky, see J. Am. Chem. Soc. 1986, 108, 6808-6809, involving 2-lithiation of the 1-carboxylic acid lithium salt, formed *in situ*, because we found the yield to be superior to that using the 1-phenylsulphonyl-7-azaindole and additionally, the two separate steps of introduction and removal of the N-protecting group are avoided. Thus, reaction of the bislithio-derivative (7) with aldehyde (6) afforded the alcohol (8) in 44% yield. Protection of the alcohol as a tetrahydropyranyl ether gave a diastereomeric mixture which was not

separated because both stereogenic centers are lost later in the synthesis. Hydrazinolysis of the phthalimide residue yielded the amine (9) quantitatively, and this was converted into tetrahydropyrimidone (10) in 76% yield on treatment with triphosgene in CH_2Cl_2 with diisopropyl ethylamine (DIPEA) as base. The dihydro-pyrimidone (11) was obtained after removing the hydroxy-protecting group by acid hydrolysis followed by dehydration of the alcohol via the mesylate (Scheme 1).

Scheme 1: Synthesis of pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidin-1-one (11)⁹

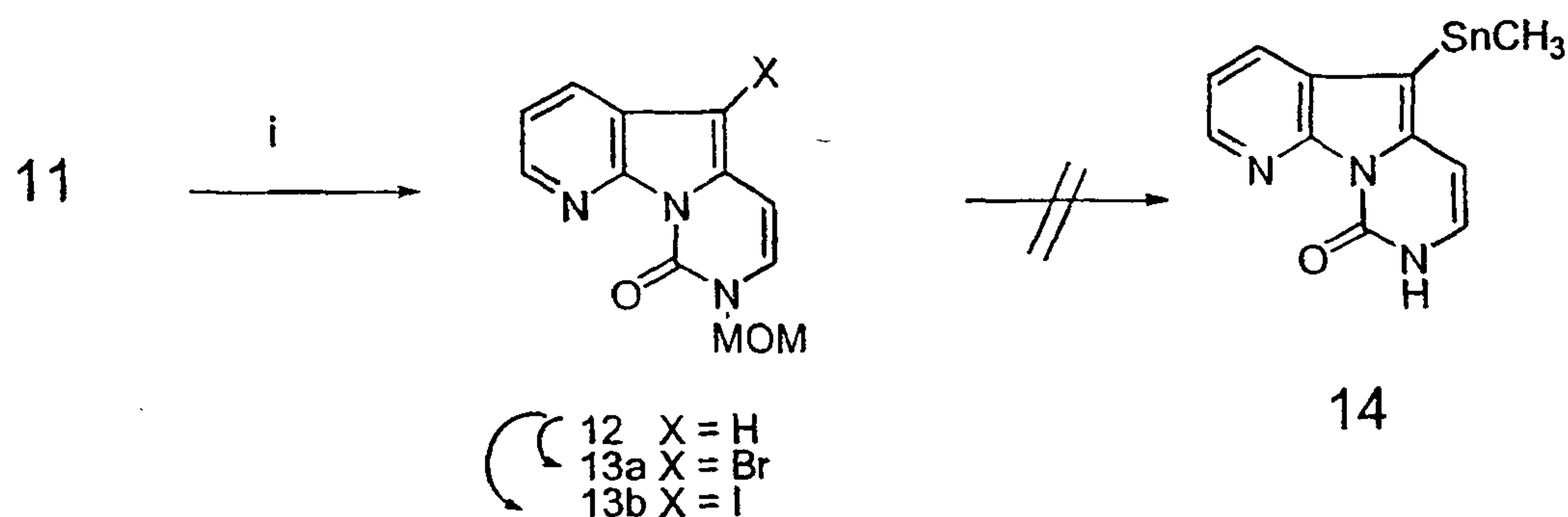


- i: n-BuLi, THF, -78°C to rt;
- ii: CO₂, -78°C;
- iii: t-BuLi, THF, -78°C;
- iv: 5 THF, -78°C to rt (44%);
- v: DHP, HCl-benzene, CHCl₃, (87%);
- vi: NH₂NH₂. H₂O, EtOH, (100%);
- vii: (C₁₃CO)₂CO, DIPEA, CH₂Cl₂, rt (76%);
- viii: 4N HCl, CH₂Cl₂ (100%);
- ix: MsCl, TEA, CH₂Cl₂, 0°C (95%)

With our previous experience in the heteroaryl coupling with 7-azaindole, see Synthesis 1999, 615-620, and in the lithiation of dihydropyrrolo[1,2-c]pyrimidin-1-ones, see J. Soc. Chem. Perkin Trans. I, 1999, 249-255, we planned the preparation of the tin derivative (14) from the protected halo-derivative (13). Protection of the tricyclic pyrimidone (11) was achieved with methyl chloromethyl ether using sodium hydride as base in DMF giving (12). Halogenation of (12) using N-bromosuccinimide (NBS) or iodine in potassium hydroxide afforded (13a) (80%) and (13b) (62%) respectively. That the halogen had been introduced at C-5 was confirmed by comparison of ¹H-NMR spectra: the H-5 singlet at δ 6.41 ppm present in (12) was not present in the spectra of (13a) and (13b). Unfortunately we were unable to isolate a tin derivative (14), for example treatment of (13a) with butyllithium then quenching with trimethyltin chloride, see Synthesis 1999, 615-620, gave a complex mixture which it was not possible to resolve. Attempted iodine-tin interchange by treatment of (13b) with hexamethylditin catalysed with Pd(PPh₃)₄ in dioxane afforded a mixture of (14) and (12) in a ratio of 7:3 but isolation of 14 by column chromatography failed.

Scheme 2

14



i: MOMCl, NaH, DMF, 0°C (87%);

ii: NBS, CH₂Cl₂, 0°C (80%);

ii: I₂, KOH, DMF, 0°C (62%)

We changed the strategy for the coupling reaction using now the trimethylstannylpyrimidine (15) and the iodo-7-azaindole (13b). The preparation of pyrimidine (15), see Tetrahedron 1989, 45, 993-1006, was improved using Pd(OAc)₂ and PPh₃ in THF and by reduction of the amount TBAF and the reaction time in comparison with the previously described work.



A solution of iododerivative (1 mmol), (15) (3 mmol), catalyst A or B, LiCl (3 mmol) in dioxane (20 ml) was refluxed for 5 hours. The solvent was evaporated and the residue purified by flash column chromatography. The coupling reaction between (13b) and (15) gave in all the experimental conditions a mixture of (12) and (16) which were impossible to separate (Table 1).

Table 1. Coupling reaction between (13b) and (15) in dioxane.

(15)/(13b) ^a	Catal/Lig ^b	LiCl/CuI ^c	16/12 ^d	% ^e
1.1	A	3 / --	2 : 1	56
1.2	B	3 / --	2 : 1	52
2	B	3 / 0.1	3 : 1	53

a: molar ratio;

b: A = Pd(PPh₃)₄, 0.1 equivalent; B = Pd₂(dba)₃ 0.1 equivalent and PPh₃ 0.2 equivalent;

c: relative to 1 equivalent of 13b;

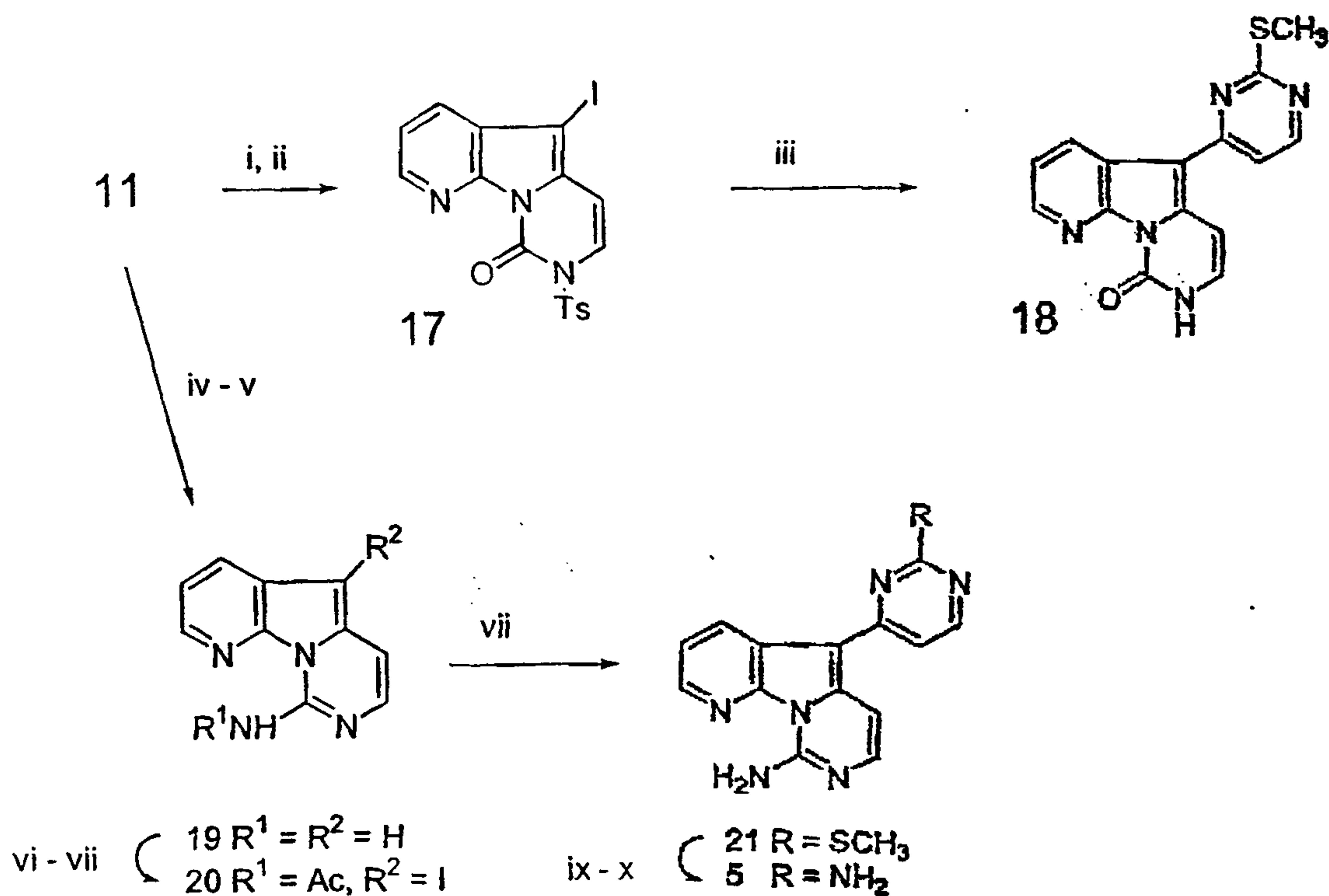
d: ratio measured by ¹H-NMR;

e: yield of (16) calculated from the crude reaction mixture by ¹H-NMR.

Because the difficulties of purification of (16) we tried with a new protecting group. The iodo compound (17) which differs of (13b) in the protecting group was synthesised by reaction of (11) with tosyl chloride and sodium hydride in DMF followed by iodination with NIS.

The coupling reaction between (17) and the trimethylstannylpyrimidine (15) afforded the tetracyclic compound (18) but only in 10% yield even using the best reaction conditions shown in Table 1 for the coupling between (13b) and (15).

Scheme 4. Synthesis of deoxyvariolin B

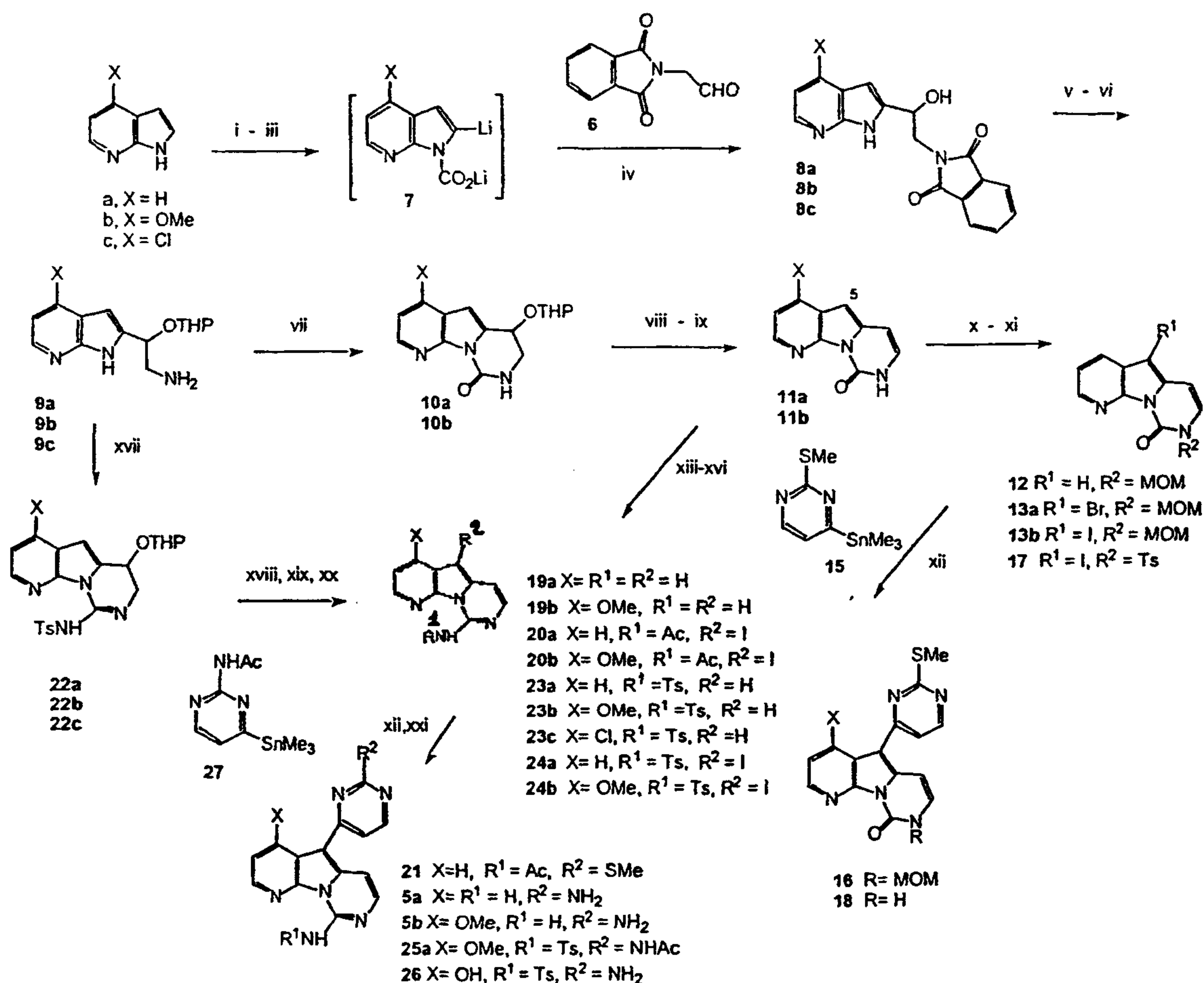


- i: TsCl, NaH, DMF (40%);
 ii, NIS. CHCl₃, rt (80%);
 iii: 15, Pd₂(dba)₃, PPh₃, LiCl, CuI (10%);
 iv: TMSCl, HMDSA, 2,6-lutidine;
 v: NH₃, 150°C, 60psi (30% two steps);
 vi: Ac₂O, THF (75%);
 vii: NIS. CHCl₃ (95%);
 viii: iii then HCl-MeOH, (45%);
 ix: MCPBA, CH₂Cl₂, 0°C (90%);
 x: NH₄OH, dioxane, 80°C (90%)

Next approximation was the change of functionalization of the C ring by transformation of the pyrimidone (11) into the iodoanilopyrimidine (20). The amino-derivative 19 was produced by O-silylation of (11) with TMSCl and hexanethyldisilazane (HMDSA) as silylating agent, followed by nucleophilic substitution with ammonia, see Lebgs Ann. Chem., 1975, 988-1002. Acylation of amine (19) and halogenation on the free position of the π -rich ring was proceeded in an excellent yield.

The heteroaryl coupling between (20) and (15) with the same reaction conditions and catalyst as before gave a mixture of acylated and deprotected amines which by methanolysis with dry HCl in methanol yielded the amine (21) in a 45% yield. Deoxyvariolin B (5) was prepared by substitution of the methylthio group of the new pyrimidine ring for an amino group. Oxidation of (21) using *m*-chloroperbenzoic acid followed by substitution of the resulting sulphone for an amino group using ammonium hydroxide afforded (5) in excellent yield, see Tetrahedron 1989, 45, 993-1006 and Katrizky, A. R.; Rees, C. W. Comprehensive Heterocyclic Chemistry, Pergamon Press, Oxford, 1984, vol. 3, page 111.

A more general synthetic scheme is:



Reagents:

i: *n*-BuLi, THF, -78°C to rt;

ii: CO₂, -78°C;

- iii: *t*-BuLi, THF, -78°C;
- iv: **6**, THF, -78°C to rt ;
- v: DHP, HCl, benzene, CHCl₃, Δ;
- vi: NH₂NH₂.H₂O, EtOH, Δ;
- vii: (Cl₃CO)₂CO, DIPEA, CH₂Cl₂, rt ;
- viii: 4N HCl, CH₂Cl₂;
- ix: MsCl, TEA, CH₂Cl₂, 0°C ;
- x: MOMCl or TsCl, NaH, DMF, 0°C;
- xi: NBS / NIS, CH₂Cl₂, 0°C or I₂, KOH, , 0°C;
- xii: **15**, Pd₂(dba)₃, PPh₃, LiCl, CuI, dioxane, Δ;
- xiii: TMSCl, HMDSA, lutidine, D;
- xiv: NH₃, 150°C, 60 psi;
- xv: Ac₂O, THF, r.t;
- xvi: NIS, CHCl₃, 0°C;
- xvii: TsN=CCl₂, DIPEA, CH₂Cl₂, r.t;
- xviii: 4N HCl, CHCl₃, r.t;
- xix: MsCl, TEA, CH₂Cl₂, rt;
- xx: NIS, CHCl₃, -30 °C;
- xxi: dry MeOH- HCl or 48% HBr, Δ.

The tricyclic comp. **11b** (X = OMe) was prepared from 4-methoxy-7-azaindole, see *J. Heterocyclic Chem.* **1989**, 26, 317, following the same way as the used for **11a**. Transformation of **11b** in **19b** was produced with only a 22 % yield by by *O*-silylation with trimethylsilyl chloride (TMSCl) and hexamethyldisilazane (HMDSA) hexamethyldisylazane followed by nucleophilic substitution with ammonia. Acylation of **19b** and iodination of the resulting acethyl derivative afforded the iodoacetamide **20b**. The ¹HNMR of **20b** shows two independent AB aromatic systems due to the H3-H4 and H7-H8 coupled protons. Palladium catalysed coupling between **20b** and 2-acethylamino-4-trimethylstannylpyrimidine (**27**) followed by acid treatment gave the *O*-methylvarioline B (**5b**). The stannylpyrimidine (**27**) was prepared with a 40% yield from 4-chloro-2-methanesulfonylpyrimidine, see *Heterocycles*, **1977**, 8, 299, by nucleophylic substitution of the methanesulfonyl group with

ammonia in *i*-PrOH followed by acylation with Ac₂O and interchange halogen metal using hexamethylditin in dioxane with Pd(PPh₃)₄ as catalyst.

The pyrimidone ring formation was omitted for improving the preparation of the tricyclic systems **19**. Tricyclic compounds **22a-c** were obtained from **9a-c** by reaction with *N*-dichloromethylene-4-methylbenzenesulfonamide, see Chem. Ver. **1966**, 99, 1252, and DIPEA in CH₂Cl₂ followed by *O*-deprotection and dehydration. *N*-Tosyl derivatives **23** were prepared from **22** by acid catalysed *O*-deprotection followed by dehydration in a similar way as described for the transformation of **10** → **11**. Elimination of the *N*-tosyl protecting group in **23** was afforded using Na in ammonia or Na in naphthalene giving **19** with moderate yield.

Heteroaryl coupling reaction of **23** and the stannyl derivative **27** in similar conditions as described previously gave **25** with a very good yield.

Deprotection of the *N*-acetyl could be produced by acid catalysed methanolysis with MeOH in HCl. Transformation of **25a** → **26** could be produced by treatment with HBr. Compound **26** is a new derivative of varioline B protected only in one nitrogen

Several derivatives of varioline B have been obtained three of them with only one variation: **5a** is the dehydroxyvarioline B, **5b** is the methylvarioline B and **26** is the tosylvarioline B.

From **26** the elimination of the tosyl could be done in the same conditions as for **23** and will be obtained varioline B.

From **23c** with a similar experimental procedure compound **25c** would be produced and from that the derivatives in the pyridine ring.

Our previous experience indicates a predictable good results in the coupling between heteroaromatic tin derivatives and **13b**, **17** and **24** giving the diversity of the R¹ in the general formula.

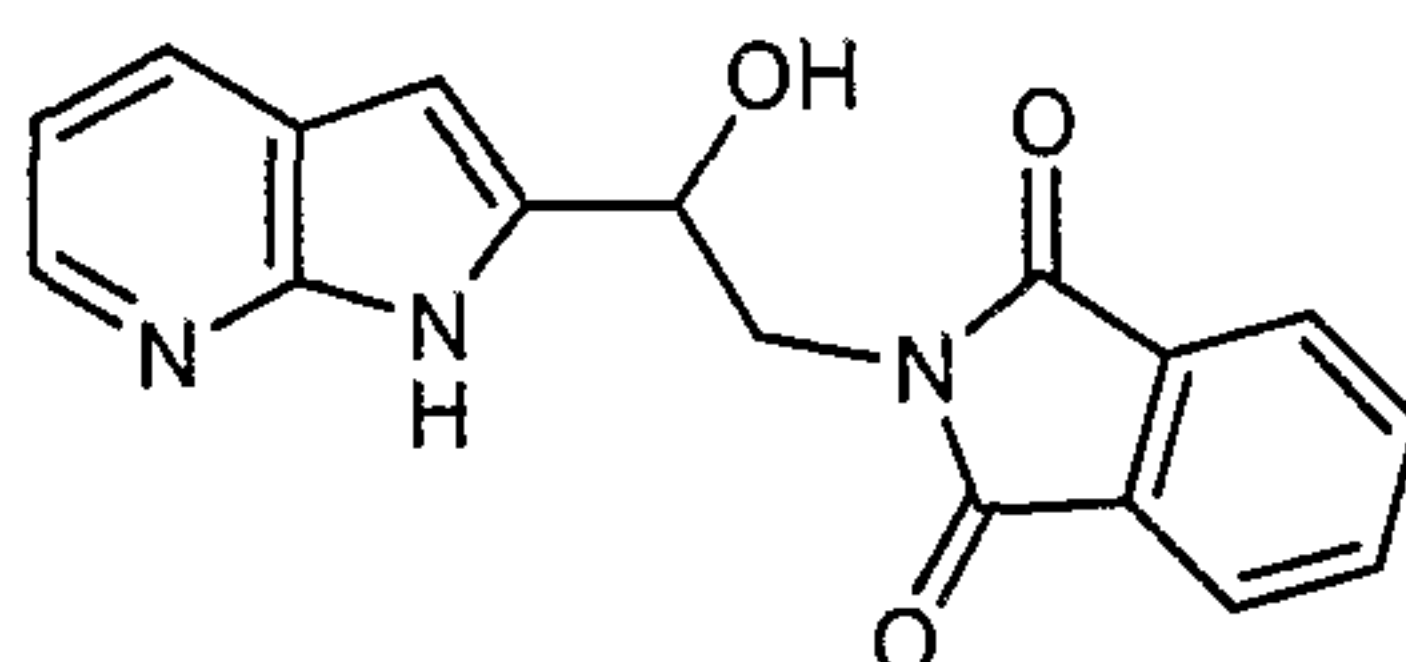
We have developed a versatile synthetic procedure which is potentially useful not only for the synthesis of this group of marine alkaloids but also for other derivatives of the natural products.

The present application claims priority from an earlier filing. To the extent that there is any disclosure in that priority filing which is not included in the present text, we specifically incorporate by reference that disclosure.

EXAMPLES OF THE INVENTION

Example 1

2-(1-Hydroxy-2-phthalimidoethyl)-7-azaindole (8a)



To a cooled (-78°C) solution of 7-azaindole (7.6 g, 64 mmol) in dry THF (150 ml) *n*-BuLi (44 ml, 1.6 M in hexane) was added and the mixture was stirred for 10 min. Dry CO_2 was bubbled through the mixture for 40 min. The solvent was evaporated and the residue was dissolved in fresh dry THF (400 ml). The solution was cooled at -78°C and *t*-BuLi (42 ml, 1.7 M in hexane) was added. The mixture was stirred for 20 min. A solution of phthalimidoacetaldehyde (14 g, 71 mmol) in THF (400 ml) was slowly added. After 1.5 h. the reaction was quenched with saturated aq. NH_4Cl (100 ml) and the organic solvent evaporated. The mixture was dissolved in CH_2Cl_2 and washed with water. The organic solution was dried and evaporated. The mixture was purified by flash column chromatography. Elution with CH_2Cl_2 /acetone (95/5) gave 7-azaindole (3.8 g, 50%) and with CH_2Cl_2 /MeOH(98/2) afforded **8a** (8.7 g, 44%) as a white solid.

mp 231-232°C (CH₂Cl₂/MeOH).

IR (KBr) ν 3200 (m, NH), 1760 (s, C=O), 1704 (s, NCO), 1427 (m, C-N), 1395 (m, C-O).

¹H-NMR (DMSO-*d*⁶, 200 MHz) δ 3.88 (dd, *J* 13.6 and 6.0, 1H, H2'), 4.00 (dd, *J* 13.6 and 7.8, 1H, H2'), 5.06 (ddd, *J* 7.8, 6.0 and 5.2, 1H, H1'), 5.83 (d, *J* 5.2, 1H, OH), 6.34 (d, *J* 1.8, 1H, H3), 6.99 (dd, *J* 8.0 and 4.8, 1H, H5), 7.81-7.88 (m, 4H, Phth), 7.89 (dd, *J* 8.0 and 1.4, 1H, H4), 8.14 (dd, *J* 4.8 and 1.4, 1H, H6), 11.75 (brs, 1H, NH).

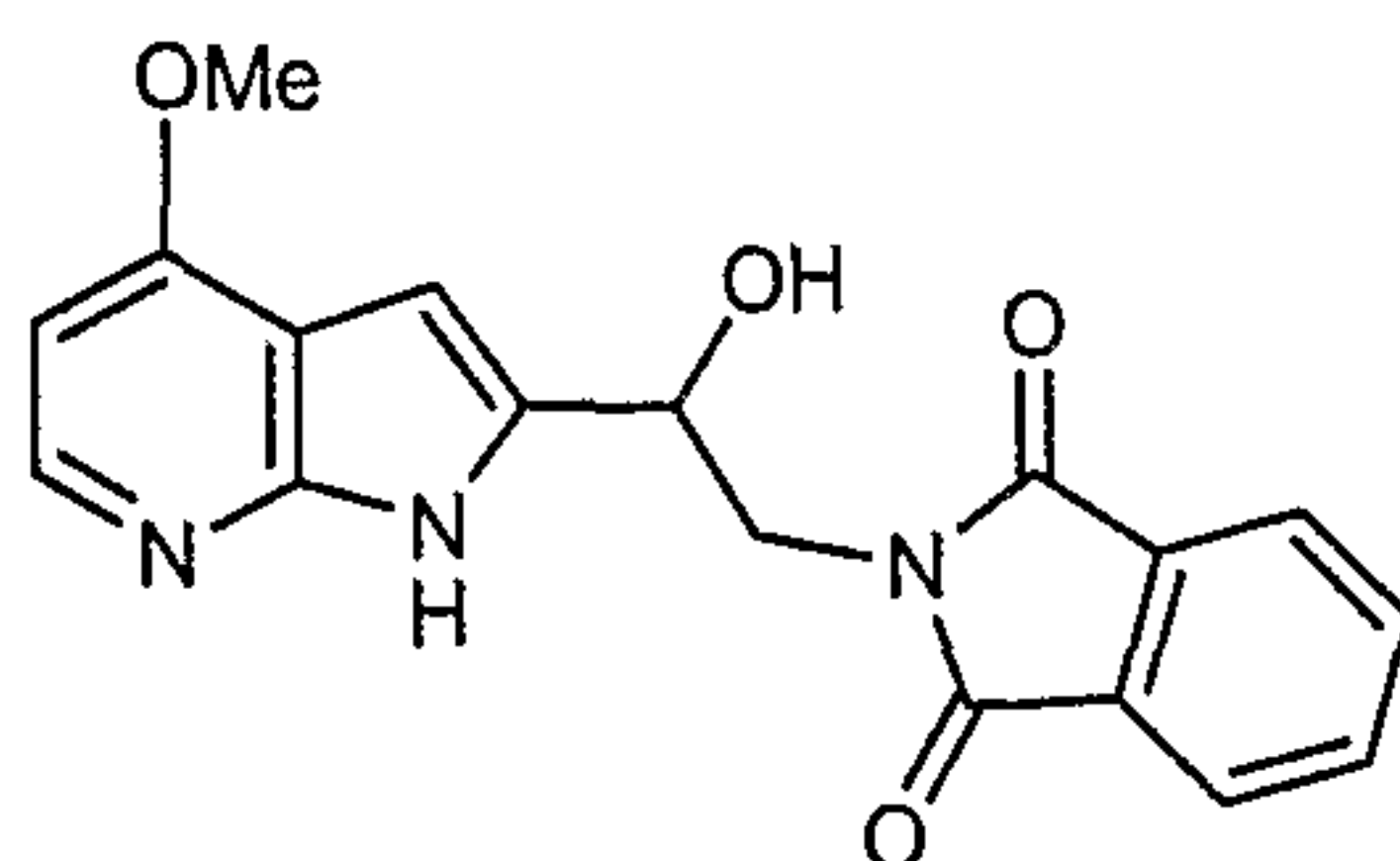
¹³C-NMR (DMSO-*d*⁶, 75 MHz) δ 43.6 (t, C2'), 64.4 (d, C1'), 96.8 (d, C3), 115.4 (d, C5), 119.8 (s, C3a), 123.0 (d, Phth- β), 127.6 (d, C4), 131.6 (s, Phth-ipso), 134.3 (d, Phth- α), 140.8 (s, C2), 142.1 (d, C6), 148.6 (s, C7a), 167.7 (s, Phth-CO).

MS (EI) *m/z* 308 (M+1, 6), 307 (M⁺, 25), 244 (8), 160 (43), 147 (phthalimide, 100), 119 (azaindole, 52).

Analysis calculated for C₁₇H₁₃N₃O₃: C (66.44), H (4.26), N (13.67); found: C (65.11), H (4.26), N (13.37).

Example 2

2-(1-Hydroxy-2-phthalimidoethyl)-4-methoxy-7-azaindole (8b)



Following the previous methodology, from 4-methoxy-7-azaindole (3.55 g, 24 mmol) in THF (75 ml) *n*-BuLi (16.5 ml, 1.6 M in hexane), *t*-BuLi (16 ml, 1.7 M in hexane) and a solution of phthalimidoacetaldehyde (5 g, 26 mmol) in THF (100 ml) a crude mixture was obtained, which was purified by flash column chromatography. Elution with CH₂Cl₂/acetone (95/5) gave 4-methoxyazaindole (2.06 g, 58%) and with CH₂Cl₂/MeOH(98/2) afforded **8b** (3.68 g, 43%) as a white solid.

mp 225-226°C (CH₂Cl₂/MeOH).

IR (KBr) ν 3500 (s, NH/OH), 1702 (s, C=O), 1594 (m), 1395 (m).

¹H-NMR (DMSO-*d*⁶, 300 MHz) δ 3.88 (s, 3H, Me), 3.86 (dd, *J* 13.8 and 6.0, 1H, H2'), 3.95 (dd, *J* 13.8 and 7.8, 1H, H2'), 5.00 (ddd, *J* 7.8, 6.0 and 5.1, 1H, H1'), 5.73 (d, *J* 5.1, 1H, OH), 6.30 (d, *J* 1.8, 1H, H3), 6.58 (d, *J* 5.4, 1H, H5), 7.83 (m, 4H, Phth), 8.02 (d, *J* 5.4, 1H, H6), 11.65 (br, 1H, NH).

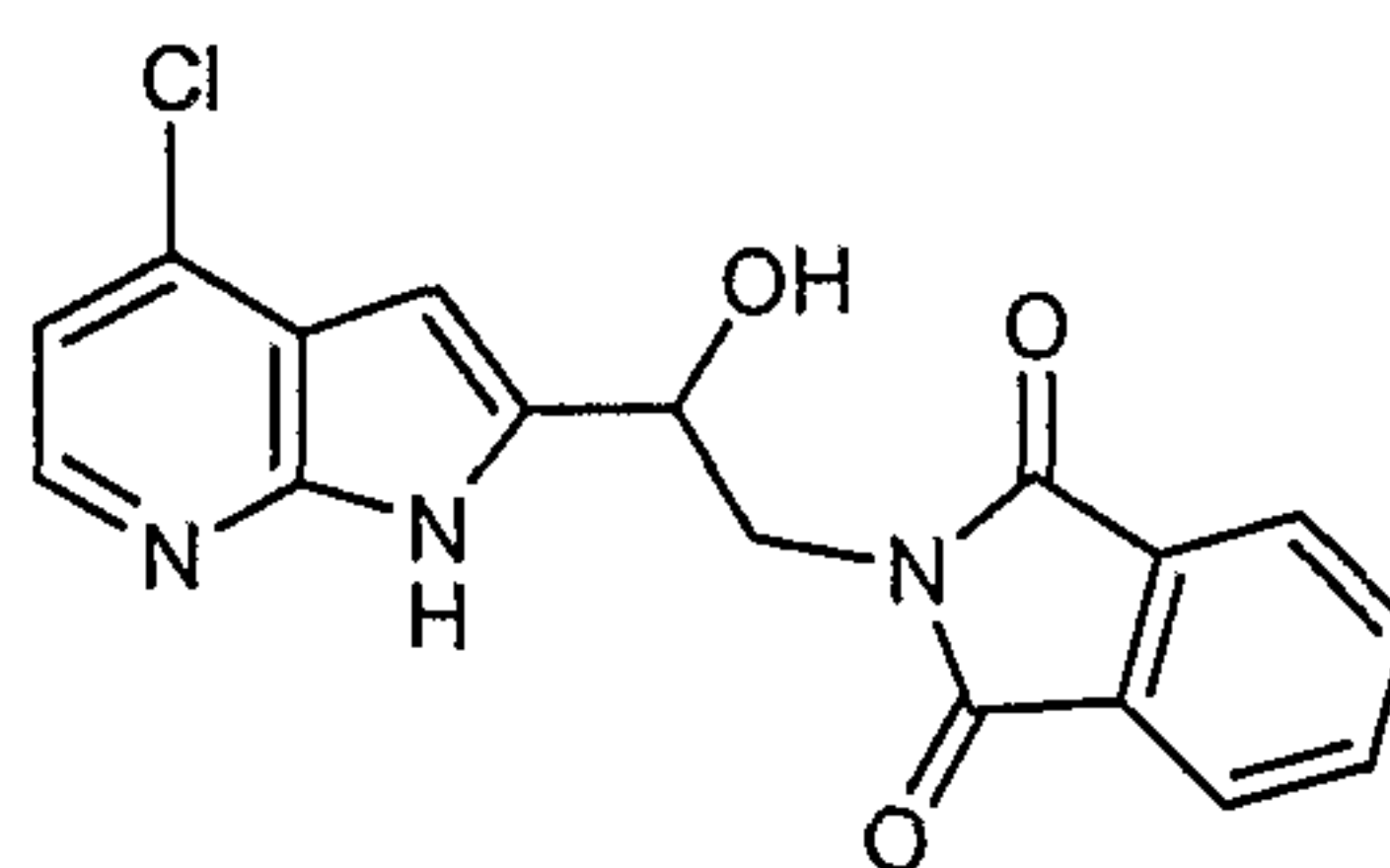
¹³C-NMR (DMSO-*d*⁶, 75 MHz) δ 43.6 (t, C2'), 55.3 (q, Me), 64.2 (d, C1'), 94.0 (d, C5), 97.8 (d, C3), 109.5 (s, C3a), 123.0 (d, Phth- β), 131.6 (s, Phth-ipso), 134.3 (d, Phth- α), 138.1 (s, C2), 144.2 (d, C6), 150.3 (s, C7a*), 158.5 (s, C4*), 167.7 (s, Phth-CO).

MS (EI) *m/z* 338 (M+1, 4), 337 (M⁺, 20), 319 (M-H₂O, 44), 177 (100).

Analysis calculated for C₁₈H₁₅N₃O₄.1/4H₂O: C (63.25), H (4.57), N (12.29); found: C (63.32), H (4.54), N (12.07).

Example 3

4-Chloro-2-(1-Hydroxy-2-phthalimidoethyl)-7-azaindole (8c)



Following the previous methodology, from 4-Chloro-7-azaindole (5 g, 33 mmol) in THF (100 ml) *n*-BuLi (20 ml, 1.6 M in hexane), *t*-BuLi (20 ml, 1.7 M in hexane) and a solution of phthalimidoacetaldehyde (7.5 g, 39 mmol) in THF (140 ml) a crude mixture was obtained, which was purified by flash column chromatography. Elution with CH₂Cl₂/acetone (95/5) gave 4-chloroazaindole (4 g, 80%) and with CH₂Cl₂/MeOH(98/2) afforded 8c (1.5 g, 12%) as a white solid.

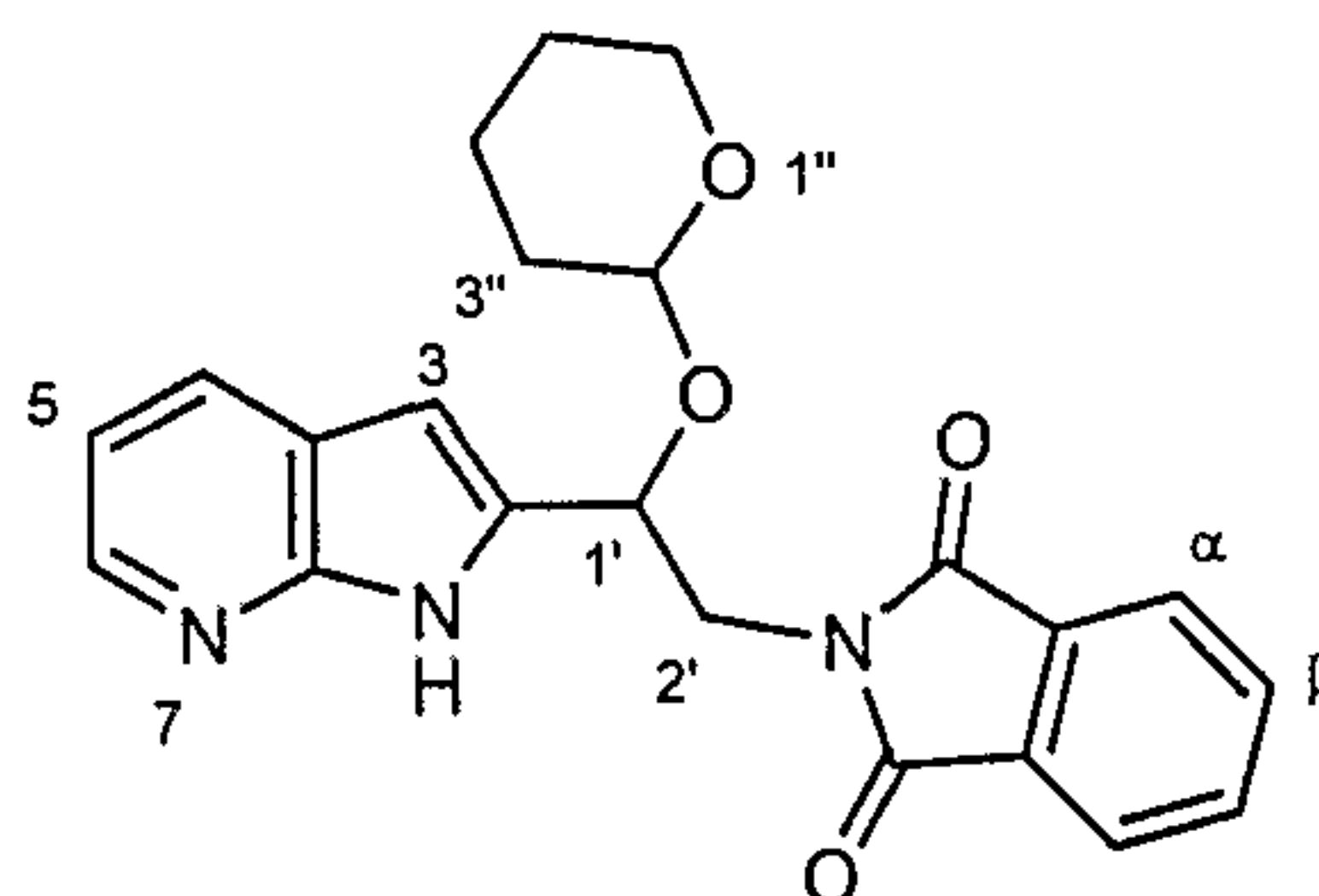
$^1\text{H-NMR}$ ($\text{DMSO-}d^6$, 200 MHz) δ 3.86 (m, 1H, H2'), 3.95 (m, 1H, H2'), 5.01 (m, 1H, H1'), 5.92 (d, J 5.2, 1H, OH), 6.41 (s, 1H, H3), 7.14 (d, J 5.6, 1H, H5), 7.84 (m, 4H, Phth), 8.11 (d, J 5.6, 1H, H6), 11.75 (br, 1H, NH).

$^{13}\text{C-NMR}$ ($\text{DMSO-}d^6$, 75 MHz) δ 43.6 (t, C2'), 64.3 (d, C1'), 94.9 (d, C3), 115.3 (d, C5), 118.7 (s, C3a), 123.0 (d, Phth- β), 131.6 (s, Phth-ipso), 133.3 (s, C2), 134.3 (d, Phth- α), 142.2 (s, C4), 142.8 (d, C6), 49.2 (s, C7a), 167.7 (s, Phth-CO).

MS (EI) m/z 342 ($M+1$, 4), 341 (M^+ , 20), 323 ($M-\text{H}_2\text{O}$, 44), 177 (100).

Example 4

2-[2-Phthalimido-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-7-azaindole



To a solution of **8a** (10.2 g, 33 mmol) in CHCl_3 (1 l) 6N HCl in dry benzene (180 ml) was added. To the mixture 2,3-dihydropyran (46 ml, 330 mmol) was added. The reaction was refluxed for 7 h. After cooling the mixture was washed with saturated aq. NaHCO_3 , dried and evaporated. The mixture was purified by flash column chromatography. Elution with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (97/3) gave 2-[2-phthalimido-1-(2,3,5,6-tetrahydropyran-2-yl)oxy-ethyl]-7-azaindole (10.8 g, 87%) as a diastereomeric mixture (1:1) as a white solid.

IR (film) ν 1717 (s, C=O), 1390 (m, C-O), 1026 (m, C-O).

$^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ 1.30-1.80 (m, 6H, H3'', H4'' and H5''), 3.25-3.45 (m, 2H, H2'), 3.80, 3.98, 4.22 and 4.38 (m, dd, J 14.0 and 4.4, dd, J 14.8 and 2.0 and dd, J 14.0 and

9.4, 2H, H6''), 4.58 and 4.72 (dd, J 3.2 and 2.8 and dd, J 3.4 and 3.0, 1H, H2''), 5.30 and 5.39 (dd, J 8.4 and 5.2 and dd, J 9.2 and 4.0, 1H, H1'), 6.47 and 6.51 (d, J 1.8 and d, J 1.8, 1H, H3), 7.08 and 7.15 (dd, J 8.2 and 4.8 and dd, J 8.2 and 5.2, 1H, H5), 7.69 (m, 2H, Phth- β), 7.86 (m, 2H, Phth- α), 7.86 (m, 1H, H4), 8.43 and 8.63 (dd, J 4.8 and 1.6 and dd, J 5.0 and 1.7, 1H, H7), 10.8 and 12.5 (br, 1H, NH).

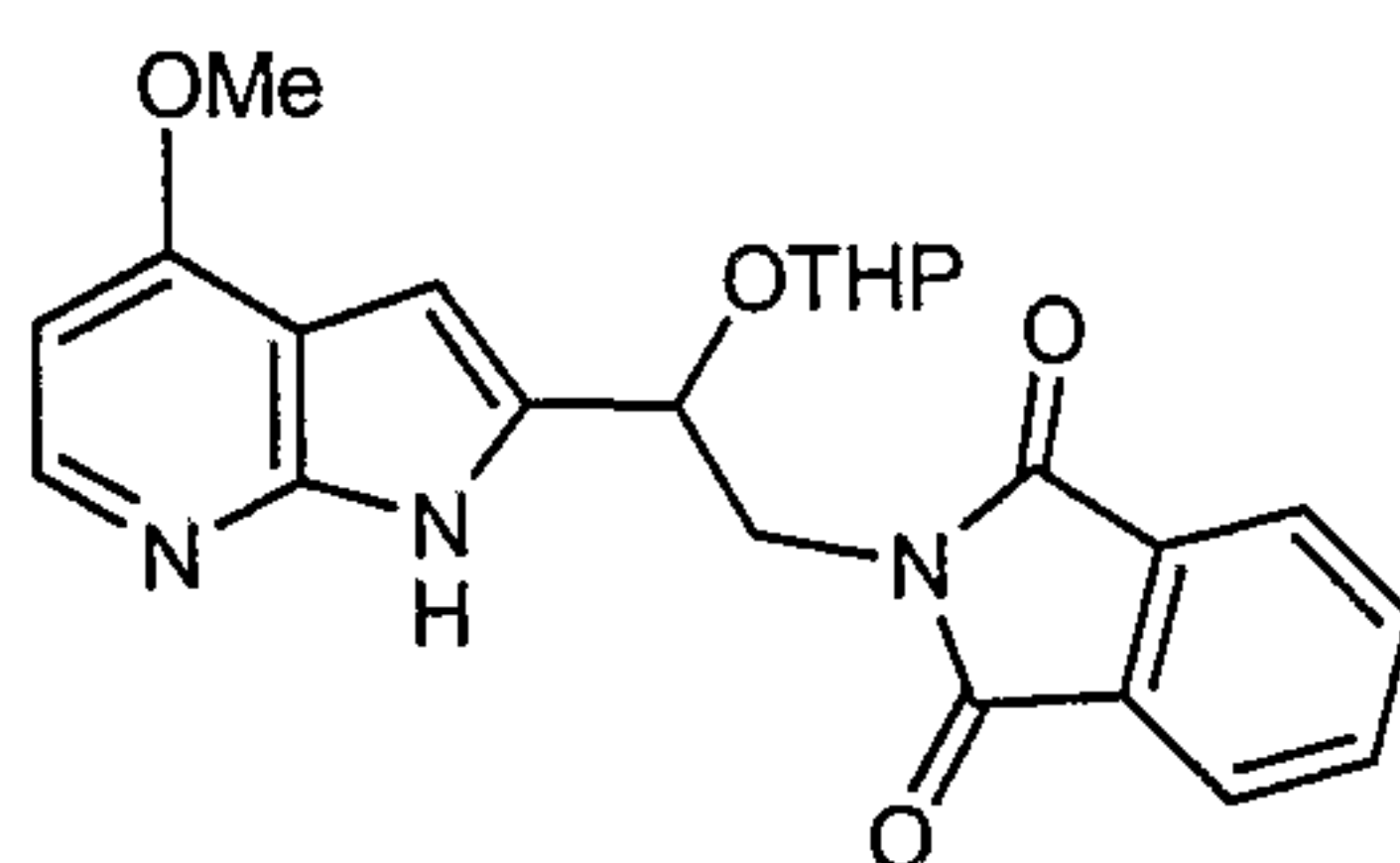
^{13}C -NMR (CDCl_3 , 50 MHz) δ 18.8 and 19.9 (t, C3''*), 25.0 and 25.2 (t, C4''*), 30.2 and 30.8 (t, C5''*), 41.6 and 42.8 (t, C6''), 61.8 and 63.6 (t, C2'), 69.3 and 71.7 (d, C1'), 95.5 and 97.9 (d, C2''), 100.3 and 100.8 (d, C3), 115.9 (d, C5), 120.6 and 120.7 (s, C3a), 123.2 and 123.4 (d, Phth- β), 128.7 and 128.8 (d, C4), 131.8 and 132.0 (s, Phth-ipso), 133.9 and 134.0 (d, Phth- α), 136.5 and 137.8 (s, C2), 143.1 (d, C6), 148.7 and 149.2 (s, C7a), 168.1 (s, Phth-CO).

MS (EI) m/z 391 (M^+ , 1), 307 (M-THP, 9), 147 (38), 85 (100).

Analysis calculated for $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_4 \cdot 1/2\text{H}_2\text{O}$: C (65.99), H (5.54), N (10.49); found: C (66.02), H (5.80), N (10.28).

Example 5

4-Methoxy-2-[2-phthalimido-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-7-azaindole



Following the same procedure as for 2-[2-Phthalimido-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-7-azaindole. From **8b** (3.8 g, 11 mmol) in CHCl_3 (350 ml), 6N HCl in benzene (35 ml) and 2,3-dihydropyran (10 ml, 110 mmol).

4-Methoxy-2-[2-phthalimido-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-7-azaindole (3.07 g, 65%) as a diastereomeric mixture (1:1) was obtained.

IR (film) ν 1714 (s, C=O), 1392 (m, C-O), 1026 (m, C-O).

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 1.30-1.80 (m, 6H, H3'', H4'' and H5''), 3.25-3.45 (m, 2H, H2'), 3.99 and 4.01 (s, 3H, OMe), 3.96, 4.08, 4.28 and 4.39 (dd, J 13.5 and 3.9, dd, J 13.8 and 4.6, dd, J 13.8 and 8.5 and dd, J 13.5 and 9.6, 2H, H6''), 4.57 and 4.73 (brt, J 3.2 and brt, J 3.4, 1H, H2''), 5.25 and 5.33 (dd, J 6.9 and 2.4 and dd, J 9.9 and 4.1, 1H, H1'), 6.54 and 6.58 (brs and brs, 1H, H3), 6.56 and 6.62 (d, J 5.7 and d, J 5.7, 1H, H5), 7.68 (m, 2H, Phth- β), 7.83 (m, 2H, Phth- α), 8.38 and 8.57 (d, J 5.7 and d, J 5.7, 1H, H7), 11.7 (br, 1H, NH).

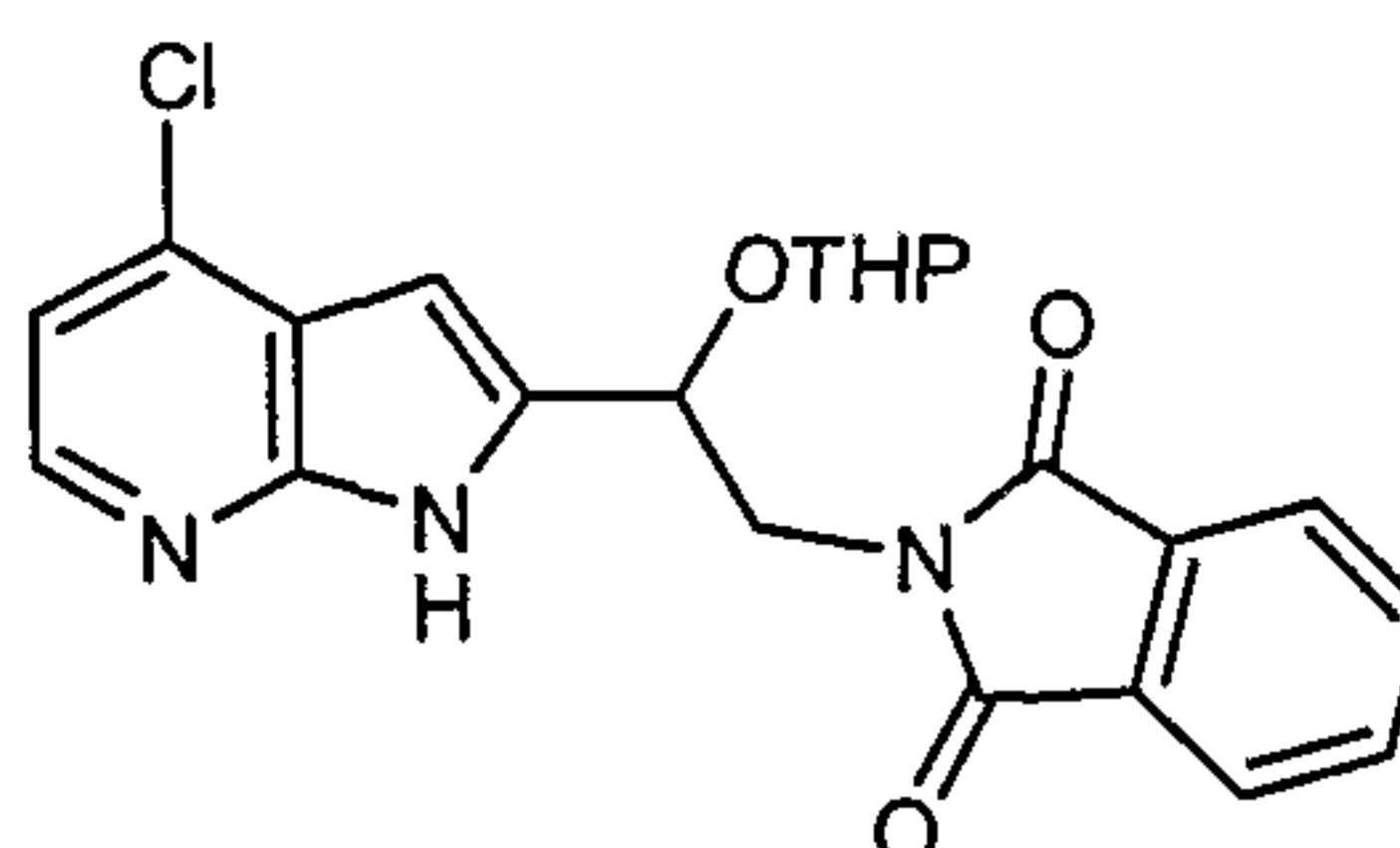
$^{13}\text{C-NMR}$ (CDCl_3 , 50 MHz) δ 18.9 and 19.5 (t, C3''*), 25.0 and 25.3 (t, C4''*), 30.2 and 30.7 (t, C5''*), 42.0 and 43.0 (t, C6''), 55.4 (q, MeO), 61.7 and 62.9 (t, C2'), 69.4 and 71.5 (d, C1'), 94.4 and 95.3 (d, C2''), 97.7 (d, C5), 97.8 and 100.1 (d, C3), 110.5 (s, C3a), 123.1 and 123.2 (d, Phth- β), 132.1 and 132.1 (s, Phth-ipso), 133.8 and 133.9 (d, Phth- α), 134.0 and 135.2 (s, C2), 144.9 and 145.1 (d, C6), 150.6 and 151.1 (s, C7a*), 159.8 (s, C4*), 168.1 (s, Phth-CO).

MS (EI) m/z 422 ($M+1$, 2), 421 (M^+ , 4), 337 (M -THP, 15), 177 (100).

HRMS m/z calculated for $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_5$: 421.1637; found: 421.1625.

Example 6

4-Chloro-2-[2-phthalimido-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-7-azaindole



Following the same procedure as for 2-[2-Phthalimido-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-7-azaindole, from **8c** (1.3 g, 3.8 mmol) in CHCl_3 (50 ml), 6N HCl in benzene (5 ml) and 2,3-dihydropyran (1.7 ml, 19 mmol), 4-chloro-2-[2-phthalimido-1-(2,3,5,6-

tetrahydropyran-2-yl)oxyethyl]-7-azaindole (1.0 g, 63%) as a diastereomeric mixture (1:1) was obtained.

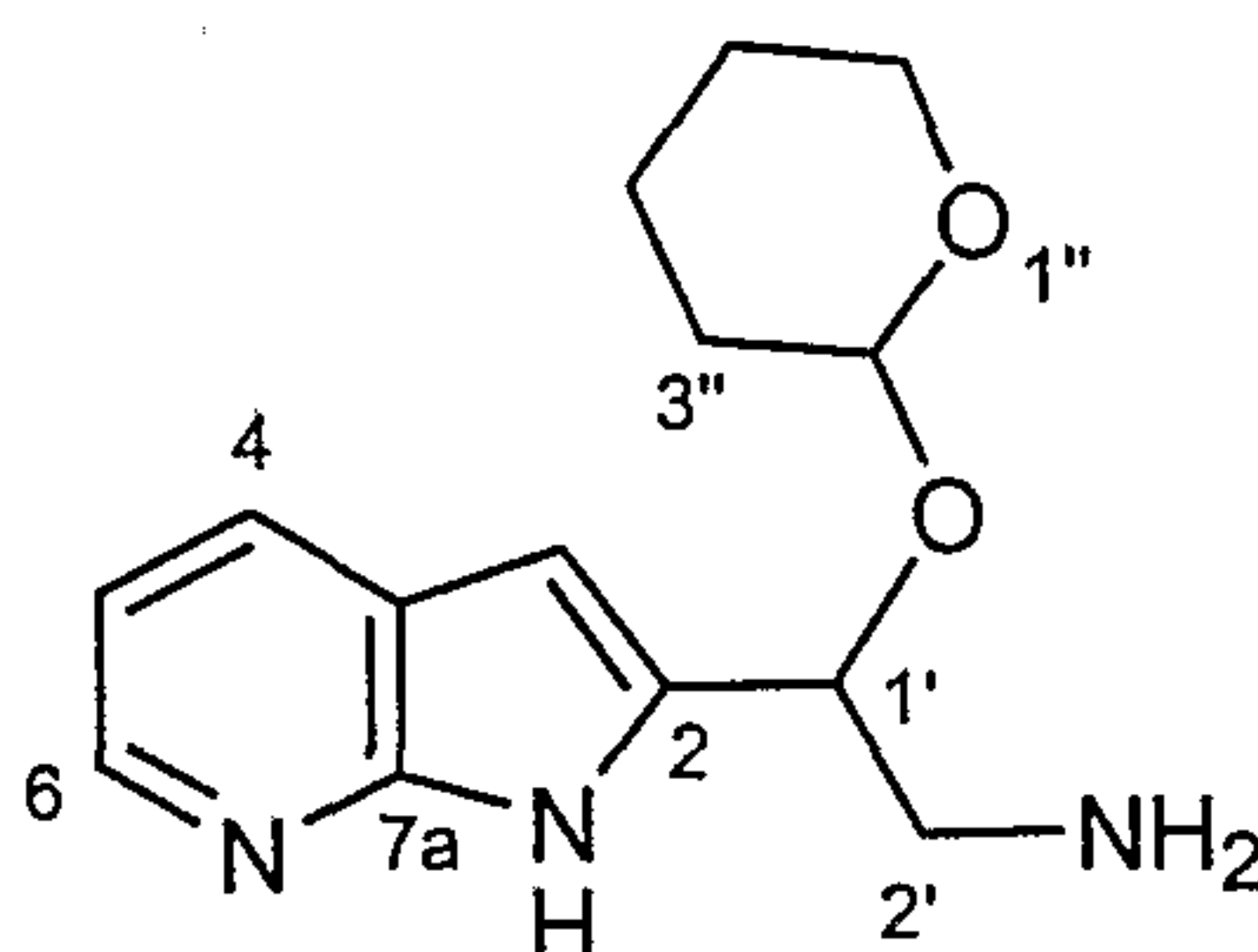
$^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ 1.30-1.80 (m, 6H, H3'' , H4'' and H5''), 3.25-3.45 (m, 2H, H2'), 3.96-4.39 (m, 2H, H6''), 4.58 and 4.72 (m, 1H, H2''), 5.30 and 5.40 (dd, J 8.4 and 4.4 and dd, J 9.2 and 4.0, 1H, H1'), 6.58 and 6.63 (d, J 2.2 and d, J 2.2, 1H, H3), 7.13 and 7.20 (d, J 5.2 and d, J 5.2, 1H, H5), 7.70 (m, 2H, Phth- β), 7.86 (m, 2H, Phth- α), 8.35 and 8.55 (d, J 5.2 and d, J 5.2, 1H, H7), 11.7 (br, 1H, NH).

$^{13}\text{C-NMR}$ (CDCl_3 , 50 MHz) δ 18.9 and 19.5 (t, C3''*), 25.0 and 25.3 (t, C4''*), 30.2 and 30.8 (t, C5''*), 41.8 and 42.9 (t, C6''), 61.9 and 63.5 (t, C2'), 69.2 and 71.6 (d, C1'), 95.5 and 96.4 (d, C2''), 98.8 and 100.7 (d, C3), 116.1 (d, C5), 116.3 (s, C3a), 123.1 and 123.3 (d, Phth- β), 131.7 and 132.0 (s, Phth-ipso), 133.8 and 133.9 (d, Phth- α), 134.0 (s, C2), 143.2 and 143.3 (d, C6).

MS (EI) m/z 426 ($\text{M}+1$, 2), 425 (M^+ , 5), 341 (M-THP , 14), 177 (100).

Example 7

2-[2-Amino-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-7-azaindole (9a)



To a solution of 2-[2-Phthalimido-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-7-azaindole (10.2 g, 26 mmol) in EtOH (630 ml) $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ (1.53 ml, 31 mmol) was added. The mixture was refluxed for 3 h. The solvent was evaporated, the residue dissolved in CH_2Cl_2 and washed with saturated aq. NaHCO_3 . The aqueous layer was extracted three times with

CH₂Cl₂. The organic solutions were evaporated together to obtain a diastereomeric mixture (1:1) of **9a** (6.72 g, 100%) as a light orange solid.

IR (film) ν 3200 (m, NH), 1421 (m, C-N), 1022 (m, C-O).

¹H-NMR (CDCl₃, 200 MHz) δ 1.40-1.90 (m, 6H, H3'', H4'' and H5''), 3.20 (m, 2H, H2'), 3.48 and 3.90 (m, 1H, H6''), 4.60 and 4.85 (brt, *J* 3.5 and m, 1H, H2'') 4.85 and 4.97 (m and brt, *J* 5.7, 1H, H1'), 6.32 and 6.43 (s, 1H, H3), 7.03 and 7.07 (dd, *J* 6.6 and 4.8 and dd, *J* 6.6 and 5.0, 1H, H5), 7.85 and 7.90 (dd, *J* 6.6 and 1.4, 1H, H4), 8.29 and 8.36 (dd, *J* 4.8 and 1.4 and dd, *J* 5.0 and 1.4, 1H, H7), 10.9 and 12.5 (br, NH).

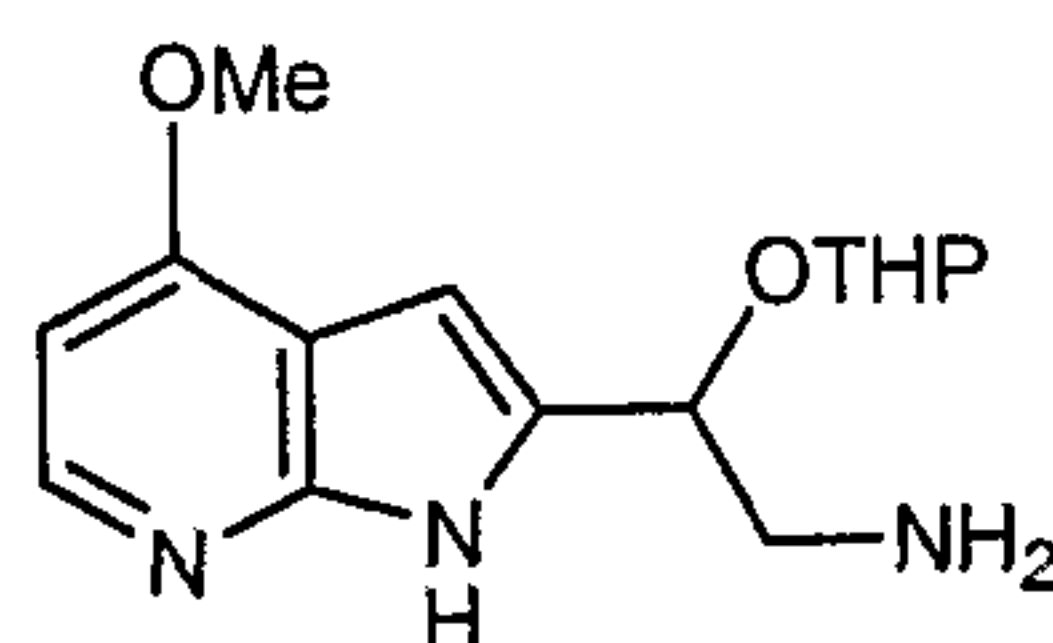
¹³C-NMR (CDCl₃, 75 MHz) δ 19.7 and 20.0 (t, C3''*), 25.1 and 25.3 (t, C4''*), 30.6 and 30.9 (t, C5''*), 45.3 and 47.3 (t, C6''), 62.9 and 63.5 (t, C2'), 73.4 and 75.5 (d, C1'), 96.1 and 97.3 (d, C2''), 99.8 and 99.9 (d, C3), 115.6 (d, C5), 120.7 (s, C3a), 128.4 and 128.5 (d, C4), 138.3 and 139.0 (s, C2), 142.2 and 142.3 (d, C6), 148.5 and 149.0 (s, C7a).

MS (CI, CH₄) *m/z* 263 (M+1,15), 262 (M⁺, 100).

HRMS *m/z* calculated for C₁₄H₁₉N₃O₂.H: 262.1555; found: 262.1557.

Example 8

2-[2-Amino-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-4-methoxy-7-azaindole (**9b**)



Following the same procedure as for **9a**. From 4-Methoxy-2-[2-phthalimido-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-7-azaindole (2.9 g, 10 mmol) in EtOH (100 ml) and NH₂NH₂.H₂O (420 μ l, 15 mmol). After a reaction time of 3 h. a diastereomeric mixture (1:1) of **9b** (1.9 g, 95%) was obtained.

IR (film) ν 3150 (m, NH), 1590 (m, C=C), 1329 (m, C-N), 1114 (m, C-O).

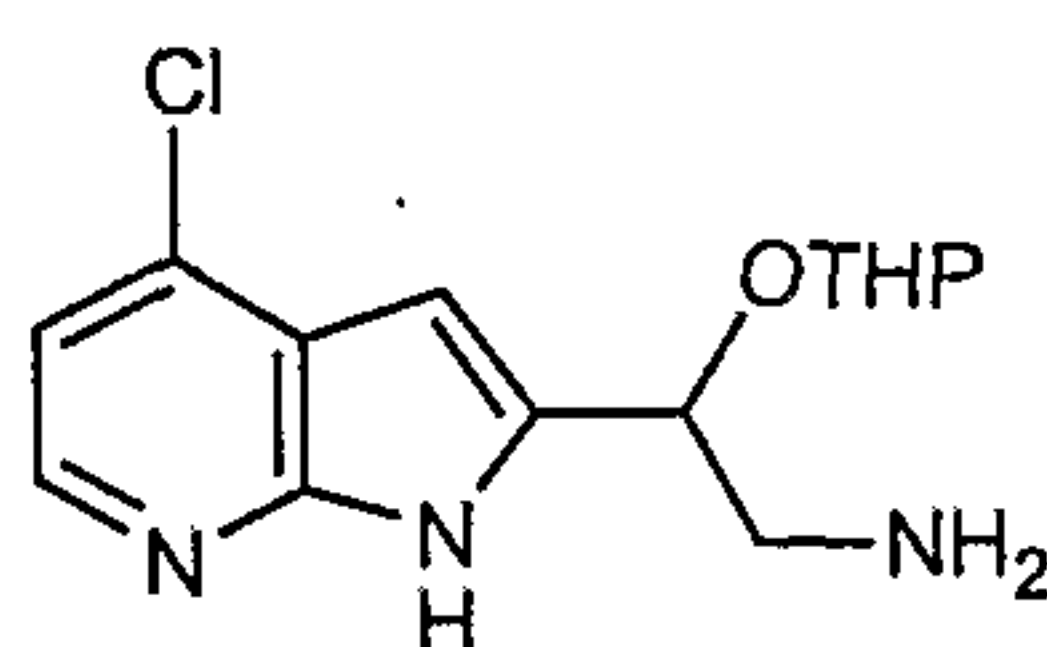
$^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ 1.40-1.90 (m, 6H, $\text{H3''}-\text{H5''}$), 3.19 (m, 2H, H2'), 3.48 and 3.90 (m, 1H, H6''), 3.99 and 4.00 (s, 3H, MeO), 4.60 and 4.85 (m, 1H, H2'') 4.85 and 4.97 (m and brt, J 5.7, 1H, H1'), 6.42 and 6.51 (s, 1H, H3), 6.51 and 6.55 (d, J 5.4, 1H, H5), 8.23 and 8.30 (d, J 5.4, 1H, H7).

$^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 20.0 (t, C3''*), 25.2 and 25.4 (t, C4''*), 30.7 and 30.9 (t, C5''*), 45.4 and 47.4 (t, C6''), 55.4 and 55.5 (q, MeO), 62.9 and 63.4 (t, C2'), 73.5 and 75.5 (d, C1'), 94.7 and 96.1 (d, C2''*), 97.1 and 99.6 (d, C3), 97.6 (d, C5), 110.5 (s, C3a), 135.8 and 136.5 (s, C2), 144.3 and 144.4 (d, C6), 150.3 and 151.3 (s, C4*), 159.4 and 159.5 (s, C7a*).

MS (CI, CH_4) m/z 291 (M^+ , 2), 262 ($\text{M}-\text{CH}_2\text{NH}_3$, 12), 190 ($\text{M}-\text{THPO}$, 8), 177 (100).

Example 9

2-[2-Amino-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-4-chloro-7-azaindole (9c)



Following the same procedure as for **9a**, from 4-Chloro-2-[2-phthalimido-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-7-azaindole (950 mg, 2.2 mmol) in EtOH (50 ml) and $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ (250 μl , 4.4 mmol). After a reaction time of 3 h. a diastereomeric mixture (1:1) of **9c** (640 mg, 97%) was obtained.

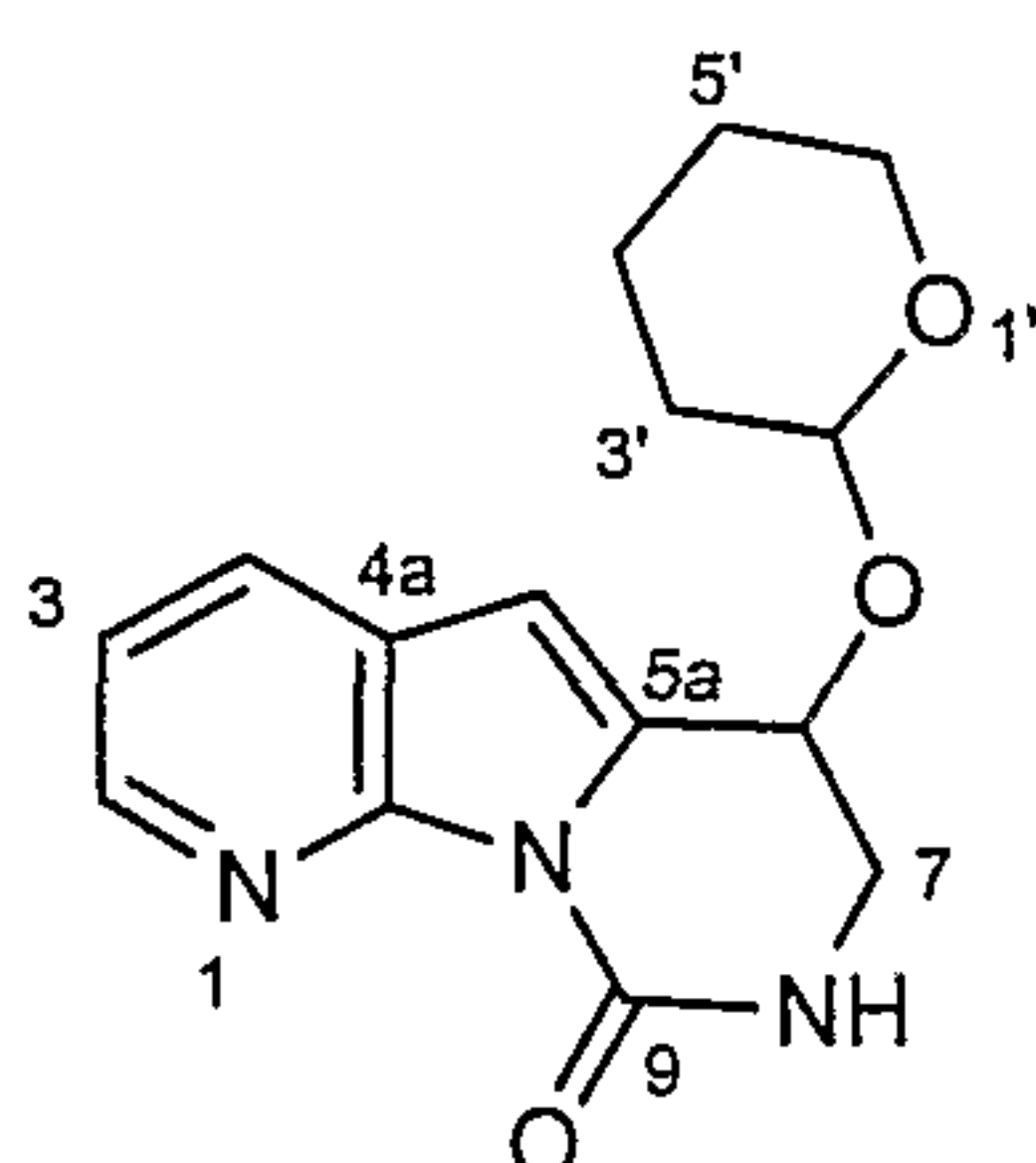
$^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ 1.40-1.90 (m, 6H, H3''-H5''), 3.19 (m, 2H, H2'), 3.50 and 3.95 (m, 1H, H6''), 4.60 and 4.85 (m, 1H, H2'') 4.85 and 4.97 (brt, 1H, H1'), 6.46 and 6.54 (s, 1H, H3), 7.07 and 7.10 (d, J 5.4, 1H, H5), 8.19 and 8.25 (d, J 5.4, 1H, H7).

$^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 19.8 and 20.1 (t, C3''*), 25.1 and 25.3 (t, C4''*), 30.6 and 30.9 (t, C5''*), 45.2 and 47.1 (t, C6''), 63.1 and 63.7 (t, C2'), 73.1 and 75.1 (d, C1'), 96.0 and 96.4 (d, C2''*), 98.3 and 100.2 (d, C3), 115.8 (d, C5), 120.1 and 120.4 (s, C4), 135.6 and 135.8 (s, C4), 139.1 and 139.8 (s, C3a), 142.4 and 142.5 (d, C6), 148.9 and 149.5 (s, C7a).

MS (Cl , CH_4) m/z 295 (M^+ , 2), 266 ($\text{M-CH}_2\text{NH}_3$, 12), 194 (M-THPO , 8), 177 (100).

Example 10

6,7,8,9-Tetrahydro-6-(2,3,5,6-tetrahydropyran-2-yl)oxypyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidin-9-one (10a)



A solution of **9a** (7.4 g, 28 mmol) and DIPEA (5 ml, 28 mmol) in CH_2Cl_2 (300 ml) was slowly added to a solution of triphosgene (2.82 g, 10 mmol) in CH_2Cl_2 (740 ml) and the mixture was stirred at room temperature for 30 min. The organic mixture was washed with saturated aq. NH_4Cl and with water. The organic solution was dried and evaporated to give a diastereomeric mixture (1:1) of **10a** (6.06 g, 76%).

IR (KBr) ν 3252 (m, NH), 1716 (s, C=O), 1407 (m, C-N), 1302 (m, C-O).

$^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ 1.40-1.80 (m, 6H, H3' , H4' and H5'), 3.45-4.00 (m, 2H, H7 and H6'), 3.90 (m, 2H, H7 and H6'), 4.71 and 4.94 (m, 1H, H2'), 5.04 and 5.10 (dd, J 3.2 and 3.0 and t, J 4.4, 1H, H6), 6.56 and 6.59 (s, 1H, H5), 6.79 and 7.00 (br, 1H, NH), 7.20 and

7.22 (dd, J 7.6 and 4.8 and dd, J 8.0 and 4.8, 1H, H3), 7.89 and 7.93 (dd, J 7.6 and 1.8 and dd, J 8.0 and 1.8, 1H, H4), 8.54 and 8.57 (dd, J 4.8 and 1.8 and dd, J 4.8 and 1.4, 1H, H2).

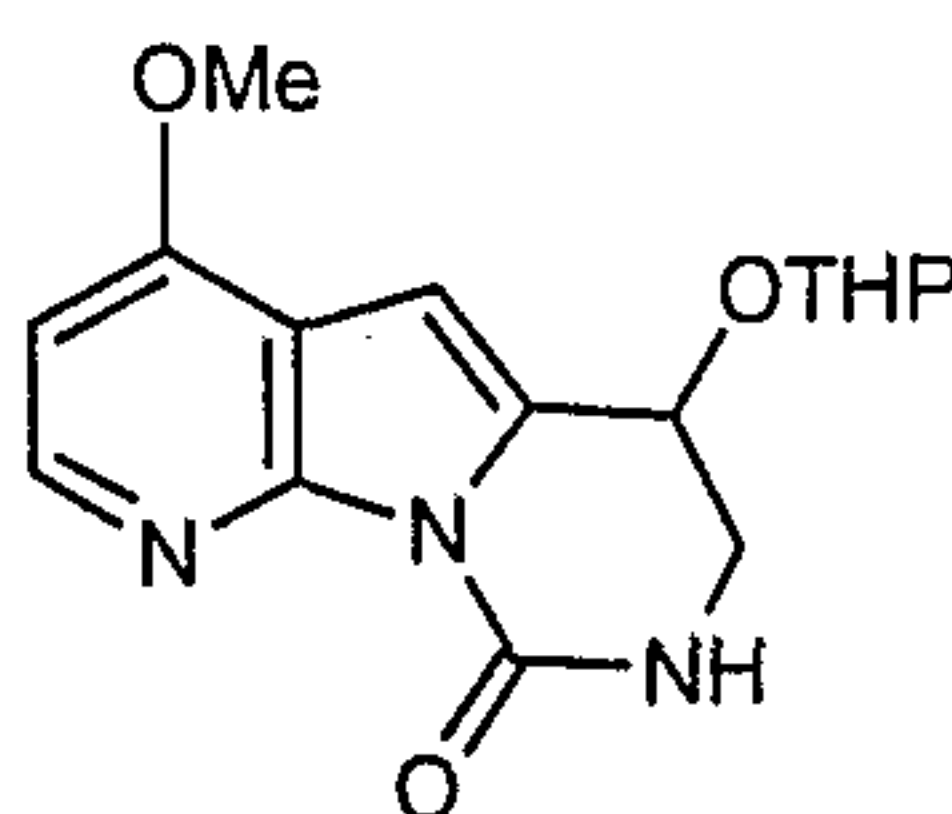
^{13}C -NMR (CDCl_3 , 50 MHz) δ 18.9 and 19.3 (t, C4'), 25.3 and 25.4 (t, C5'), 30.1 and 30.4 (t, C3'), 43.5 and 45.3 (t, C6'), 62.2 and 62.6 (t, C7), 63.2 and 64.3 (d, C6), 95.7 and 96.7 (d, C2'), 102.3 and 103.7 (d, C5), 118.6 (d, C3), 121.3 and 121.7 (s, C4a), 129.1 and 129.2 (d, C4), 133.5 and 136.1 (s, C5a), 145.2 and 145.6 (d, C2), 148.0 and 148.1 (s, C10a), 149.8 and 150.2 (s, C9).

MS (CI, CH_4) m/z 289 ($\text{M}+1$, 6), 288 (M^+ , 25), 204 ($\text{M}-\text{THP}$, 23), 85 (THP, 100).

HRMS m/z calculated for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_3\cdot\text{H}$: 288.1348; found: 288.1352.

Example 11

6,7,8,9-Tetrahydro-6-(2,3,5,6-tetrahydropyran-2-yl)oxy-4-methoxy-pyrido[3',2':4,5]-pyrrolo[1,2-*c*]pyrimidin-9-one (10b)



Following the same procedure as for **10a**, from triphosgene (20 mg, 0.07 mmol) in CH_2Cl_2 (3 ml), **9b** (58 mg, 0.20 mmol) and DIPEA (34 μl , 0.20 mmol) in CH_2Cl_2 (3 ml). Reaction time 30 min. at room temperature. The crude mixture was purified by flash column chromatography. Elution with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98/2) gave a diastereomeric mixture (1:1) of **10b** (40 g, 63%).

IR (KBr) ν 3258 (m, NH), 1714 (s, C=O), 1566 (m, C=N), 1290 (m, C-O).

^1H -NMR (CDCl_3 , 200 MHz) δ 1.40-1.80 (m, 6H, H3', H4' and H5'), 3.45 and 3.95 (m, 2H, H6'), 3.65 and 3.75 (m, 2H, H7), 4.00 (s, 3H, MeO), 4.67 and 4.94 (m, 1H, H2'), 4.99 and

5.07 (m, 1H, H6), 6.20 and 6.30 (br, 1H, NH), 6.65 and 6.66 (s, 1H, H5), 6.69 (d, *J* 5.9, 1H, H3), 8.44 and 8.46 (d, *J* 5.9, 1H, H2).

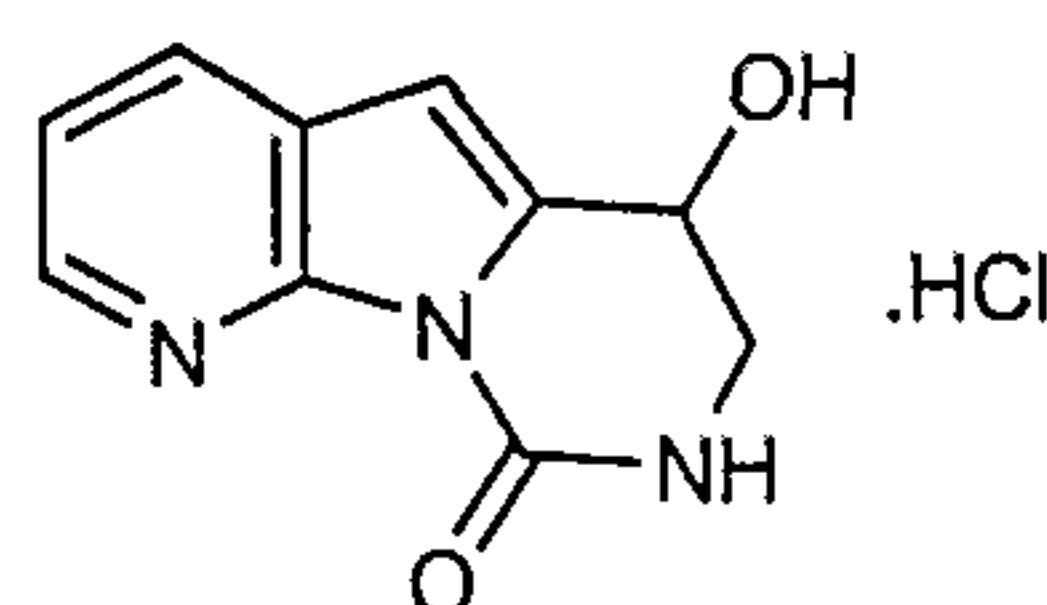
¹³C-NMR (CDCl₃, 50 MHz) δ 18.7 and 19.4 (t, C4'), 25.3 and 25.4 (t, C5'), 30.1 and 30.3 (t, C3'), 43.5 and 45.3 (t, C6'), 61.9 and 62.6 (t, C7), 62.9 and 63.9 (d, C6), 95.5 and 96.2 (d, C2'), 99.6, 100.6 and 101.1 (d, C3 and C5), 130.9 (s, C5a), 147.3 and 147.7 (d, C2), 149.9 and 150.3 (s, C10a or C4), 159.7 (s, C9).

MS (EI) *m/z* 318 (*M*+1, 2), 317 (*M*⁺, 28), 233 (22), 217 (66), 216 (65), 177 (100), 85 (THP, 100).

HRMS *m/z* calculated for C₁₆H₁₉N₃O₄: 317.1376; found: 317.1383.

Example 12

6,7,8,9-Tetrahydro-6-hydroxypyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidin-9-one



To a solution of **10a** (6 g, 21 mmol) in CH₂Cl₂ (400 ml) 4N aq. HCl (400 ml) was added. After 45 min. stirring at room temperature the two layers were separated. The organic solution was extracted with 4N aq. HCl. The aqueous solution was filtered and evaporated to obtain 6,7,8,9-Tetrahydro-6-hydroxypyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidin-9-one (5 g, 100%) as hydrochloride salt as a light orange solid.

*6,7,8,9-Tetrahydro-6-hydroxypyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidin-9-one hydrochloride*

IR (KBr) ν 3500 (s, OH), 1721 (s, C=O), 1638 (m, C=C), 1503 (m, C=N).

$^1\text{H-NMR}$ (CD_3OD , 300 MHz) δ 3.61 (dd, J 13.0 and 5.0, 1H, H7), 3.77 (dd, J 13.0 and 4.0, 1H, H7), 5.23 (dd, J 5.0 and 4.0, 1H, H6), 7.05 (s, 1H, H5), 7.86 (dd, J 8.0 and 6.0, 1H, H3), 8.56 (dd, J 6.0 and 1.2, 1H, H2), 8.86 (dd, J 8.0 and 1.2, 1H, H4).

$^{13}\text{C-NMR}$ (CD_3OD , 75 MHz) δ 45.8 (t, C7), 59.6 (d, C6), 101.9 (d, C5), 119.0 (d, C3), 127.1 (s, C4a), 124.3 (d, C4), 137.4 (s, C5a), 139.4 (d, C2), 141.9 (s, C10a), 149.0 (s, C9).

MS (CI, NH_3) m/z 205 ($M+1$, 3), 204 (M^+ , 4), 180 (100), 163 (50), 130 (90).

HRMS m/z calculated for $\text{C}_{10}\text{H}_{10}\text{N}_3\text{O}_3$: 204.0773; found: 204.0772.

A solution of 6,7,8,9-Tetrahydro-6-hydroxypyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidin-9-one hydrochloride salt in saturated aq. Na_2CO_3 was extracted in continuous with CH_2Cl_2 to give the conjugated base.

6,7,8,9-Tetrahydro-6-hydroxypyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidin-9-one

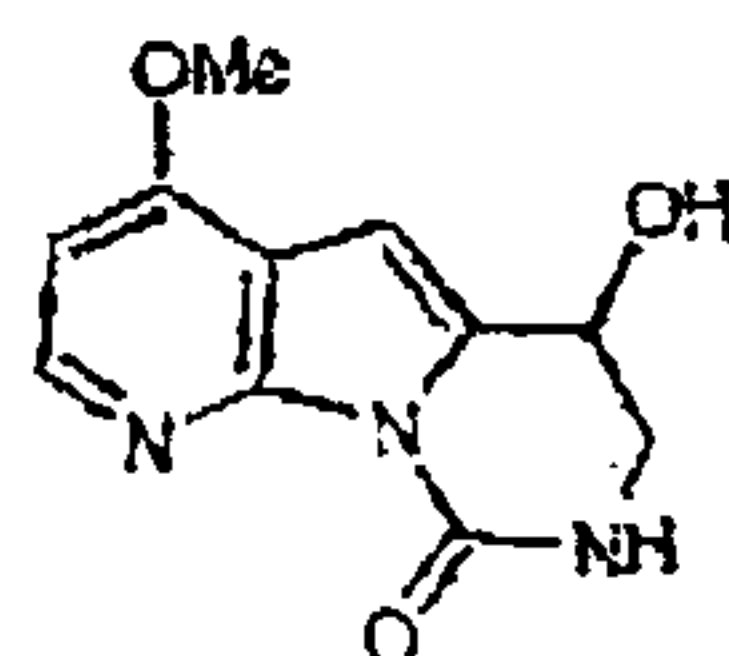
IR (KBr) ν 3400 (m, NH/OH), 1707 (s, C=O), 1468 (m, C-N), 1408 (m, C-N), 1297 (m, C-O).

$^1\text{H-NMR}$ ($\text{DMSO}-d^6$, 300 MHz) δ 3.27 (m, 1H, H7), 3.42 (m, 1H, H7), 4.90 (dd, J 9.3 and 5.1, 1H, H6), 5.88 (d, J 5.1, 1H, OH), 6.54 (s, 1H, H5), 7.21 (dd, J 7.4 and 4.2, 1H, H3), 7.88 (br, 1H, NH), 7.99 (brd, J 7.4, 1H, H2), 8.30 (brd, J 4.2, 1H, H4).

$^{13}\text{C-NMR}$ ($\text{DMSO}-d^6$, 75 MHz) δ 41.0 (t, C7), 55.7 (d, C6), 95.4 (d, C5), 113.8 (d, C3), 116.7 (s, C4a), 124.2 (d, C4), 135.4 (s, C5a), 139.3 (d, C2), 142.9 (s, C10a*), 143.8 (s, C9*).

Example 13

6,7,8,9-Tetrahydro-6-hydroxy-4-methoxypyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidin-9-one



To a solution of **10b** (25 mg, 0.08 mmol) in CH₂Cl₂ (5 ml) 4N aq. HCl (5 ml) was added and the mixture was stirred at room temperature for 45 min. The organic solution was separated and extracted with 4N aq. HCl. The aqueous solution was filtered and evaporated to obtain 6,7,8,9-Tetrahydro-6-hydroxy-4-methoxypyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidin-9-one (20 mg, 95%) as hydrochloride salt as a light orange solid.

IR (film) ν 3244 (m, NH), 1718 (s, C=O), 1627 (s, NCO), 1505 (m, C=N), 1298 (m, C-O).

¹H-NMR (CD₃OD, 200 MHz) δ 3.56 (dd, *J* 13.6 and 4.8, 1H, H7), 3.71 (dd, *J* 13.6 and 3.6, 1H, H7), 4.29 (s, 3H, MeO), 5.11 (dd, *J* 4.8 and 3.6, 1H, H6), 6.91 (s, 1H, H5), 7.40 (d, *J* 6.9, 1H, H3), 8.42 (d, *J* 6.9, 1H, H2).

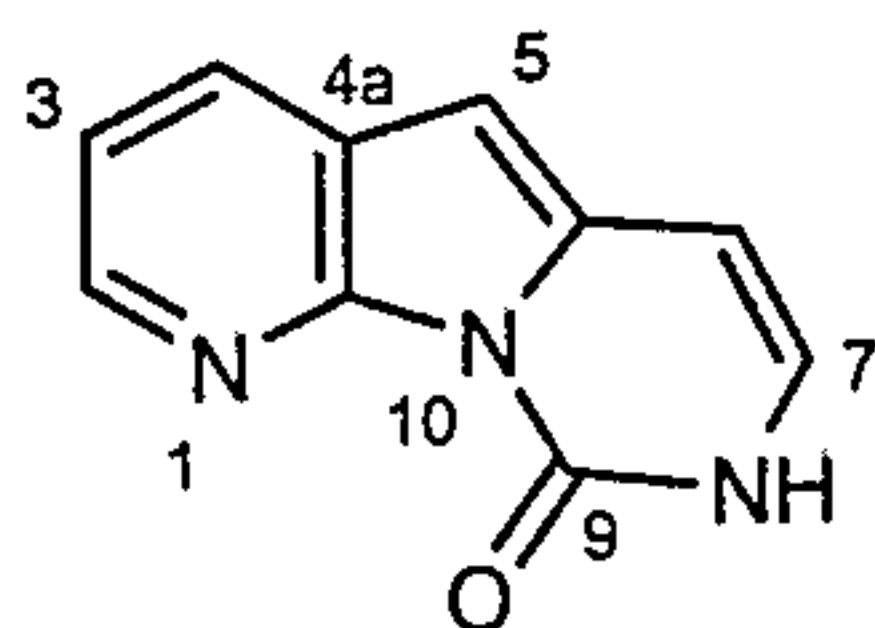
¹³C-NMR (CD₃OD, 75 MHz) δ 48.9 (t, C7), 60.5 (q, Me), 62.3 (d, C6), 101.7 (d, C5), 105.5 (d, C3), 117.4 (s, C4a), 137.0 (s, C5a), 140.6 (d, C2), 141.4 (s, C10a), 151.9 (s, C9), 169.0 (s, C4).

MS (EI) *m/z* 234 (M+1, 12), 233 (M⁺, 77), 215 (M-H₂O, 17), 55 (100).

HRMS *m/z* calculated for C₁₁H₁₁N₃O₃: 233.0800; found: 233.0813.

Example 14

8,9-Dihydropyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidin-9-one (11a)



To a cooled (0°C) solution of 6,7,8,9-Tetrahydro-6-hydroxypyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidin-9-one (1 g, 4.2 mmol) and TEA (1.74 ml, 13 mmol) in CH₂Cl₂ (200 ml) MsCl

(320 μ l, 4.2 mmol) was dropwise added. The reaction mixture was stirred for 30 min. at the same temperature and the organic solution was washed with saturated aq. NH_4Cl and with water. The organic solution was dried and evaporated to obtain **11a** (730 mg, 95%), as a white solid without further purification

mp 265-266°C (MeOH).

IR (KBr) ν 3424 (m, NH), 1721 (s, C=O), 1691 (m, NCO), 1633 (m, C=C), 1408 (m, C=N), 1380 (m), 1303 (m).

^1H -NMR (DMSO- d_6 , 300 MHz) δ 6.50 (d, J 7.4, 1H, H6), 6.60 (s, 1H, H5), 6.97 (dd, J 7.4 and 5.3, 1H, H7), 7.37 (dd, J 8.0 and 4.7, 1H, H3), 8.08 (dd, J 8.0 and 1.7, 1H, H4), 8.39 (dd, J 4.7 and 1.7, 1H, H2), 10.81 (brd, J 5.3, 1H, NH).

^{13}C -NMR (DMSO- d_6 , 75 MHz) δ 94.9 (d, C5), 98.0 (d, C6), 119.8 (d, C3), 123.1 (s, C4a), 127.5 (d, C4), 128.0 (d, C7), 137.0 (s, C5a), 142.5 (d, C2), 145.6 (s, C10a*), 146.7 (s, C9*).

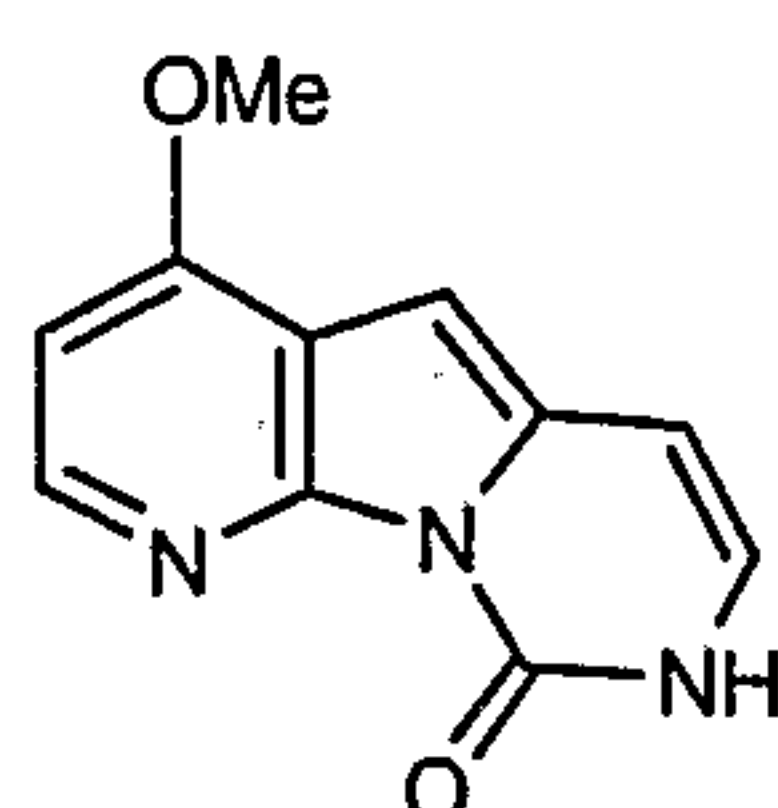
MS (EI) m/z 186 ($M+1$, 18), 185 (M^+ , 15), 157 ($M-\text{CO}$, 10)

(CI, NH_3) m/z 204 ($M+18$, 12), 187 ($M+2$, 14), 186 ($M+1$, 100), 109 (48).

HRMS m/z calculated for $\text{C}_{10}\text{H}_7\text{N}_3\text{O}$: 185.0589, found: 185.0593.

Example 15

8,9-Dihydro-4-methoxypyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidin-9-ona (**11b**)



Following the same procedure for **11a**, from 6,7,8,9-tetrahydro-6-hydroxy-4-methoxypyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidin-9-one (113 mg, 0.42 mmol), TEA (195 μ l, 1.25 mmol) and MsCl (32 μ l, 0.42 mmol) in CH₂Cl₂ (20 ml). Reaction time 30 min. **11b** (74 mg, 85%) was obtained as a white solid without further purification.

IR (KBr) ν 3380 (m, NH), 1721 (s, C=O), 1693 (m, NCO), 1633 (m, C=C), 1500 (m, C=N), 1294 (m, C-O).

¹H-NMR (DMSO-*d*⁶, 500 MHz) δ 3.98 (s, 3H, Me), 6.44 (d, *J* 7.5, 1H, H6), 6.54 (s, 1H, H5), 6.89 (dd, *J* 7.5 and 2.0, 1H, H7), 6.96 (d, *J* 5.5, 1H, H3), 8.26 (d, *J* 5.5, 1H, H2).

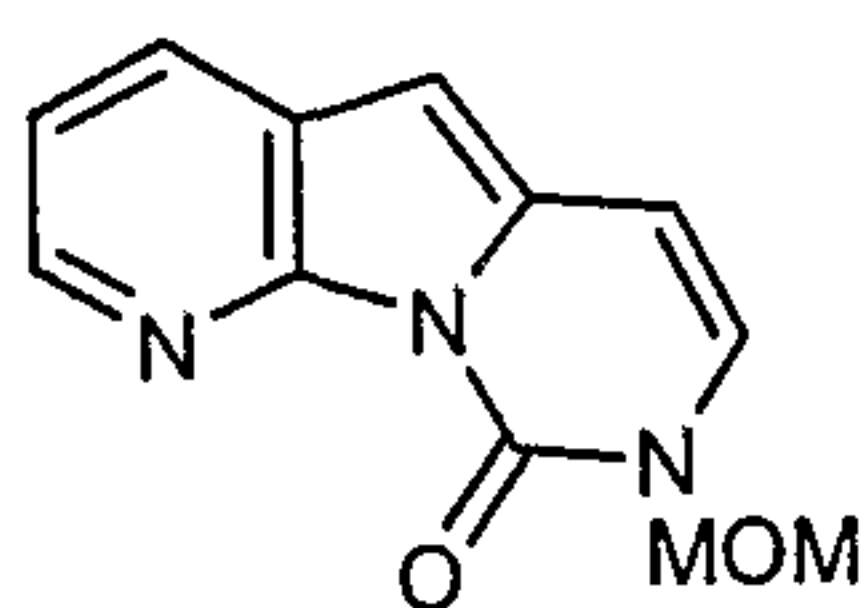
¹³C-NMR (DMSO-*d*⁶, 75 MHz) δ 55.5 (q, Me), 92.6 (d, C5), 98.9 (d, C6), 101.0 (d, C3), 124.7 (d, C7), 114.0 (s, C4a), 134.1 (s, C5a), 144.9 (d, C2), 146.5 (s, C9), 147.7 (s, C10a), 159.1 (s, C4).

MS (EI) *m/z* 216 (M+1, 17), 215 (M⁺, 100), 214 (M-1, 11), 200 (M-Me, 59), 172 (48).

HRMS *m/z* calculated for C₁₁H₉N₃O₂: 215.0694; found: 215.0690.

Example 16

8,9-Dihydro-8-methoxymethylpyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidin-9-one (12)



To a cooled (0°C) solution of **11a** (250 mg, 1.4 mmol) in DMF (10 ml), NaH (65 mg, 1.6 mmol) was added. The mixture was stirred for 10 min. and MOMCl (103 μ l, 1.4 mmol) was dropwise added. The mixture was stirred at 0°C for 1h and quenched with water (1 ml). The solvent was evaporated and the residue dissolved in CH₂Cl₂. The organic solution was

washed with aq. Na_2CO_3 , evaporated and purified by flash column chromatography. Elution with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95/5) gave **12** (267 mg, 87%) as a white solid.

IR (film) ν 1711 (s, C=O), 1642 (m, NCO), 1393 (m, C-O), 1175 (m, C-O).

^1H -NMR (CDCl_3 , 300 MHz) δ 3.41 (s, 3H, Me), 5.29 (s, 2H, CH_2), 6.37 (d, J 7.5, 1H, H6), 6.41 (s, 1H, H5), 7.81 (d, J 7.5, 1H, H7), 7.26 (dd, J 7.8 and 4.8, 1H, H3), 7.90 (dd, J 7.8 and 1.2, 1H, H4), 8.52 (dd, J 4.8 and 1.2, 1H, H2).

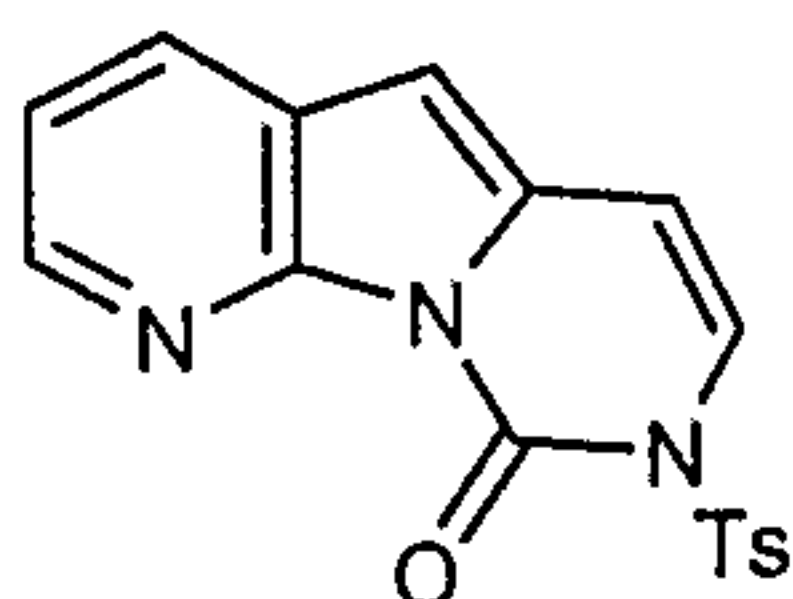
^{13}C -NMR (CDCl_3 , 50 MHz) δ 56.9 (q, Me), 78.0 (t, CH_2), 95.9 (d, C5), 99.6 (d, C6), 119.5 (d, C3), 123.3 (s, C4a), 127.9 (d, C4), 128.1 (d, C7), 135.1 (s, C5a), 143.7 (d, C2), 146.2 (s, C9), 147.1 (s, C10a).

MS (EI) m/z 230 ($M+1$, 30), 229 (M^+ , 100).

HRMS m/z calculated for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_2$: 229.0851; found: 229.0850.

Example 17

8,9-Dihydro-8-(4-methylphenylsulfonyl)pyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidin-9-one



To a cooled (0°C) solution of **11a** (500 mg, 2.7 mmol) in DMF (30 ml), NaH (130 mg, 3.2 mmol) was added. The mixture was stirred for 10 min. and a solution of *p*-toluensulphonyl chloride (570 mg, 3.0 mmol) in DMF (10 ml) was added. The mixture was stirred at room temperature for 1h. and quenched with water (1 ml). The solvent was evaporated and the residue dissolved in AcOEt. The organic solution was washed with aq. Na_2CO_3 , evaporated and purified by flash column chromatography. Elution with hexane/ CH_2Cl_2 (1/1) gave 8,9-

dihydro-8-(4-methylphenylsulfonyl)pyrido[3',2':4,5]-pyrrolo[1,2-*c*]pyrimidin-9-one (360 mg, 40%) as a white solid.

IR (film) ν 1737 (s, C=O), 1642 (m, NCO), 1393 (s, SO₂), 1175 (m).

¹H-NMR (CDCl₃, 200 MHz) δ 2.42 (s, 3H, Me), 6.45 (d, *J* 8.0, 1H, H6), 6.48 (s, 1H, H5), 7.27 (dd, *J* 8.2 and 4.7, 1H, H3), 7.34 (d, *J* 8.4, 2H, H3' and H5'), 7.65 (d, *J* 8.0, 1H, H7), 7.90 (dd, *J* 8.2 and 1.4, 1H, H4), 8.09 (d, *J* 8.4, 2H, H2' and H6'), 8.53 (dd, *J* 4.7 and 1.4, 1H, H2).

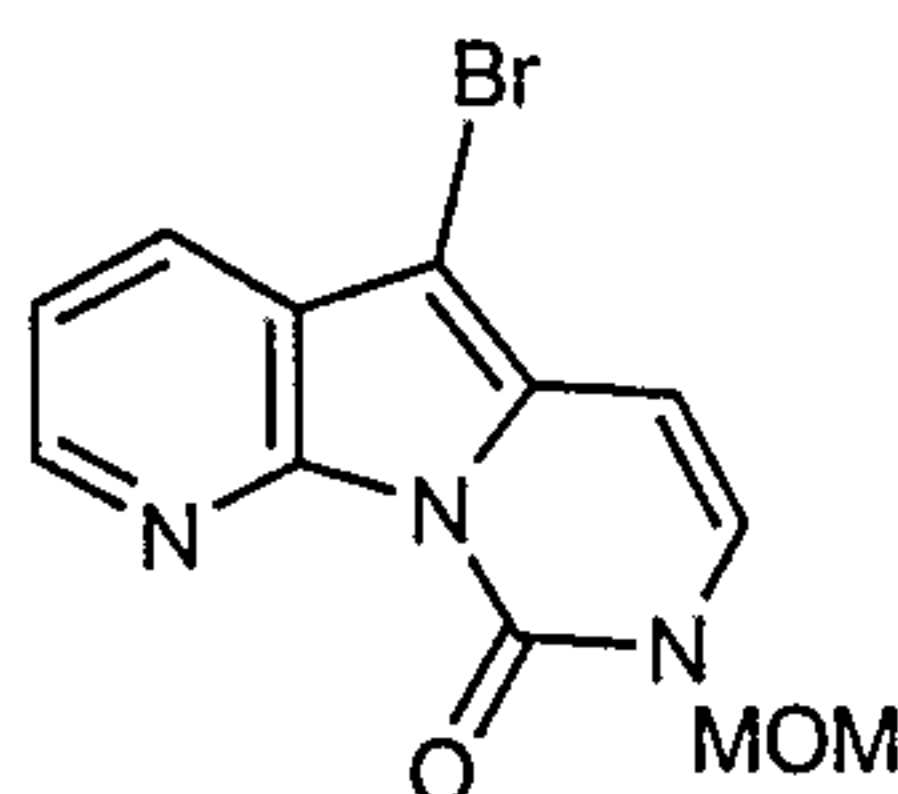
¹³C-NMR (CDCl₃, 50 MHz) δ 21.8 (q, Me), 98.3 (d, C5), 100.2 (d, C6), 118.5 (s, C4'), 120.1 (d, C3), 123.6 (s, C4a), 123.7 (d, C4), 128.6 (d, C7), 129.6 (d, C3' and C5'), 129.8 (d, C2' and C6'), 133.8 (s, C5a), 141.8 (s, C1'), 144.6 (d, C2), 146.0 (s, C9).

MS (EI) *m/z* 340 (M+1, 7), 339 (M⁺, 32), 184 (M-Ts, 100).

HRMS *m/z* calculated for C₁₇H₁₃N₃O₃S: 339.0677; found: 339.0682.

Example 18

8,9-Dihydro-5-bromo-8-methoxymethylpyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidin-9-one (13a)



NBS (78 mg, 0.44 mmol) was portionwise added to a solution of **12a** (100 mg, 0.44 mmol) in CH₂Cl₂ (30 ml) at 0°C and the mixture was stirred for 10 min. The mixture was diluted with CH₂Cl₂ (50 ml) and washed with saturated aq. NaHCO₃ three times. The organic layer was dried and evaporated to obtain **13a** (107 mg, 80%) as a light yellow solid without any further purification.

IR (film) ν 1715 (s, C=O), 1640 (m, C=C), 1092 (m, C-O).

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 3.39 (s, 3H, Me), 5.29 (s, 2H, CH_2), 6.43 (d, J 7.8, 1H, H6), 6.90 (d, J 7.8, 1H, H7), 7.33 (dd, J 8.1 and 4.8, 1H, H3), 7.86 (dd, J 8.1 and 1.5, 1H, H4), 8.54 (dd, J 4.8 and 1.5, 1H, H2).

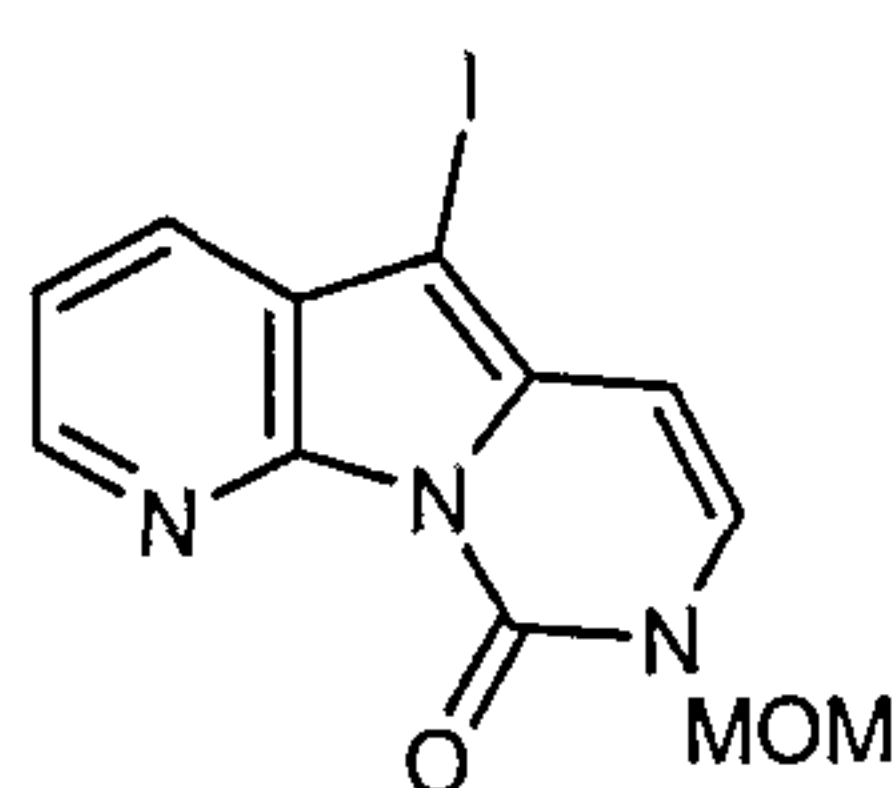
$^{13}\text{C-NMR}$ (CDCl_3 , 50 MHz) δ 57.0 (q, Me), 77.1 (s, C5), 78.3 (t, CH_2), 97.7 (d, C6), 120.1 (d, C3), 122.7 (s, C4a), 126.7 (d, C4), 129.2 (d, C7), 132.8 (s, C5a), 144.8 (d, C2), 146.2 (s, C9), 146.5 (s, C10a).

MS (EI) m/z 310 ($^{81}\text{BrM}+1$, 5), 309 ($^{81}\text{BrM}^+$, 50), 308 ($^{79}\text{BrM}+1$, 5), 307 ($^{79}\text{BrM}^+$, 50), 45 (MOM, 100).

HRMS m/z calculated for $\text{C}_{12}\text{H}_{10}^{79}\text{BrN}_3\text{O}_2$: 306.9957; found: 306.9956.

Example 19

8,9-Dihydro-5-iodo-8-methoxymethylpyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidin-9-one (13b)



To a cooled (0°C) solution of **11a** (100 mg, 0.44 mmol) in DMF (4 ml) iodine (220 mg, 0.86 mmol) and KOH (94 mg, 1.66 mmol) were simultaneously added. The mixture was stirred for 30 min. at 0°C . The mixture was quenched with an aqueous solution (25 ml) of 0.5% NH_3 and 0.1% $\text{Na}_2\text{S}_2\text{O}_5$. The solution was extracted with AcOEt and the organic solution was washed with saturated aq. NaHCO_3 twice. The organic layer was dried and evaporated to obtain **13b** (96 mg, 62%) as a light yellow solid without any further purification.

IR (film) ν 1714 (s, C=O), 1637 (m, C=C), 1089 (m, C-O).

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 3.45 (s, 3H, Me), 5.36 (s, 2H, CH_2), 6.46 (d, J 8.1, 1H, H6), 6.99 (d, J 8.1, 1H, H7), 7.40 (dd, J 8.1 and 4.8, 1H, H3), 7.81 (dd, J 8.1 and 1.8, 1H, H4), 8.59 (dd, J 4.8 and 1.8, 1H, H2).

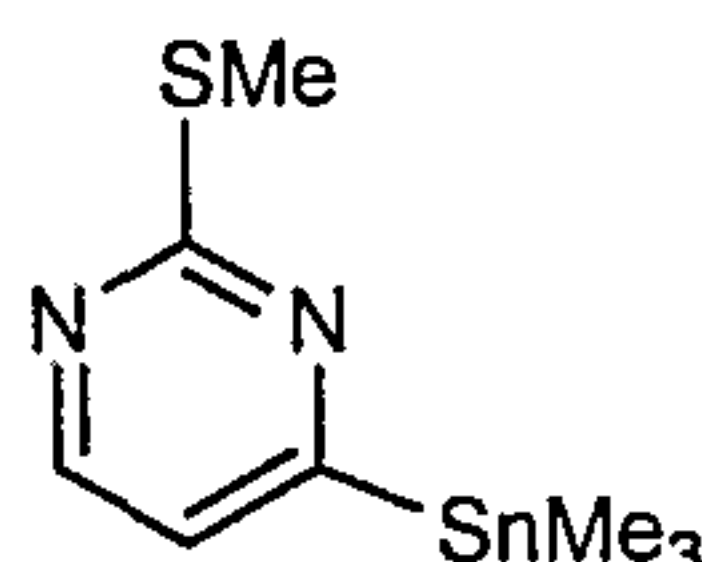
$^{13}\text{C-NMR}$ (CDCl_3 , 50 MHz) δ 54.5 (s, C5), 57.1 (q, Me), 78.3 (t, CH_2), 99.6 (d, C6), 120.3 (d, C3), 125.5 (s, C4a), 128.6 (d, C4), 129.8 (d, C7), 136.5 (s, C5a), 144.9 (d, C2), 146.0 (s, C9), 146.3 (s, C10a).

MS (CI, NH_3) m/z 357 ($M+2$, 5), 356 ($M+1$, 30), 230 (100).

HRMS m/z calculated for $\text{C}_{12}\text{H}_{10}\text{IN}_3\text{O}_2$: 354.9820; found: 354.9823.

Example 20

2-Methanesulfanyl-4-trimethylstannylpyrimidine (15)



TBAF (5 ml, 1M in THF) was dropwise added to a solution of 4-iodo-2-methanesulfenylpyrimidine (800 mg, 3.2 mmol), hexamethylditin (1 ml, 4.8 mmol), $\text{Pd}(\text{OAc})_2$ (45 mg, 0.31 mmol) and PPh_3 (90 mg, 0.62 mmol) in THF (10 ml). The mixture was stirred at room temperature for 1.5 hours. The solvent was removed under vacuum and the residue purified by neutral alumina column chromatography. Elution with hexane/AcOEt (99/1) yielded **15** (585 mg, 65%) as a colourless oil.

IR (film) ν 1539 (m, C=N), 1402 (m), 1306 (m), 1196 (m).

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 0.34 (s, 9H, 3Me), 2.54 (s, 3H, Me), 7.08 (d, J 4.5, 1H, H5), 8.26 (d, J 4.5, 1H, H6).

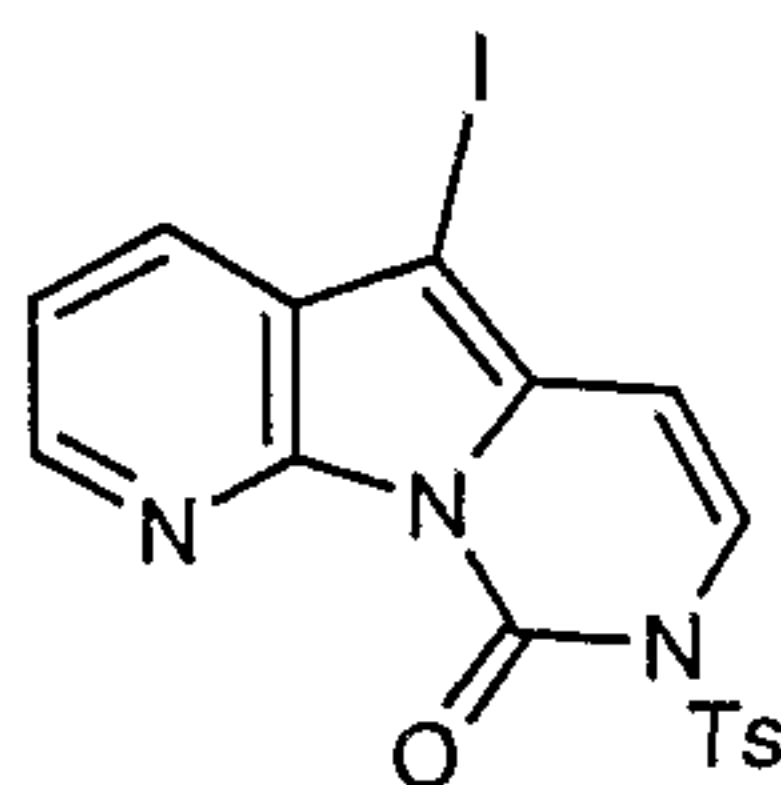
^{13}C -NMR (CDCl_3 , 75 MHz) δ -9.5 (q, Me), 14.0 (q, Me), 124.5 (d, C5), 153.6 (d, C6), 171.4 (s, C2).

MS (EI) m/z 291 ($^{120}\text{SnM}^+$, 50), 276 ($^{120}\text{SnM-Me}$, 100).

HRMS m/z calculated for $\text{C}_8\text{H}_{14}\text{N}_2\text{S}^{120}\text{Sn}$: 290.9977; found: 290.9973.

Example 21

8,9-Dihydro-5-iodo-8-(4-methylphenylsulphonyl)pyrido[3',2':4,5]pyrrolo[1,2-c]-pyrimidin-9-one (17)



NIS (133 mg, 0.59 mmol) was portionwise added to a cooled (0°C) solution of **11a** (200 mg, 0.59 mmol) in CH_2Cl_2 (20 ml) and the mixture was stirred for 30 min. at this temperature. The mixture was diluted with CH_2Cl_2 (50 ml) and washed with water twice. The organic layer was dried and evaporated to obtain **17** (218 mg, 80%) as a light yellow solid without any further purification.

IR (film) ν 1735 (s, C=O), 1636 (s, NCO), 1395 (m, C-N), 1368 (s, SO_2), 1175 (m), 1075 (m).

^1H -NMR (CDCl_3 , 300 MHz) δ 2.38 (s, 3H, Me), 6.43 (d, J 8.3, 1H, H6), 7.30 (m, 3H, H3, H3' and H5'), 7.68 (dd, J 8.1 and 1.5, 1H, H4), 7.72 (d, J 8.3, 1H, H7), 8.04 (d, J 8.4, 2H, H2' and H6'), 8.49 (dd, J 4.8 and 1.5, 1H, H2).

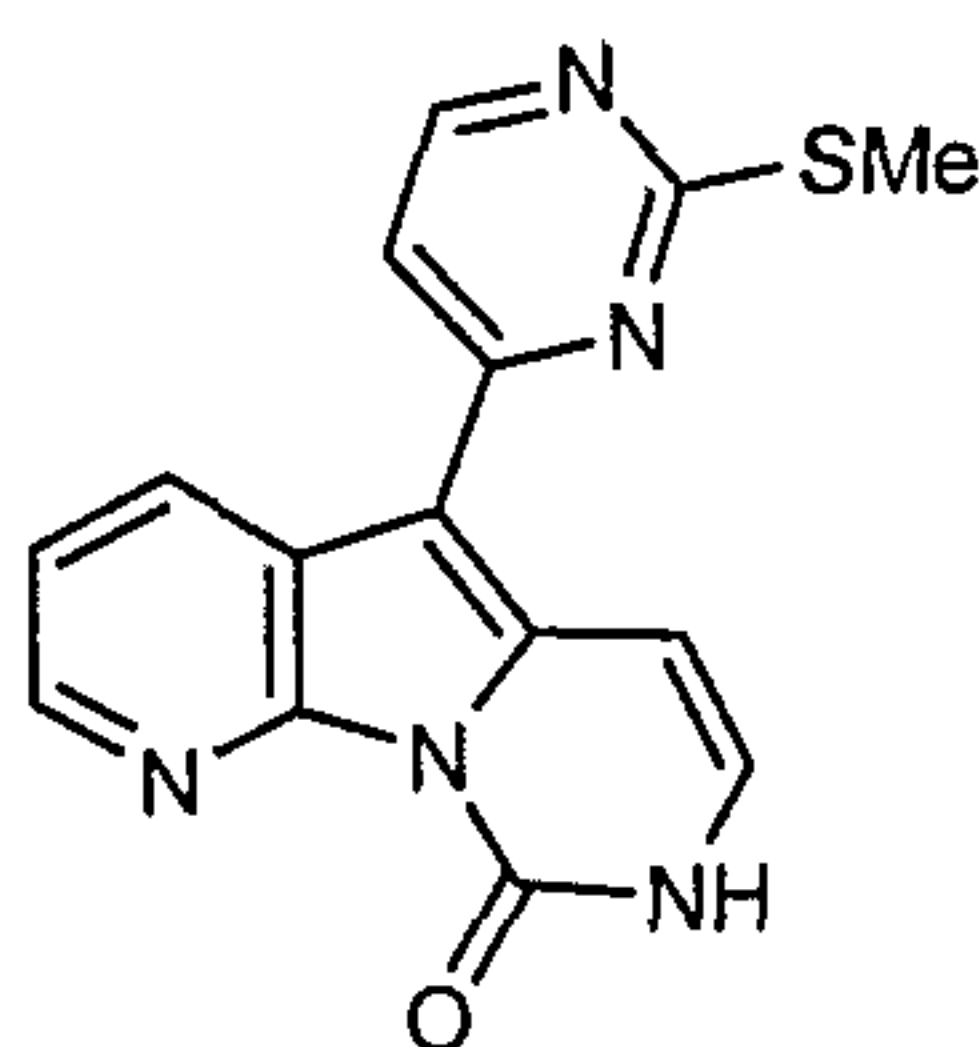
^{13}C -NMR (CDCl_3 , 75 MHz) δ 21.7 (q, Me), 56.9 (s, C5), 100.0 (d, C6), 120.7 (d, C3), 123.8 (s, C4'), 125.3 (d, C4), 125.7 (s, C4a), 129.0 (d, C7), 129.5 (s, C1'), 129.6 (d, C3' and C5'), 129.7 (d, C2' and C6'), 133.3 (s, C5a), 135.0 (s, C10a), 145.5 (d, C2), 146.1 (s, C9).

MS (EI) m/z 466 ($M+1$, 8), 465 (M^+ , 36), 310 ($M-Ts$, 100).

HRMS m/z calculated for $C_{17}H_{12}IN_3O_3S$: 464.9646; found: 464.9649.

Example 22

8,9-Dihydro-5-(2-methanesulfanylpurimidin-4-yl)pyrido[3',2':4,5]pyrrolo[1,2-*c*]-pyrimidin-9-one (18)



A solution of **17** (50 mg, 0.11 mmol), 2-methanesulfanyl-4-trimethylstannylpyrimidine (93 mg, 0.32 mmol), $Pd_2(dba)_3$ (11 mg, 0.011 mmol), PPh_3 (6 mg, 0.022 mmol), LiCl (14 mg, 0.32 mmol) and CuI (4 mg, 0.011 mmol) in dioxane (2 ml) was refluxed for 5 h. The solvent was evaporated and the crude was purified by flash column chromatography. Elution with of $CH_2Cl_2/MeOH/aq.NH_3$ (4/4/2) gave **18** (4 mg, 12%).

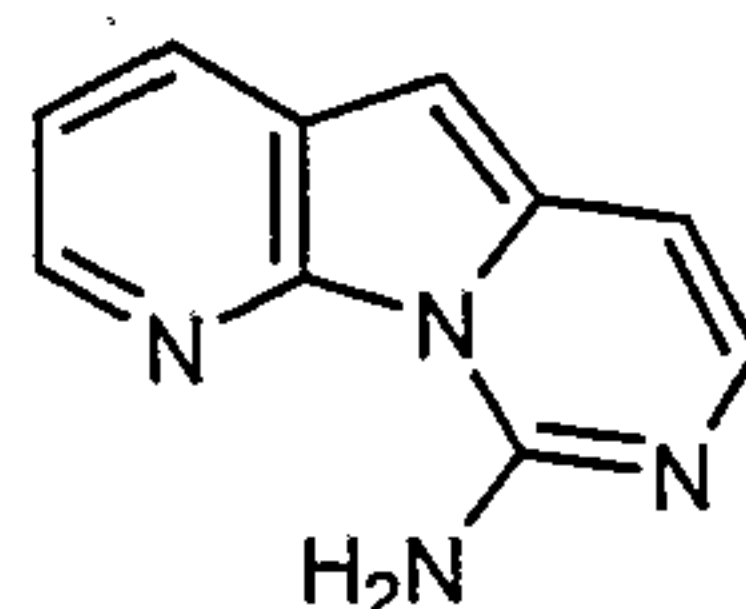
^1H -NMR ($DMSO-d_6$, 300 MHz) δ 2.60 (3H, s, MeS), 7.20 (1H, d, J 6.3, H7), 7.42 (1H, dd, J 7.5 and 4.2, H3), 7.45 (1H, d, J 5.7, H5'), 7.70 (1H, d, J 6.3, H6), 8.22 (1H, d, J 4.2, H2), 8.39 (1H, d, J 5.7, H6'), 8.73 (1H, d, J 7.5, H4).

MS (APCI) AP- m/z 309 (M^+ , 20), 308 ($M-1$, 90), 307 ($M-2$, 100); AP+ m/z 331($M+Na$, 10), 310 ($M+1$, 20), 309 (M^+ , 25).

Example 23

9-Aminopyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine (19a)

42



From 11a:

TMSCl (400 μ l, 2.70 mmol) was added to a solution of **11a** (500 mg, 2.70 mmol) in 2,6-lutidine (40 ml) and HMDSA (60 ml) and the mixture refluxed for 15 h. TMSTf (100 μ l, 0.27 mmol) was added and NH_3 was bubbled through the mixture for 15 min. at 0°C . The mixture was closed in a steel bomb reactor and heated at 150°C for 8 h. (60 psi). The solvent was evaporated and the crude purified by flash column chromatography. Elution with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98/2) gave **19a** (150 mg, 30%) as a light yellow solid.

From 23a:

A solution of **23a** (20 mg, 0.06 mmol) in liquid NH_3 (8 ml) at -78°C . Small portions of Na were added until blue color was maintained for 10 min. NH_4Cl was portionwise added until blue color disappeared, and the reaction was stirred at room temperature until solvent was evaporated. The solid residue was dissolved in water and extracted with CH_2Cl_2 . The organic solution was dried and evaporated to obtain **19a** (4 mg, 38%) as a yellow solid.

mp $214\text{--}215^\circ\text{C}$ (dec.), (CH_2Cl_2 /hexane).

IR (KBr) ν 3452 (m, NH), 3304 (m, NH), 1654 (m, C=C), 1618 (m, C=C), 1570 (m, C=N), 1403 (m, C-N).

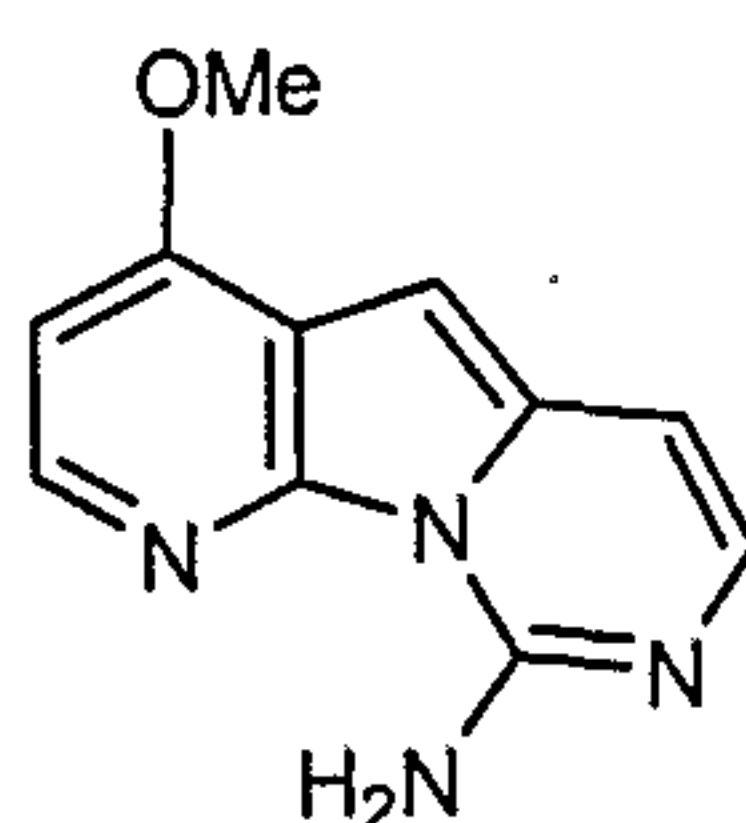
^1H -NMR ($\text{DMSO-}d^6$, 300 MHz) δ 6.49 (s, 1H, H5), 6.72 (d, J 6.6, 1H, H6), 6.80 (br, 1H, NH), 7.30 (d, J 6.6, 1H, H7), 7.42 (dd, J 7.8 and 4.6, 1H, H3), 8.14 (dd, J 7.8 and 1.5, 1H, H4), 8.33 (dd, J 4.6 and 1.5, 1H, H2), 8.60 (br, 1H, NH).

^{13}C -NMR ($\text{DMSO-}d^6$, 75 MHz) δ 88.8 (d, C5), 101.0 (d, C6), 119.6 (d, C3), 122.9 (s, C4a), 127.5 (d, C4), 136.8 (s, C5a), 138.9 (d, C2), 139.4 (d, C7), 141.8 (s, C10a), 148.8 (s, C9).

MS (EI) m/z 185($M+1$, 15), 184 (M^+ , 100), 183 ($M-1$, 7).

HRMS m/z calculated for $\text{C}_{10}\text{H}_8\text{N}_4$: 184.0749; found: 184.0747.

Example 24

9-Amino-4-methoxypyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine (19b)*From 11b:*

Following the same procedure for **19a**, from **11b** (60 mg, 0.27 mmol), HMDSA (30 ml), 2,6-lutidine (15 ml) and TMSCl (36 μ l, 0.27 mmol). Reaction time 15 h. TMSTf (12 μ l, 0.06 mmol) was added and NH_3 was bubbled through the mixture for 15 min. at 0°C. Reaction time in a steel bomb reactor 8 h. heated at 150°C (60 psi). The solvent was evaporated and the crude purified by flash column chromatography. Elution with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (99/1) gave **19b** (13 mg, 22%) and elution with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95/5) gave **11b** (9 mg, 15%).

From 23b:

To a solution of **23b** (200 mg, 0.54 mmol) in THF (25 ml) at 0°C was dropwise added a previously prepared green solution of Na/naphthalene in THF (1.43 ml, 0.54 mmol). After 20 min. The solution was stirred at room temperature and Na/naphthalene in THF (7.2 ml, 2.70 mmol) was dropwise added and the mixture was stirred for 15 min. The solvent was removed and the crude dissolved in AcOEt. The organic solution was extracted three times with 4N HCl. The aqueous layers were basified together with NaHCO_3 and extracted with CH_2Cl_2 . The organic solution was dried and evaporated and the residue was purified by flash column chromatography. Elution with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95/5) gave **19b** (27 mg, 23%) as a light yellow solid.

^1H -NMR ($\text{CDCl}_3+\text{CD}_3\text{OD}$, 300 MHz) δ 4.01 (s, 3H, Me), 6.45 (s, 1H, H5), 6.61 (d, J 6.6, 1H, H6), 6.75 (d, J 5.6, 1H, H3), 7.14 (d, J 6.6, 1H, H7), 8.18 (d, J 5.6, 1H, H2).

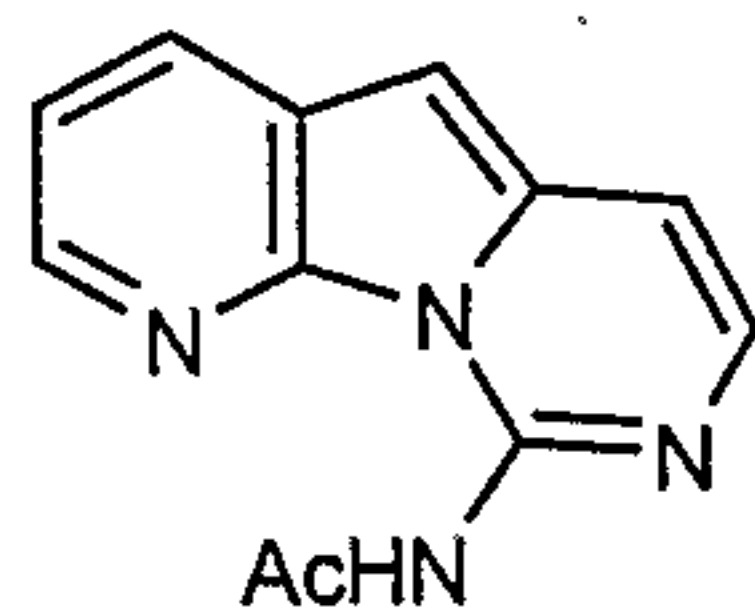
^{13}C -RMN ($\text{CDCl}_3 + \text{CD}_3\text{OD}$, 75 MHz) δ 55.6 (q, Me), 87.5 (d, C5), 100.6 (d, C6), 102.2 (d, C3), 114.3 (s, C4a), 134.4 (s, C5a), 136.0 (d, C2), 141.7 (d, C7), 142.8 (s, C10a), 149.0 (s, C9), 158.8 (s, C4).

MS (EI) m/z 215 ($M+1$, 7), 214 (M^+ , 36), 213 ($M-1$, 6), 199 ($M-\text{Me}$, 36), 57 (100).

(ES+) m/z 216 ($M+2$, 20), 215 ($M+1$, 100).

Example 25

9-Acetylamino pyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine



Acetic anhydride (200 μL , 2.04 mmol) was added to a solution of **19a** (250 mg, 1.36 mmol) in THF (20 ml) and the mixture was stirred at room temperature for 20 h. The solvent was removed and taken up in CH_2Cl_2 . The solution was washed with saturated aq. NaHCO_3 . The organic layer was dried and evaporated. The crude was purified by flash column chromatography. Elution with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (99/1) gave 9-acetylamino pyrido[3',2':4,5]-pyrrolo[1,2-*c*]pyrimidine (225 mg, 75%) as a bright yellow solid.

mp 160-161°C, (CH_2Cl_2 /hexane).

IR (KBr) ν 3150 (m, NH), 1708 (s, C=O), 1626 (m, NCO), 1574 (m, C=N), 1372 (m, C-N), 1269 (m).

^1H -NMR (CDCl_3 , 300 MHz) δ 2.63 (s, 3H, Me), 6.53 (s, 1H, H5), 6.97 (d, J 6.6, 1H, H6), 7.41 (dd, J 8.0 and 4.8, 1H, H3), 7.51 (d, J 6.6, 1H, H7), 8.10 (dd, J 8.0 and 1.5, 1H, H4), 8.41 (dd, J 4.8 and 1.5, 1H, H2).

^{13}C -NMR (CDCl_3 , 75 MHz) δ 26.2 (q, Me), 90.5 (d, C5), 107.2 (d, C6), 119.6 (d, C3), 122.8 (s, C4a), 128.4 (d, C4), 136.0 (s, C5a), 136.5 (d, C2), 139.6 (d, C7), 141.3 (s, C10a), 142.3 (s, C9), 170.0 (s, CO).

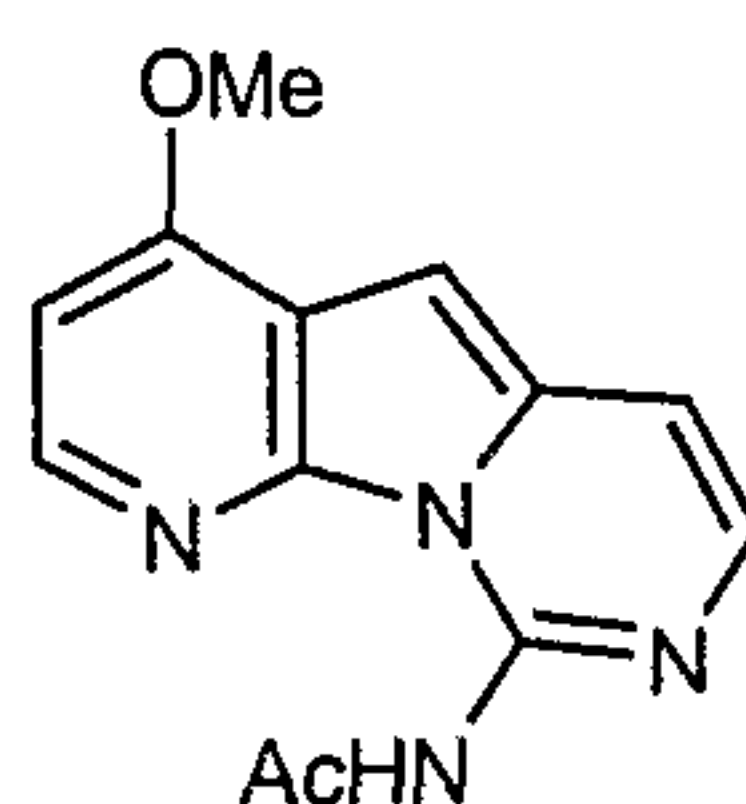
MS (EI) m/z 227 ($M+1$, 3), 226 (M^+ , 18), 184 ($M\text{-Ac}$, 100).

HRMS m/z calculated for $\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}$: 226.0855; found: 226.0852.

Analysis calculated for $\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}$: C (63.71), H (4.46), N (24.77); found: C (63.65), H (4.59), N (24.80).

Example 26

9-Acetylamino-4-methoxypyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine



Acetic anhydride (10 μL , 0.05 mmol) was added to a solution of **19b** (16 mg, 0.08 mmol) in THF (2 ml) and the mixture was stirred at room temperature for 20 h. The solvent was removed and taken up in CH_2Cl_2 . The solution was washed with saturated aq. NaHCO_3 . The organic layer was dried and evaporated. 9-Acetylamino-4-methoxypyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine (17 mg, 95%) was obtained without any further purification.

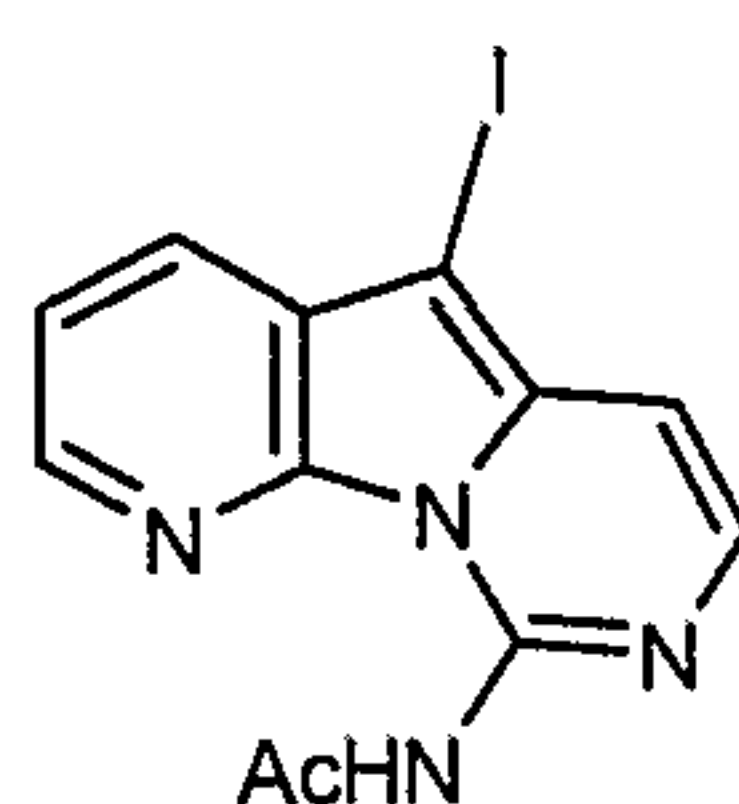
^1H -NMR (CDCl_3 , 300 MHz) δ 2.60 (s, 3H, Me), 4.07 (s, 3H, Me), 6.60 (s, 1H, H5), 6.82 (d, J 5.7, 1H, H3), 6.96 (d, J 6.6, 1H, H6), 7.47 (d, J 6.6, 1H, H7), 8.29 (d, J 5.7, 1H, H2).

^{13}C -NMR (CDCl_3 , 75 MHz) δ 26.3 (q, Me), 55.8 (q, Me), 88.1 (d, C5), 100.7 (d, C6), 107.7 (d, C3), 114.1 (s, C4a), 134.5 (s, C5a), 135.9 (d, C2), 142.1 (d, C7), 159.5 (s, C4), 170.1 (s, CO).

MS (ES+) m/z 258 (M+2, 30), 257 (M+1, 100).

Example 27

9-Acetylamino-5-iodopyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine (20a)



NIS (100 mg, 0.44 mmol) was portionwise added to a cooled (0°C) solution of 9-Acetylamino-5-iodopyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine (100 mg, 0.44 mmol) in CH₂Cl₂ (20 ml). The mixture was stirred for 15 min. The solution was diluted with CH₂Cl₂ (50 ml) and washed twice with water. The organic layer was dried and evaporated to obtain **20a** (142 mg, 93%) as a bright yellow solid

mp 163-164°C(dec.), (CH₂Cl₂/hexane).

IR (KBr) ν 3050 (m, NH), 1694 (m, C=O), 1573 (m, C=N), 1372 (m, C-N), 1307 (m).

¹H-NMR (CDCl₃, 200 MHz) δ 2.63 (s, 3H, Me), 6.94 (d, *J* 6.4, 1H, H6), 7.47 (dd, *J* 8.2 and 4.8, 1H, H3), 7.61 (d, *J* 6.4, 1H, H7), 7.93 (dd, *J* 8.2 and 1.6, 1H, H4), 8.40 (dd, *J* 4.8 and 1.6, 1H, H2).

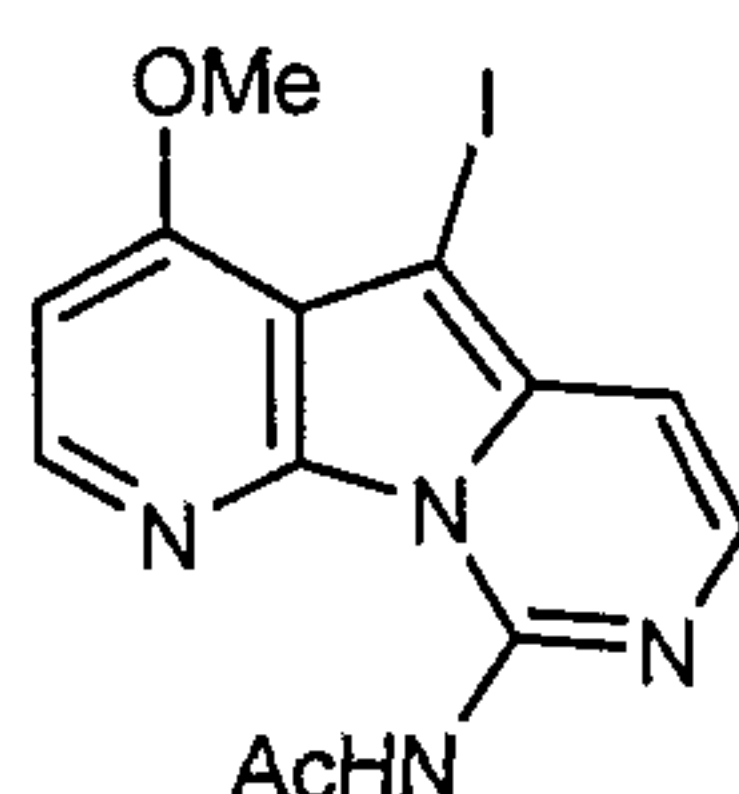
¹³C-NMR (CDCl₃, 75 MHz) δ 26.4 (q, Me), 46.7 (s, C5), 107.0 (d, C6), 120.6 (d, C3), 125.2 (s, C4a), 128.8 (d, C4), 136.9 (s, C5a), 138.6 (d, C7), 140.9 (d, C2), 141.5 (s, C10a), 142.7 (s, C9), 170.2 (s, CO).

MS (EI) m/z 353 (M+1, 3), 352 (M⁺, 22), 310 (M-Ac, 100).

HRMS m/z calculated for C₁₂H₉IN₄O: 351.9821; found: 351.9821.

Analysis calculated for C₁₂H₉IN₄O: C (40.93), H (2.58), N (15.91); found: C (40.91), H (2.64), N (15.79).

Example 28

9-Acetylamino-5-iodo-4-methoxypyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine (20b)

NIS (18 mg, 0.078 mmol) was portionwise added to a cooled (0°C) solution of 9-Acetylamino-4-methoxypyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine (20 mg, 0.078 mmol) in CH₂Cl₂ (15 ml). The mixture was stirred for 15 min. The solution was diluted with CH₂Cl₂ (50 ml) and washed twice with water. The organic layer was dried and evaporated to obtain **20b** (27 mg, 93%).

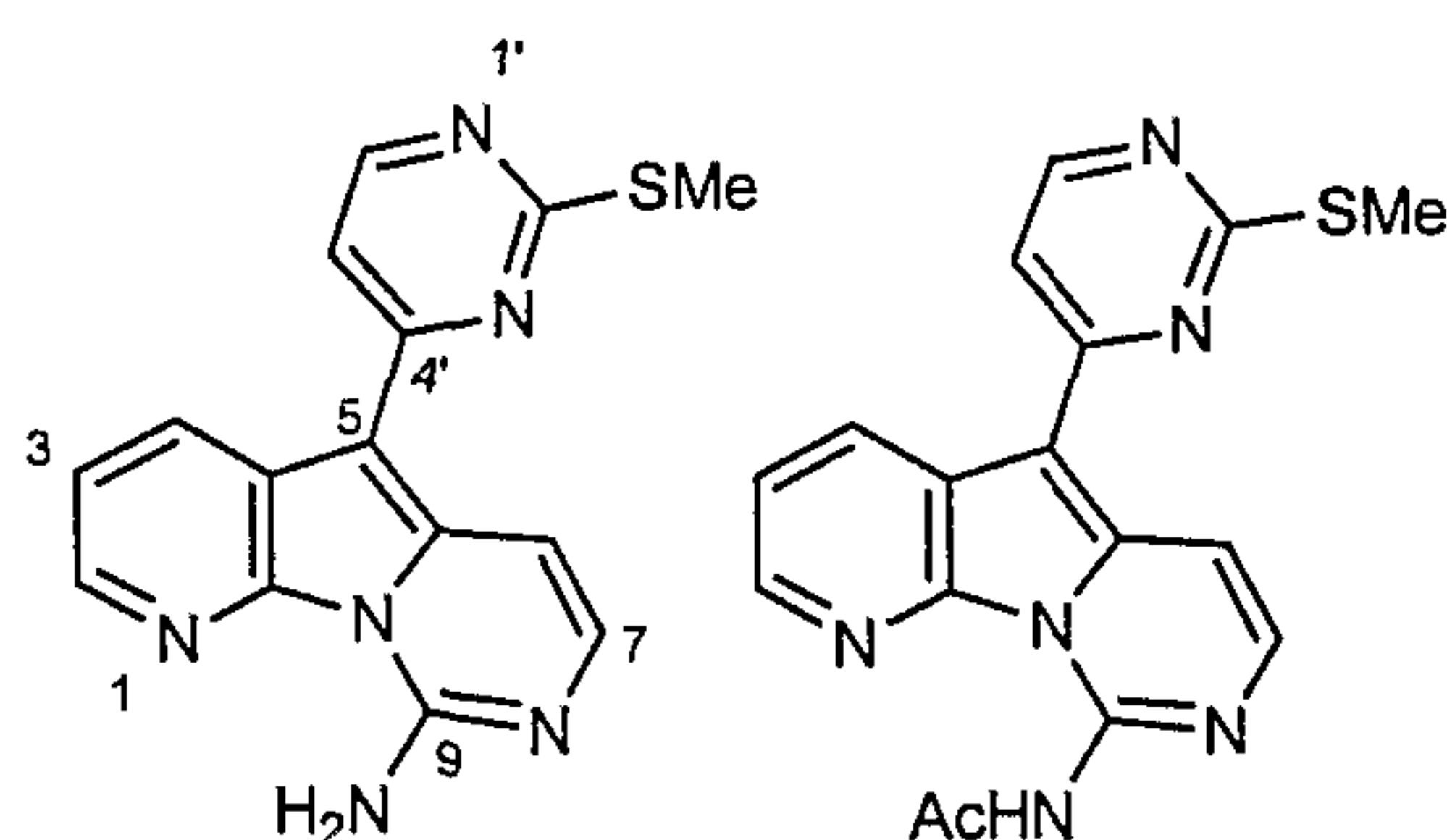
¹H-NMR (CDCl₃, 200 MHz) δ 2.61 (s, 3H, Me), 4.08 (s, 3H, Me), 6.84 (d, *J* 5.7, 1H, H3), 6.97 (d, *J* 6.6, 1H, H6), 7.57 (d, *J* 6.6, 1H, H7), 8.31 (d, *J* 5.7, 1H, H2).

¹³C-NMR (CDCl₃, 75 MHz) δ 26.3 (q, Me), 55.8 (q, Me), 101.2 (d, C6), 107.7 (d, C3), 114.1 (s, C4a), 133.5 (s, C5a), 137.7 (d, C2), 142.5 (d, C7), 142.6 (s, C10a), 151.8 (s, C9), 170.4 (s, C4), 176.8 (s, CO).

MS (ES⁺) *m/z* 384 (M+2, 15), 383 (M+1, 100), 192 (M+2⁺, 50), 191 (M+1⁺, 22).

Example 29

9-Amino-5-(2-methanesulfanylpirimidin-4-yl)pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine (21) and 9-Acetylamino-5-(2-methanesulfanylpirimidin-4-yl)pyrido[3',2':4,5]-pyrrolo[1,2-c]pyrimidine



A solution of **20a** (130 mg, 0.37 mmol), 2-methanesulfenyl-4-trimethylstannylpyrimidine (93 mg, 1.10 mmol), Pd₂(dba)₃ (76 mg, 0.07 mmol), PPh₃ (39 mg, 0.15 mmol), LiCl (47 mg, 1.10 mmol) and CuI (14 mg, 0.07 mmol) in dioxane (10 ml) was refluxed for 1.5 hours. The organic solvent was removed and the oil dissolved in CH₂Cl₂. The organic solution was extracted four times with 4N HCl and the aqueous solution basified with solid Na₂CO₃. The aqueous solution was extracted with CH₂Cl₂. The organic layer was evaporated and purified by flash column chromatography. Elution with CH₂Cl₂/MeOH (99/1) gave 9-Acetylamino-5-(2-methanesulfenylpyrimidin-4-yl)pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine (21 mg, 16%) as a yellow solid and with CH₂Cl₂/MeOH (95/5) gave **21** (30 mg, 26%) as a yellow solid.

A solution of 9-acetylamino-5-(2-methanesulfenylpyrimidin-4-yl)pyrido[3',2':4,5]-pyrrolo[1,2-c]pyrimidine (15 mg, 0.043 mmol) in 5N HCl/MeOH (5 ml) was refluxed for 1 hour. The solvent was removed and the residue dissolved in saturated aq. Na₂CO₃. The solution was extracted with CH₂Cl₂. The organic solvent was evaporated. **21** (12 mg, 90%) was obtained.

When the reaction was repeated and the HCl/MeOH treatment was done just before the purification by flash column chromatography **21** (45%) was obtained as only product.

9-Amino-5-(2-methanesulfenylpyrimidin-4-yl)pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine (21)
mp 223-224°C (CH₂Cl₂/hexane).

IR (KBr) ν 3390 (m, NH), 1632 (m, C=C), 1557 (m, C=N), 1517 (m), 1464 (m, C-N), 1265 (m).

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 2.68 (s, 3H, Me), 7.33 (d, J 5.4, 1H, H5'), 7.49 (dd, J 8.4 and 4.8, 1H, H3), 7.58 (d, J 6.6, 1H, H7), 7.68 (d, J 6.6, 1H, H6), 8.40 (dd, J 4.8 and 1.6, 1H, H2), 8.48 (d, J 5.4, 1H, H6'), 8.73 (dd, J 8.4 and 1.6, 1H, H4).

$^{13}\text{C-NMR}$ (CDCl_3 , 50 MHz) δ 14.4 (q, MeS), 100.3 (s, C5), 102.1 (d, C6), 112.6 (d, C5'), 120.7 (d, C3), 122.0 (s, C4a), 128.6 (d, C4), 138.7 (s, C5a), 140.3 (d, C2), 142.1 (s, C10a), 143.4 (d, C7), 149.8 (s, C9), 156.5 (d, C6'), 161.2 (s, C4'), 172.3 (s, C2').

MS (EI) m/z 309 ($M+1$, 7), 308 (M^+ , 33).

HRMS m/z calculated for $\text{C}_{15}\text{H}_{12}\text{N}_6\text{S}$: 308.0844; found: 308.0839.

UV (MeOH) λ 217 (16,324), 252 (21,415), 400 (11,692).

9-Acetylamino-5-(2-methanesulphenylpyrimidin-4-yl)pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine

mp 160-162°C (CH_2Cl_2 /hexane).

IR (KBr) ν 1704 (s, C=O), 1620 (m, C=C), 1556 (m), 1536 (m, C=N), 1517 (m), 1502 (m), 1476 (m, C-N), 1265 (m).

$^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ 2.67 (s, 3H, Me), 2.69 (s, 3H, MeS), 7.36 (d, J 5.2, 1H, H5'), 7.58 (dd, J 8.2 and 4.8, 1H, H3), 7.83 (d, J 6.6, 1H, H7), 7.93 (d, J 6.6, 1H, H6), 8.52 (dd, J 4.8 and 1.4, 1H, H2), 8.54 (d, J 5.2, 1H, H6'), 8.77 (dd, J 8.2 and 1.4, 1H, H4).

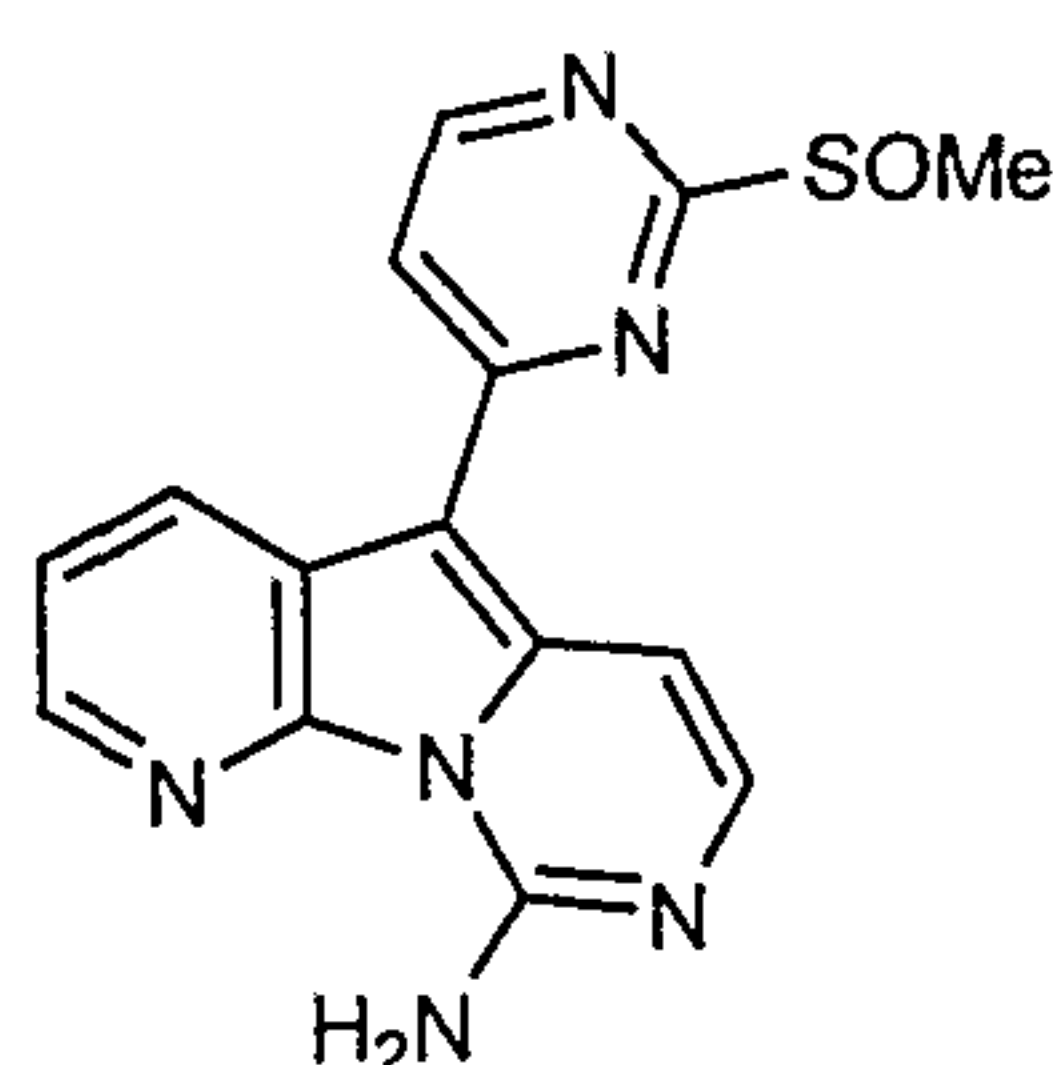
$^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 14.4 (q, MeS), 26.4 (q, Me), 104.5 (s, C5), 107.4 (d, C6), 113.0 (d, C5'), 121.1 (d, C3), 121.6 (s, C4a), 129.5 (d, C4), 137.7 (s, C5a), 141.0 (d, C2), 141.1 (d, C7), 142.5 (s, C10a), 143.3 (s, C9), 156.8 (d, C6'), 160.7 (s, C4'), 170.2 (s, C2'), 172.7 (s, CO).

MS (EI) m/z 351 ($M+1$, 3), 350 (M^+ , 33), 308 ($M\text{-Ac}$, 100).

HRMS m/z calculated for $\text{C}_{17}\text{H}_{14}\text{N}_6\text{OS}$: 350.0949; found: 350.0940.

UV (MeOH) λ 255 (25,480), 400 (17,710).

Example 30

9-Amino-5-(2-methanesulfinylpyrimidin-4-yl)pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine

To a cooled (0°C) solution of **21** (20 mg, 0.07 mmol) in CH₂Cl₂ (5 ml) *m*CPBA (32 mg, 0.13 mmol) was added. The mixture was stirred for 30 min. A saturated aq. Na₂S₂O₃ solution was added (1 ml) and was basified with saturated aq. Na₂CO₃. The organic layer was separated and the aqueous layer extracted with CH₂Cl₂. The organic solutions were dried and evaporated together to give 9-amino-5-(2-methanesulfinylpyrimidin-4-yl)pyrido[3',2':4,5]-pyrrolo[1,2-*c*]pyrimidine (20 mg, 90%).

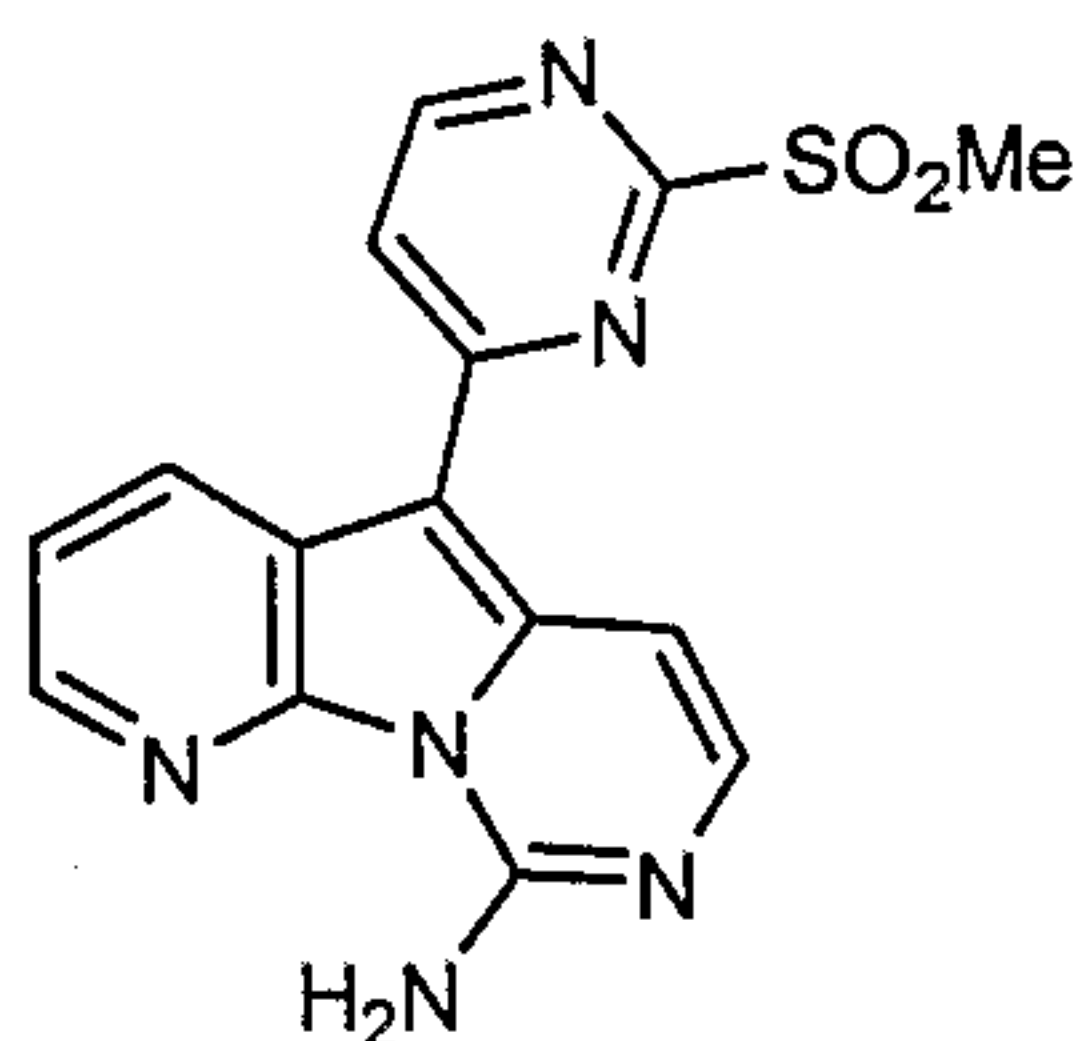
IR (film) ν 3388 (m, NH), 1635 (m, C=C), 1569 (m), 1519 (m, C=N), 1467 (m), 1267 (s, S=O).

¹H-NMR (CDCl₃, 200 MHz) δ 3.03 (s, 3H, Me), 7.53 (dd, *J* 8.2 and 4.8, 1H, H3), 7.63-7.78 (m, 3H, H7, H6 and H5'), 8.42 (dd, *J* 4.8 and 1.4, 1H, H2), 8.73 (d, *J* 5.4, 1H, H6'), 8.84 (dd, *J* 8.2 and 1.4, 1H, H4).

¹³C-NMR (CDCl₃, 50 MHz) δ 40.3 (q, Me), 99.5 (s, C5), 102.2 (d, C6), 116.5 (d, C5'), 121.3 (d, C3), 121.9 (s, C4a), 129.1 (d, C4), 140.0 (s, C5a), 140.8 (d, C2), 143.8 (s, C10a), 144.6 (d, C7), 150.0 (s, C9), 157.3 (d, C6'), 162.6 (s, C4'), 163.5 (s, C2').

MS (EI) *m/z* 324 (M⁺, 47), 261 (M-SOMe, 100); (ES⁺) *m/z* 326 (M+2, 20), 325 (M+1, 100).

Example 31

9-Amino-5-(2-methanesulfonylpyrimidin-4-yl)pyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine*Method A*

To a solution of 9-Amino-5-(2-methanesulfonylpyrimidin-4-yl)-pyrido[3',2':4,5]-pyrrolo[1,2-*c*]pyrimidine (50 mg, 0.16 mmol) in CH₂Cl₂ (15 ml) *m*CPBA (88 mg, 0.36 mmol) was added at room temperature. The mixture was stirred for 2 h. A saturated aq. Na₂S₂O₃ solution was added (1 ml) and was basified with saturated aq. Na₂CO₃. The organic layer was separated and the aqueous layer extracted with CH₂Cl₂. The organic solutions were evaporated together and 9-Amino-5-(2-methanesulfonylpyrimidin-4-yl)pyrido[3',2':4,5]-pyrrolo[1,2-*c*]pyrimidine (50 mg, 91%) as a light orange solid was obtained.

Method B

To solution of **21** (200 mg, 0.65 mmol) in CH₂Cl₂ (50 ml) *m*CPBA (320 mg, 1.30 mmol) was added. The mixture was stirred for 2 hours at room temperature. A saturated aq. Na₂S₂O₃ solution was added (5 ml) and was basified with saturated aq. Na₂CO₃. The organic layer was separated and the aqueous layer extracted with CH₂Cl₂. The organic solutions were dried and evaporated together to give 9-Amino-5-(2-methanesulfonylpyrimidin-4-yl)pyrido[3',2':4,5]-pyrrolo[1,2-*c*]pyrimidine (201 mg, 91%).

mp 118-189°C (CH₂Cl₂/hexane).

IR (film) ν 3340 (m, NH), 1569 (m, C=C), 1517 (m), 1462 (m), 1262 (s, SO₂).

^1H -NMR (CDCl_3 , 300 MHz) δ 3.41 (s, 3H, Me), 7.56 (dd, J 8.1 and 4.8, 1H, H3), 7.69 (d, J 6.6, 1H, H7), 7.78 (d, J 5.7, 1H, H5'), 7.80 (d, J 6.6, 1H, H6), 8.44 (dd, J 4.8 and 1.5, 1H, H2), 8.75 (d, J 5.7, 1H, H6'), 8.84 (dd, J 8.1 and 1.5, 1H, H4).

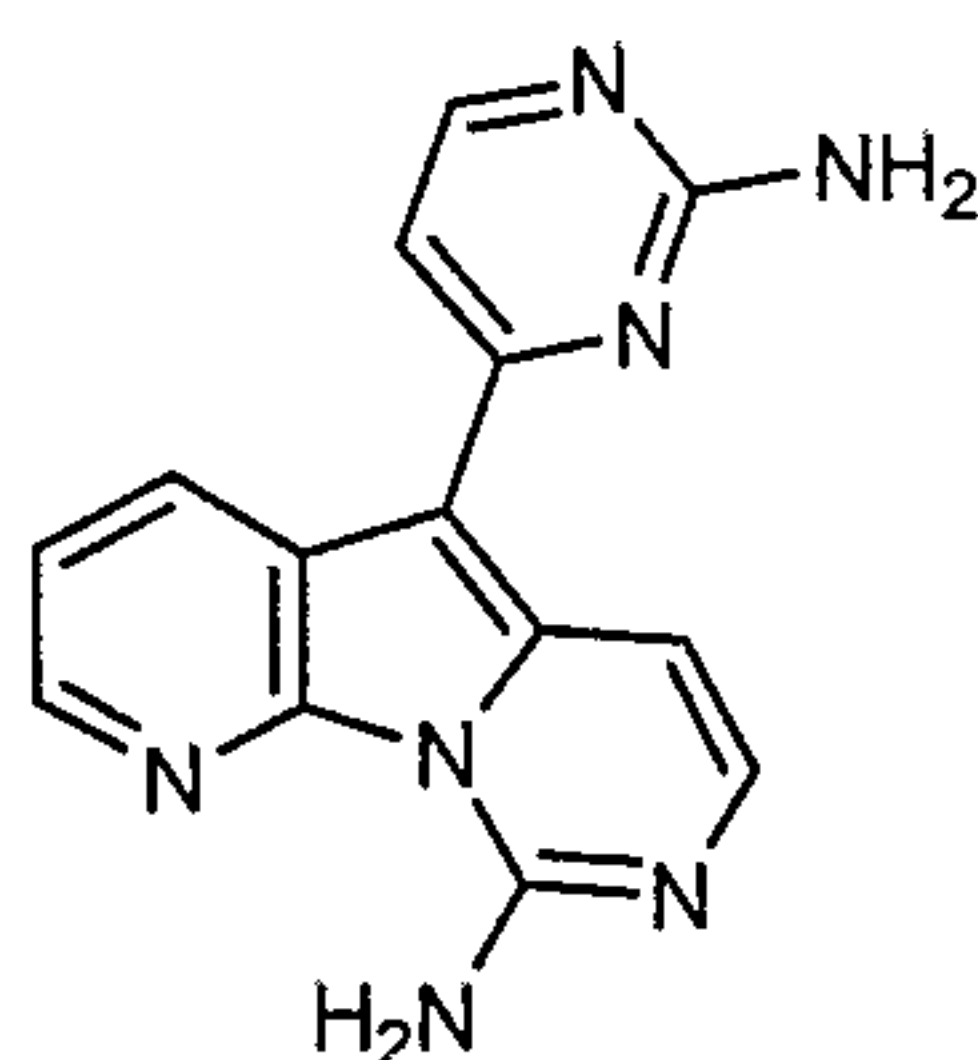
^{13}C -NMR ($\text{DMSO}-d^6$, 50 MHz) δ 39.8 (q, Me), 97.4 (s, C5), 101.0 (d, C6), 118.4 (d, C5'), 121.0 (s, C4a), 121.2 (d, C3), 128.6 (d, C4), 130.3 (s, C5a), 140.5 (d, C2), 143.3 (s, C10a), 146.8 (d, C7), 149.9 (s, C9), 157.5 (d, C6'), 161.5 (s, C4'), 165.2 (s, C2').

MS (CI, NH_3) m/z 342 ($\text{M}+2$, 6), 341 ($\text{M}+1$, 20), 340 (M^+ , 100), 309 ($\text{M}-\text{O}_2$, 5), 263 ($\text{M}-\text{SO}_2\text{Me}$, 25).

HRMS m/z calculated for $\text{C}_{15}\text{H}_{12}\text{N}_3\text{O}_2\text{S}$: 340.0742; found: 340.0740.

Example 32

9-Amino-5-(2-aminopyrimidin-4-yl)pyrido[3',2':4,5]pyrrolo[1,2-*c*]-pyrimidine (5a)



Method A

A solution of 9-Amino-5-(2-methanesulfonylpyrimidin-4-yl)pyrido-[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine (25 mg, 0.04 mmol) in dioxane (3 ml) and 23% aq. NH_3 (5 ml) was heated in a sealed tube at 80°C for 6 h. The mixture was cooled and the solvent removed. The residue was dissolved in saturated aq. Na_2CO_3 and extracted with CH_2Cl_2 several times. The organic layers were dried and evaporated. The crude was purified by flash column chromatography. Elution with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (97/3) gave **5a** (18 mg, 90%) as a yellow solid.

Method B

A solution of **20a** (120 mg, 0.36 mmol), **27** (200 mg, 0.72 mmol), Pd₂(dba)₃ (75 mg, 0.06 mmol), PPh₃ (35 mg, 0.14 mmol), LiCl (42 mg, 1.10 mmol) and CuI (12 mg, 0.06 mmol) in dioxane (4ml) was refluxed for 1.5 hours. The organic solvent was removed and the oil dissolved and refluxed in HCl/MeOH for 1 h. The solvent was evaporated and dissolved in CH₂Cl₂. The organic solution was extracted with 4N HCl four times and the aqueous solution basified with solid Na₂CO₃. The aqueous solution was extracted with CH₂Cl₂. After evaporation of the solvent the mixture was purified by flash column chromatography. Elution with CH₂Cl₂/MeOH (95/5) **5a** (50 mg, 54%) as a yellow solid was obtained.

mp 160-162°C (CH₂Cl₂/hexane).

IR (film) ν 3332 (m, NH), 1632 (m, C=C), 1574 (m, C=N), 1454 (m, C-N), 1262 (m).

¹H-NMR (DMSO-*d*⁶, 500 MHz) δ 6.63 (br, 2H, 2'NH₂), 7.12 (d, *J* 5.5, 1H, H5'), 7.64 (d, *J* 8.0 and 4.4, 1H, H3), 7.70 (d, *J* 6.6, 1H, H7), 7.76 (d, *J* 6.6, 1H, H6), 8.29 (d, *J* 5.5, 1H, H6'), 8.51 (dd, *J* 4.4 and 1.4, 1H, H2), 8.52 (br, 1H, 9NH), 8.99 (dd, *J* 8.0 and 1.4, 1H, H4), 9.35 (br, 1H, 9NH).

¹³C-NMR (DMSO-*d*⁶, 50 MHz) δ 99.5 (s, C5), 101.7 (d, C6), 106.8 (d, C5'), 120.7 (d, C3), 121.6 (s, C4a), 129.1 (d, C4), 138.2 (s, C5a), 140.1 (d, C2), 142.8 (s, C10a), 143.8 (d, C7), 149.7 (s, C9), 158.0 (d, C6'), 161.4 (s, C4'), 163.5 (s, C2').

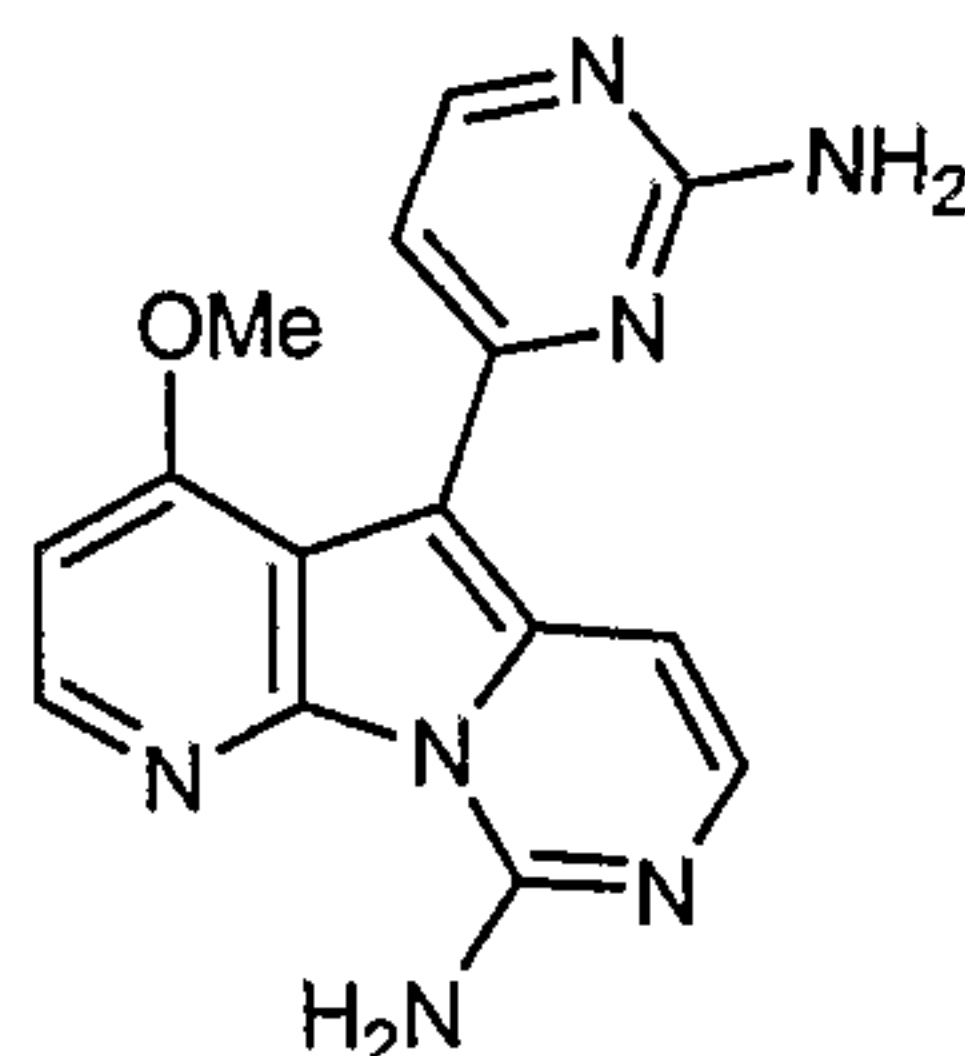
MS (ES+) *m/z* 279 (M+2, 20), 278 (M+1, 100), 277 (M⁺, 10).

HRMS *m/z* calculated for C₁₅H₁₁N₇: 277.1075; found: 277.1071.

UV (MeOH) 225 (36,010), 250 (34,126), 350 (20,942), 400 (26,481).

Example 33

9-Amino-5-(2-aminopyrimidin-4-yl)pyrido[3',2':4,5]pyrrolo[1,2-*c*]-pyrimidine (**5b**)



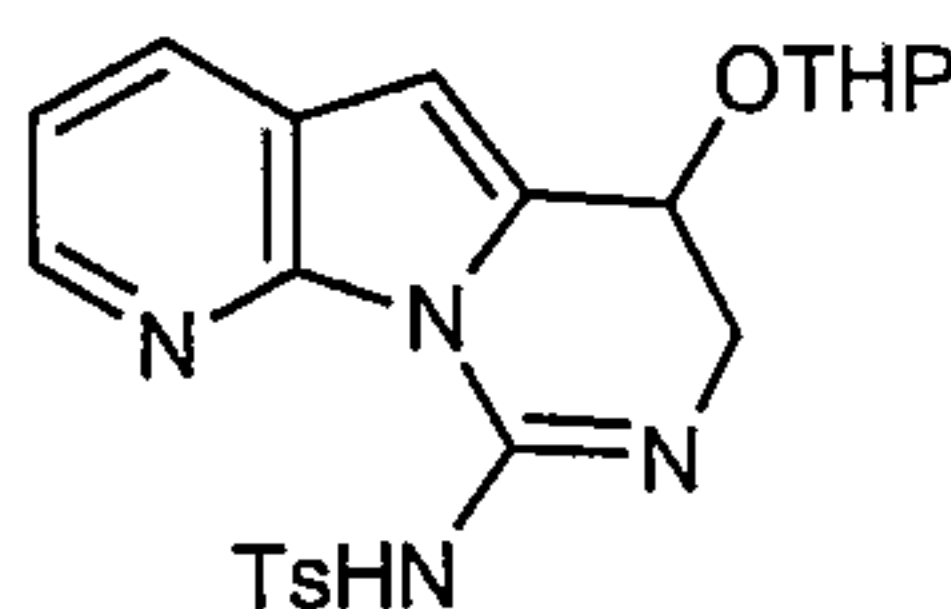
Following the same procedure for **5a** (Method B). From **20b** (26 mg, 0.07 mmol), **27** (32 mg, 0.11 mmol), Pd₂(dba)₃ (15 mg, 0.014 mmol), PPh₃ (7 mg, 0.028 mmol), LiCl (9 mg, 0.21 mmol) and CuI (3 mg, 0.014 mmol) in dioxane (3 ml), refluxed for 1 h. After purification by flash column chromatography **5b** (8 mg, 38 %) was obtained.

¹H-NMR (CDCl₃, 200 MHz) δ 4.03 (s, 3H, Me), 6.90 (d, *J* 5.4, 1H, H3), 7.08 (d, *J* 5.4, 1H, H6), 7.50 (d, *J* 5.4, 1H, H7), 7.54 (d, *J* 5.0, 1H, H5'), 8.28 (d, *J* 5.4, 1H, H2), 8.47 (d, *J* 5.0, 1H, H6')

MS (ES+) *m/z* 308 (M+1, 100), 307 (M⁺, 20).

Example 34

9-Tosylamino-6-tetrahydropyranoxyprido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine (**22a**)



A solution of **9a** (235 mg, 0.88 mmol) and DIPEA (505 μl, 1.98 mmol) in CH₂Cl₂ (20 ml) was slowly added to a solution of TsNCCl₂ (250 mg, 0.99 mmol) in CH₂Cl₂ (20 ml). The solution was stirred for 30 min. and washed with water. The organic solution was dried, filtered and evaporated to give a crude which was purified by flash column

chromatography. Elution with DCM/MeOH (99/1) gave **22a** (235 mg, 60%) as a light orange solid.

IR (film) ν 3312 (m, NH), 1639 (s, N=C), 1472 (m, C-N), 1277 (m, C-O).

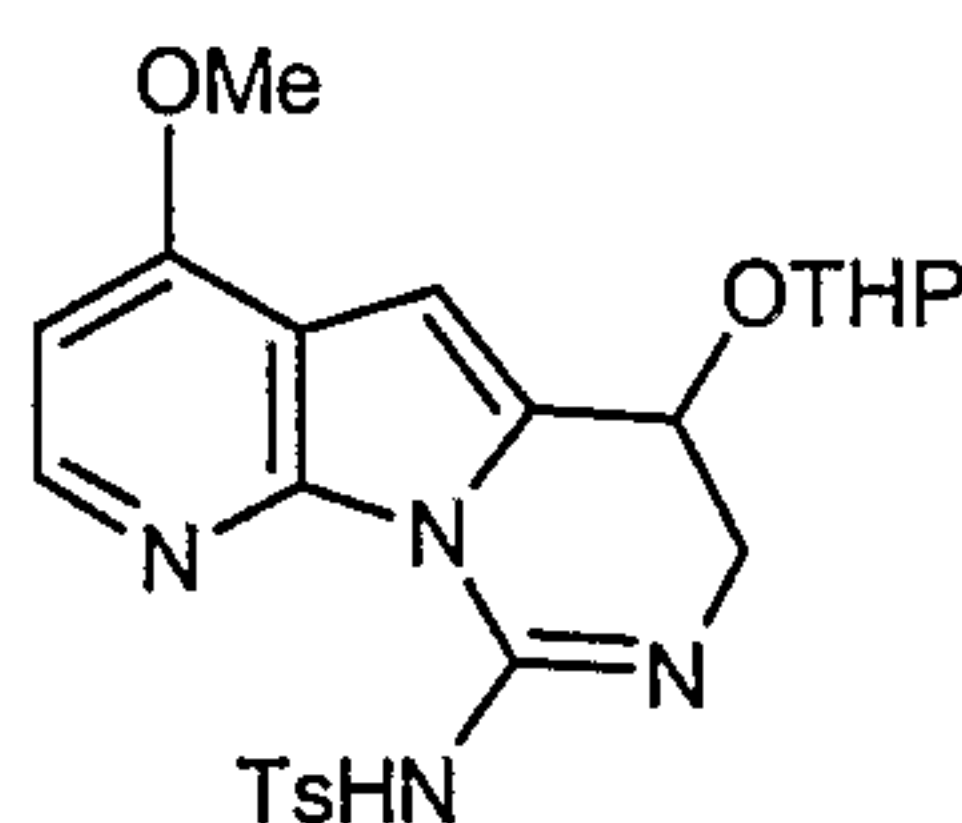
$^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ 1.40-1.80 (m, 6H, H3', H4' and H5'), 2.38 (s, 3H, Me), 3.45-4.00 (m, 4H, H7 and H6'), 4.65 and 4.95 (bt, 1H, H2'), 5.02 and 5.05 (bt, 1H, H6), 6.59 and 6.61 (s, 1H, H5), 7.20 and 7.21 (dd, J 7.8 and 4.8, 1H, H3), 7.27 (d, J 8.4, 2H, Ts), 7.84 and 7.85 (dd, J 7.8 and 1.5, 1H, H4), 8.12 (d, J 8.4, 2H, Ts), 8.40 (br, 1H, NH), 8.50 and 8.52 (dd, J 4.8 and 1.5, 1H, H2).

$^{13}\text{C-NMR}$ (CDCl_3 , 50 MHz) δ 18.7 and 19.1 (t, C4'), 21.5 (q, Ts), 25.2 and 25.3 (t, C5'), 29.9 and 30.3 (t, C3'), 43.1 and 44.7 (t, C6'), 62.2 and 62.5 (t, C7), 62.6 and 63.8 (d, C6), 95.7 and 96.8 (d, C2'), 104.1 and 105.5 (d, C5), 119.2 (d, C3), 121.5 (s, C4a), 126.4 (d, Ts), 129.2 (d, Ts), 129.2 (d, C4), 131.9 and 134.7 (s, C5a), 140.0 and 142.5 (s, C10a), 145.6 and 145.9 (d, C2), 148.1 (s, C9).

MS (EI) m/z 440 (M^+ , 1), 376 (M-SO_2 , 19).

Example 35

4-Methoxy-9-Tosylamino-6-tetrahydropyranoxyprido[3',2':4,5]pyrrolo[1,2-c]-pyrimidine (**22b**)



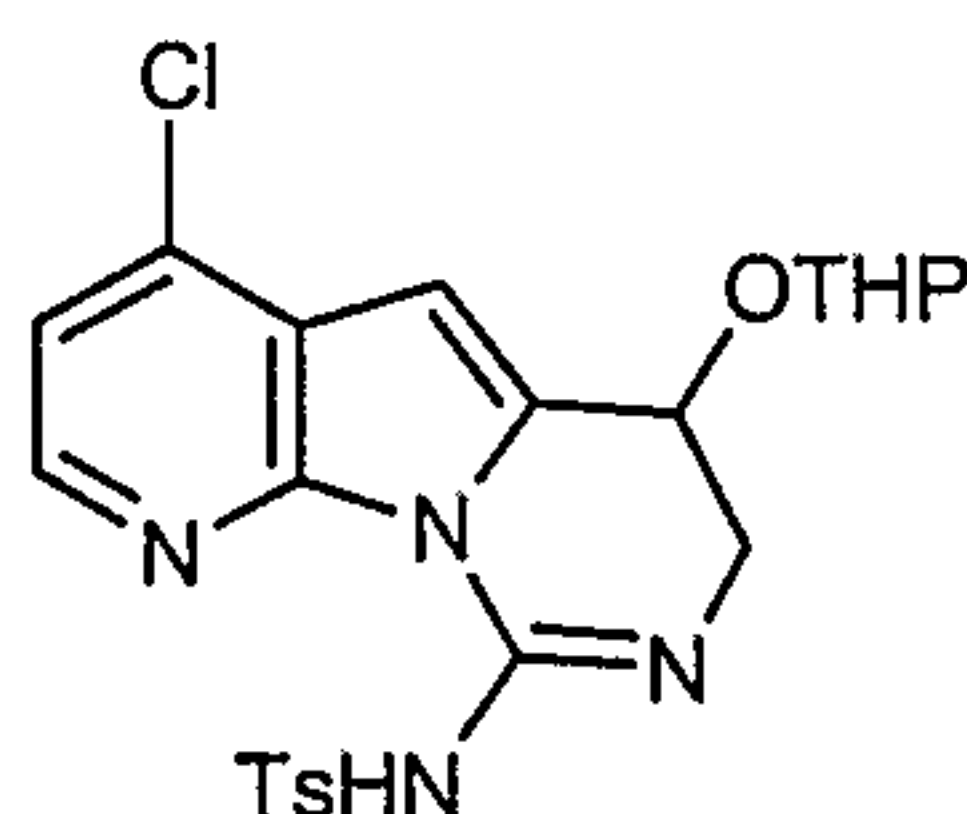
Following the methodology for **22a**, from **9b** (1 g, 3.44 mmol), DIPEA (1.9 ml, 7.58 mmol) and TsNCCl_2 (952 mg, 3.78 mmol) compound **22b** (1.05 g, 65%) as a light orange solid was obtained.

$^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ 1.40-1.80 (m, 6H, H3', H4' and H5'), 2.38 (s, 3H, Me), 3.45-3.95 (m, 4H, H7 and H6'), 3.97 (s, 3H, Me), 4.62 and 4.95 (bt, 1H, H2'), 5.01 (m, 1H, H6), 6.69 (m, 1H, H3 and H5), 7.26 (d, J 8.4, 2H, Ts), 8.10 (d, J 8.4, 2H, Ts), 8.41 and 8.42 (d, J 5.8, 1H, H2).

$^{13}\text{C-NMR}$ (CDCl_3 , 50 MHz) δ 18.5 and 19.3 (t, C4'), 21.6 (q, Ts), 25.2 and 25.3 (t, C5'), 30.0 and 30.2 (t, C3'), 43.3 and 44.9 (t, C6'), 55.6 (q, Me), 61.9 and 62.3 (t, C7), 62.7 and 63.5 (d, C6), 95.5 and 96.4 (d, C2'), 101.3 (d, C3), 101.5 and 102.9 (d, C5), 126.2 (s, C4a), 126.5 (d, Ts), 129.2 (d, Ts), 129.3 and 129.5 (s, C5a), 132.2 (s, Ts), 142.5 (s, C10a), 147.6 and 147.9 (d, C2), 159.7 (s, C9).

Example 36

4-Chloro-9-Tosylamino-6-tetrahydropyranoxyprido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine (22c)



Following the methodology for 22a. From 9c (175 mg, 0.59 mmol), DIPEA (225 μl , 1.30 mmol) and TsNCCl_2 (164 mg, 0.65 mmol) compound 22c (165 mg, 60%) was obtained.

IR (film) ν 3309 (m, NH), 1634 (s, N=C), 1471 (m, C-N), 1358 (m, SO_2), 1280 (m, C-O).

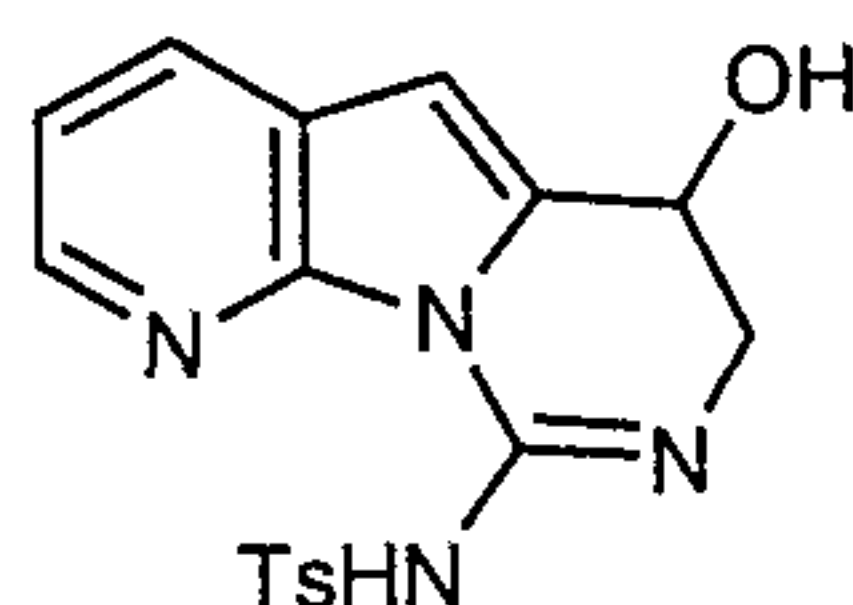
$^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ 1.40-1.80 (m, 6H, H3', H4' and H5'), 2.38 (s, 3H, Me), 3.45-3.95 (m, 4H, H7 and H6'), 4.65 and 4.95 (m, 1H, H2'), 5.01 (m, 1H, H6), 6.71 and 6.72 (s, 1H, H5), 7.24 and 7.25 (d, J 5.4, 1H, H3), 7.27 (d, J 8.0, 2H, Ts), 8.10 (d, J 8.4, 2H, Ts), 8.39 and 8.41 (d, J 4.8, 1H, H2) 8.48 (br, 1H, NH).

^{13}C -NMR (CDCl_3 , 50 MHz) δ 18.8 and 19.1 (t, C4'), 21.6 (q, Ts), 25.2 and 25.3 (t, C5'), 30.0 and 30.3 (t, C3'), 43.1 and 44.7 (t, C6'), 62.5 and 62.6 (t, C7), 63.3 and 63.6 (d, C6), 95.8 and 96.8 (d, C2'), 101.9 and 103.2 (d, C5), 119.3 (d, C3), 127.3 (s, C4a), 126.4 (d, Ts), 129.2 (d, Ts), 132.2 (s, Ts), 135.5 and 136.4 (s, C5a), 139.8 (s, Ts), 142.6 (s, C10a), 145.8 and 146.2 (d, C2), 147.9 and 148.1 (s, C9).

MS (EI) m/z 475 (M^+ , 1), 410 ($\text{M}-\text{SO}_2$, 20).

Example 37

9-Tosylamino-6-hydroxypyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine



A solution of **22a** (210 mg, 0.48 mmol) was dissolved in CH_2Cl_2 (25 mL), 4N HCl aqueous solution (25 mL) was added and the mixture was energetically stirred for 20 min. The solution was basified and the organic solution was separated. The aqueous layer was extracted twice with CH_2Cl_2 . The organic solutions were evaporated together and purified by flash column chromatography. Elution with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95/5) gave 9-tosylamino-6-hydroxypyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine (160 mg, 95%) as a pale yellow solid.

IR (film) ν 3315 (m, NH), 1624 (s, C=N), 1473 (s, N-C), 1276 (m, SO_2), 1135 (m, C-O).

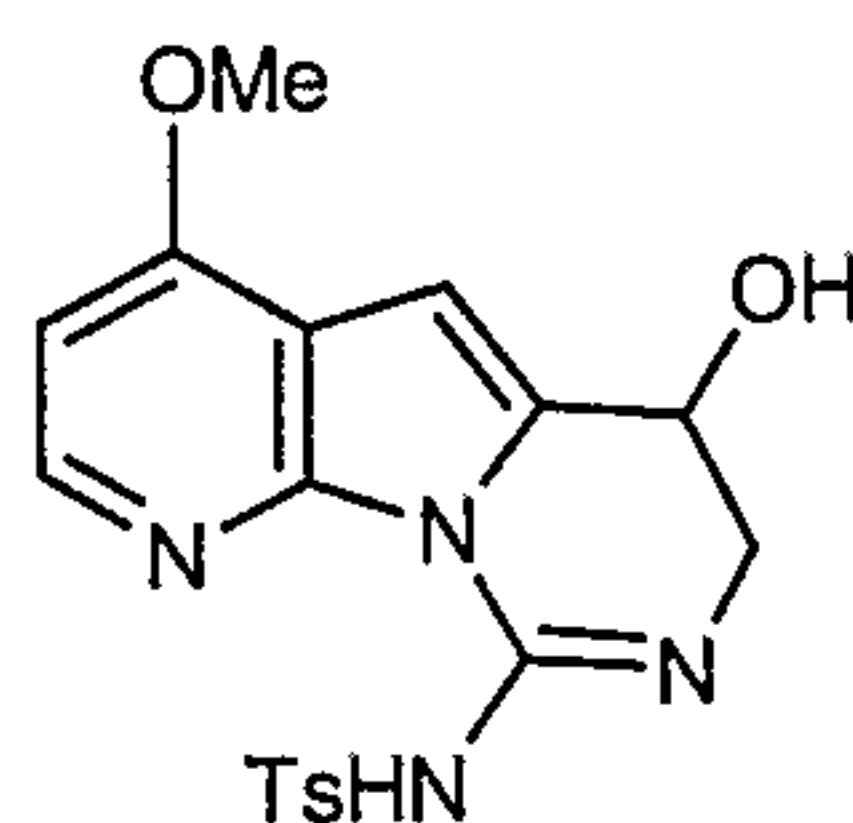
^1H -NMR (CDCl_3 , 300 MHz) δ 2.35 (s, 3H, Me), 3.50 (m, 1H, H7), 3.75 (m, 1H, H7), 5.04 (br, 1H, H6), 6.55 (s, 1H, H5), 7.00 (dd, J 7.8 and 4.8, 1H, H3), 7.24 (d, J 8.4, 2H, Ts), 7.71 (dd, J 7.8 and 1.5, 1H, H4), 8.03 (d, J 8.4, 2H, Ts), 8.27 (dd, J 4.8 and 1.5, 1H, H2), 8.42 (br, 1H, NH).

^{13}C -NMR (CDCl_3 , 75 MHz) δ 21.5 (q, Me), 45.8 (t, C7), 60.4 (d, C6), 101.7 (d, C5), 103.7 (d, C3), 119.1 (d, C4), 122.2 (s, C4a), 126.5 (d, Ts), 129.2 (d, Ts), 129.4 (d, C4), 136.7 (s, C5a), 139.6 (s, Ts), 142.7 (s, C10a), 144.9 (d, C2), 147.5 (s, Ts), 148.5 (s, C9).

MS (EI) m/z 357 ($M+1$, 1), 356 (M^+ , 3), 338 ($M-\text{H}_2\text{O}$, 2), 292 ($M-\text{SO}_2$, 18).

Example 38

4-Methoxy-9-tosylamino-6-hydroxypyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine



Following the methodology for previous compound, from **22b** (1.05 g, 2.23 mmol) compound 4-methoxy-9-tosylamino-6-hydroxypyrido-[3',2':4,5]pyrrolo[1,2-c]pyrimidine (819 mg, 95%) was obtained as a light yellow solid.

IR (film) ν 3317 (m, NH), 1627 (s, C=N), 1475 (s, N-C), 1293 (m, SO_2), 1139 (m, C-O).

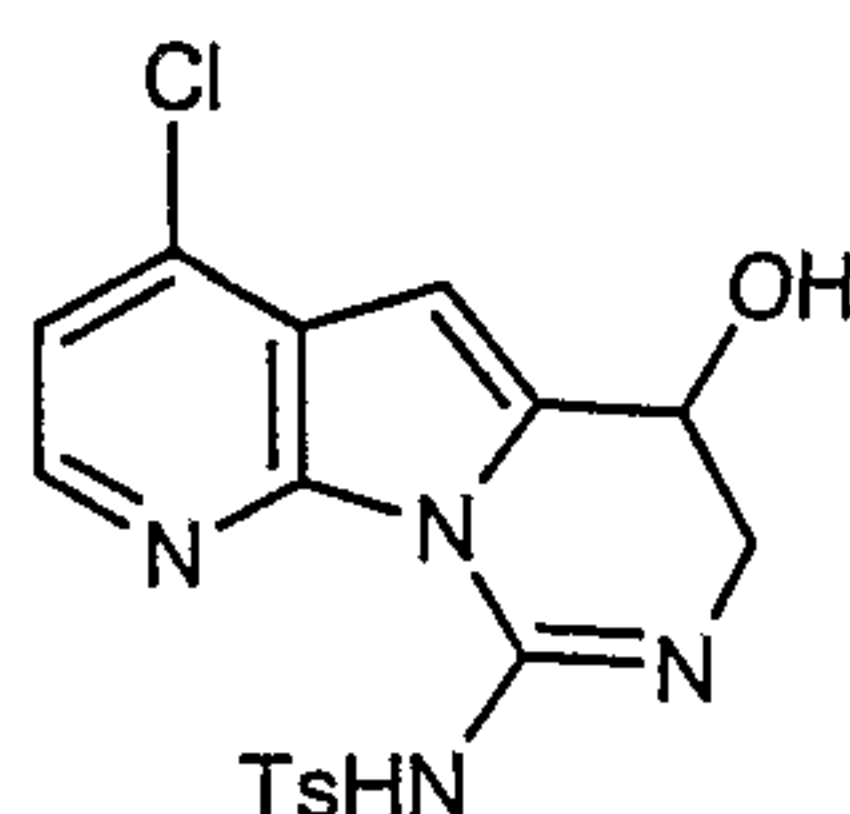
^1H -NMR (CDCl_3 , 200 MHz) δ 2.35 (s, 3H, Me), 3.50 (m, 1H, H7), 3.75 (m, 1H, H7), 3.85 (s, 3H, Me), 5.02 (br, 1H, H6), 6.43 (d, J 5.4, 1H, H3), 6.52 (s, 1H, H5), 7.24 (d, J 8.0, 2H, Ts), 8.04 (d, J 8.0, 2H, Ts), 8.09 (d, J 5.4, 1H, H2), 8.41 (br, 1H, NH).

^{13}C -NMR (CDCl_3 , 50 MHz) δ 21.5 (q, Me), 45.9 (t, C7), 55.6 (q, Me), 60.1 (d, C6), 100.8 (d, C3), 101.4 (d, C5), 112.1 (s, C4a), 126.5 (d, Ts), 129.3 (d, Ts), 134.3 (s, C5a), 139.6 (s, Ts), 142.7 (s, C10a), 146.7 (d, C2), 148.6 (s, C9), 159.6 (s, C4).

Example 39

4-Chloro-9-Tosylamino-6-hydroxypyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine

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Following the methodology for previous compound, from **22c** (50 mg, 0.11 mmol) compound 4-chloro-9-tosylamino-6-hydroxypyrido-[3',2':4,5]pyrrolo[1,2-c]pyrimidine (37 mg, 90%) was obtained.

IR (film) ν 3316 (m, NH), 1632 (s, C=N), 1472 (s, N-C), 1277 (m, SO₂), 1082 (m, C-O).

¹H-NMR (CDCl₃, 200 MHz) δ 2.35 (s, 3H, Me), 3.56 (brd, *J* 13.6, 1H, H7), 3.80 (dt, *J* 13.6 and 2.6, 1H, H7), 4.80 (br, 1H, OH), 5.10 (br, 1H, H6), 6.61 (s, 1H, H5), 7.04 (d, *J* 5.0, 1H, H3), 7.24 (d, *J* 8.2, 2H, Ts), 8.03 (d, *J* 8.2, 2H, Ts), 8.16 (d, *J* 5.0, 1H, H2), 8.46 (br, 1H, NH).

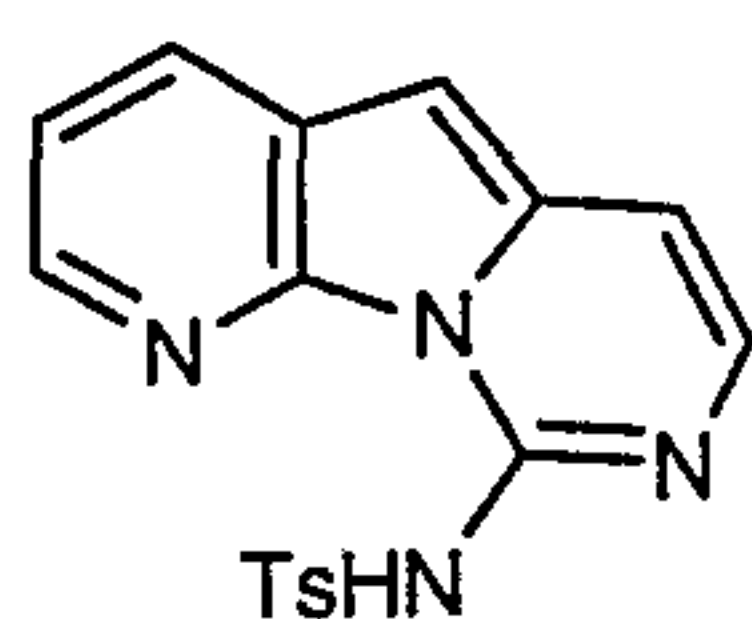
¹³C-NMR (CDCl₃, 50 MHz) δ 21.6 (q, Me), 45.7 (t, C7), 60.4 (d, C6), 101.5 (d, C5), 119.2 (d, C3), 121.4 (s, C4a), 126.5 (d, Ts), 129.3 (d, Ts), 131.0 (s, Ts), 136.5 (s, C5a), 137.4 (s, Ts), 142.8 (s, C10a), 145.2 (d, C2), 148.3 (s, C9).

MS (EI) *m/z* 392 (³⁷ClM⁺, 2), 390 (³⁵ClM⁺, 6), 328 (³⁷ClM-SO₂, 10), 326 (³⁵ClM-SO₂, 31).

HRMS *m/z* calculated for C₁₇H₁₅ClN₄O₅S: 390.0553; found: 390.0548.

Example 40

9-Tosylaminopyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine (23a)



A solution of 9-tosylamino-6-hydroxypyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine (170 mg, 0.48 mmol) and TEA (133 μ l, 0.96 mmol) was dissolved in CH₂Cl₂ (25 ml), methanesulfonylchloride (37 μ l, 0.48 mmol) was dropwise added and the mixture was stirred for 20 min. The solution was washed with water and the organic solutions was dried and evaporated. The crude mixture was purified by flash column chromatography. Elution with CH₂Cl₂/MeOH (98/2) gave **23a** (124 mg, 78%) as a yellow solid.

IR (KBr) ν 3266 (m, NH), 1604 (s, C=N), 1399, 1281 (m, SO₂).

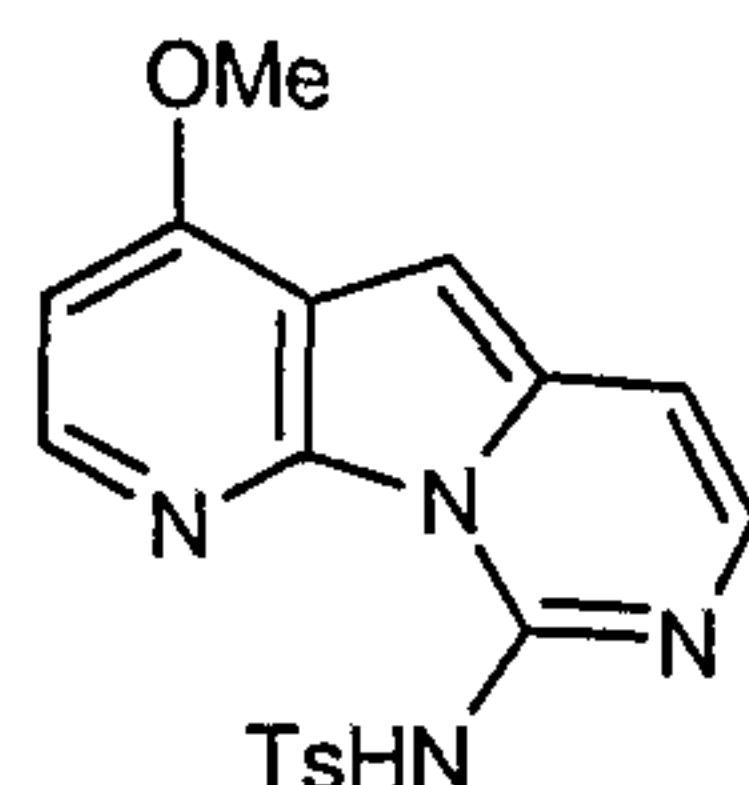
¹H-NMR (CD₃OD, 300 MHz) δ 2.35 (s, 3H, Me), 6.69 (s, 1H, H5), 6.73 (d, *J* 7.8, 1H, H6), 7.04 (d, *J* 7.8, 1H, H7), 7.31 (d, *J* 8.4, 2H, Ts), 7.44 (dd, *J* 8.1 and 5.1, 1H, H3), 7.99 (d, *J* 8.4, 2H, Ts), 8.15 (d, *J* 8.1, 1H, H4), 8.46 (d, *J* 5.1, 1H, H2).

MS (EI) *m/z* 339 (M+1, 4), 338 (M⁺, 19), 273 (M-SO₂, 100).

HRMS *m/z* calculated for C₁₇H₁₄N₄O₂S: 338.0837; found: 338.0841.

Example 41

4-Methoxy-9-tosylaminopyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine (**23b**)



Following the methodology for **23a**, from 4-methoxy-9-tosylamino-6-hydroxypyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine (170 mg, 0.48 mmol) compound **23b** (124 mg, 78%) was obtained as a light yellow solid.

IR (KBr) ν 3266 (m, NH), 1604 (s, C=N), 1399, 1293 (m, SO₂), 1141.

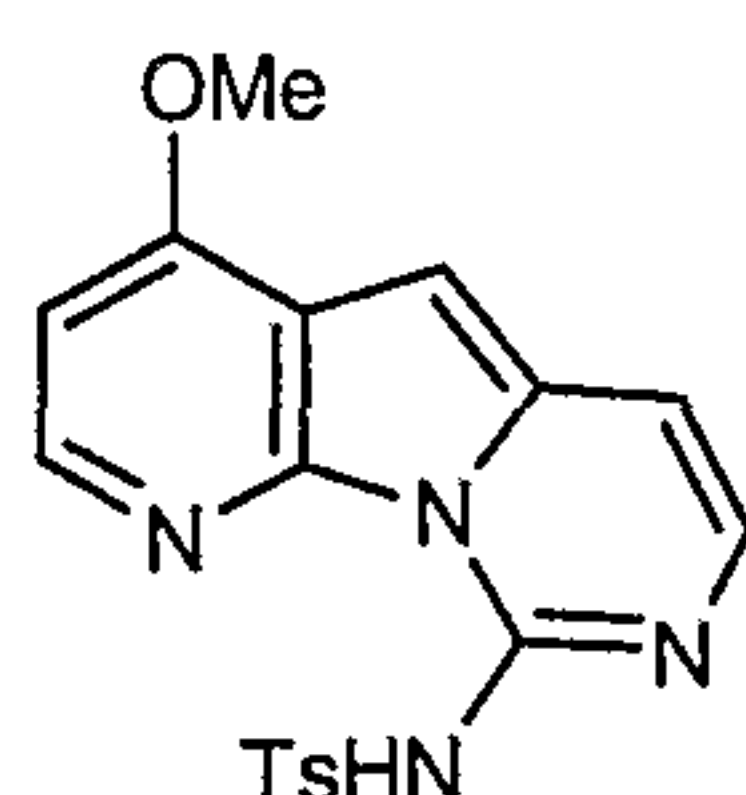
¹H-NMR (CD₃OD, 300 MHz) δ 2.35 (s, 3H, Me), 4.01 (s, 3H, Me), 6.57 (s, 1H, H5), 6.64 (d, *J* 7.5, 1H, H6), 6.93 (d, *J* 6.0, 1H, H3), 6.98 (d, *J* 7.5, 1H, H7), 7.30 (d, *J* 8.1, 2H, Ts), 8.00 (d, *J* 8.1, 2H, Ts), 8.30 (d, *J* 6.0, 1H, H2).

¹³C-NMR (DMSO-*d*⁶, 50 MHz) δ 21.0 (q, Me), 55.9 (q, Me), 93.0 (d, C5), 101.5 (d, C6), 102.1 (d, C3), 113.9 (s, C4a), 125.9 (d, Ts), 129.3 (d, C2 and Ts), 132.6 (s, C5a), 142.3 (s, C10a), 143.9 (s, C9), 145.1 (d, C7), 158.4 (s, C4).

HRMS *m/z* calculated for C₁₈H₁₆N₄O₅S: 368.0943; found: 368.0941.

Example 41

4-Chloro-9-tosylaminopyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine (23c)



Following the methodology for **23a.**, from 4-chloro-9-tosylamino-6-hydroxypyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine (165 mg, 0.42 mmol) compound **23c** (104 mg, 66%) was obtained.

IR (KBr) ν 3265 (m, NH), 1602 (s, C=N), 1396, 1281 (m, SO₂), 1141.

¹H-NMR (DMSO-*d*⁶, 300 MHz) δ 2.34 (s, 3H, Me), 6.80 (s, 1H, H5), 6.84 (d, *J* 7.8, 1H, H6), 7.17 (d, *J* 7.8, 1H, H7), 7.37 (d, *J* 7.8, 2H, Ts), 7.58 (d, *J* 4.8, 1H, H3), 8.03 (d, *J* 7.8, 2H, Ts), 8.45 (d, *J* 4.8, 1H, H2), 11.20 (br, 1H, NH).

¹³C-NMR (DMSO-*d*⁶, 50 MHz) δ 21.0 (q, Me), 93.7 (d, C5), 101.3 (d, C6), 119.9 (d, C3),

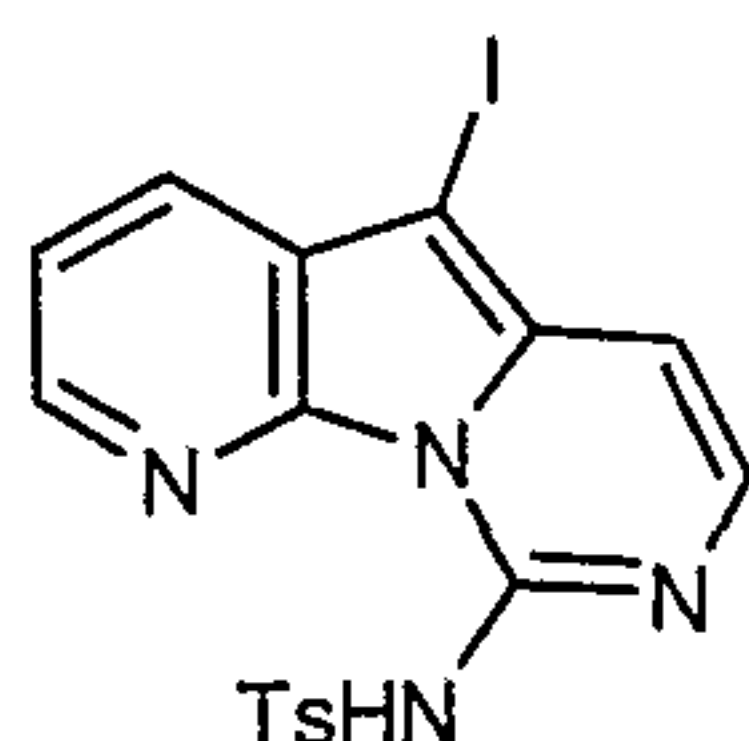
122.5 (s, C4a), 125.9 (d, Ts), 126.3 (d, C2), 129.4 (d, Ts), 133.5 (s, C5a), 135.6 (s, Ts), 142.5 (s, C10a), 143.5 (d, C7), 143.8 (s, C9), 145.3 (s, C4).

MS (EI) m/z 374 ($^{37}\text{ClM}^+$, 5), 372 ($^{35}\text{ClM}^+$, 12), 309 ($^{37}\text{ClM-SO}_2$, 24), 307 ($^{35}\text{ClM-SO}_2$, 63).

HRMS m/z calculated for $\text{C}_{17}\text{H}_{13}\text{ClN}_4\text{O}_2\text{S}$: 372.0448; found: 372.0444.

Example 43

5-Iodo-9-tosylaminopyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine (24a)



To a solution of **23a** (10 mg, 0.03 mmol) in CH_2Cl_2 (5 ml) at -30°C *N*-iodosuccinimide (7 mg, 0.03 mmol) was portionwise added and the mixture was stirred for 15 min. The solution was washed with water and the organic solutions was dried, filtered and evaporated to obtain **24a** (14 mg, 95%) as a yellow solid.

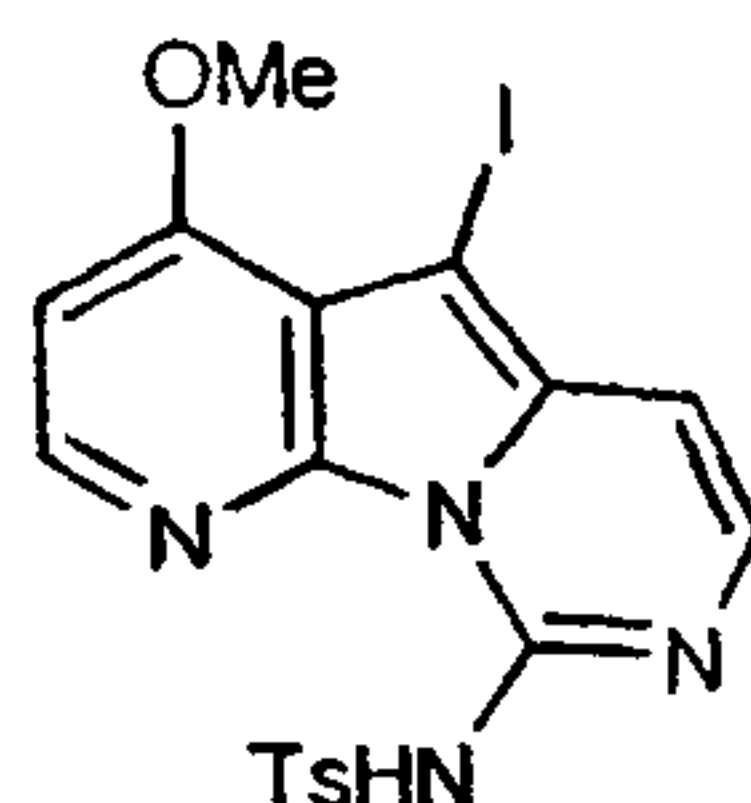
IR (KBr) ν 3264 (m, NH), 1599 (m, N=C), 1393 (m, C-N), 1140.

$^1\text{H-NMR}$ (CD_3OD , 300 MHz) δ 2.37 (s, 3H, Me), 6.61 (d, J 7.5, 1H, H6), 7.15 (d, J 7.5, 1H, H7), 7.34 (d, J 8.4, 2H, Ts), 7.46 (dd, J 7.5 and 4.8, 1H, H3), 7.81 (dd, J 7.5 and 1.5, 1H, H4), 8.07 (d, J 8.4, 2H, Ts), 8.46 (dd, J 4.8 and 1.5, 1H, H2).

MS (EI) m/z 464 (M^+ , 13), 399 (M-SO_2 , 32), 338 (M-I , 1), 309 (M-Ts , 5), 273 ($\text{M-SO}_2\text{-I}$, 33), 182 (M-Ts-I , 58).

HRMS m/z calculated for $\text{C}_{17}\text{H}_{13}\text{IN}_4\text{O}_2\text{S}$: 463.9804; found: 493.9799.

Example 44

5-Iodo-4-methoxy-9-tosylaminopyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine (24b)

Following the methodology for **24a**, from **23b** (250 mg, 0.68 mmol) compound **24b** (295 mg, 95%) was obtained as a light yellow solid.

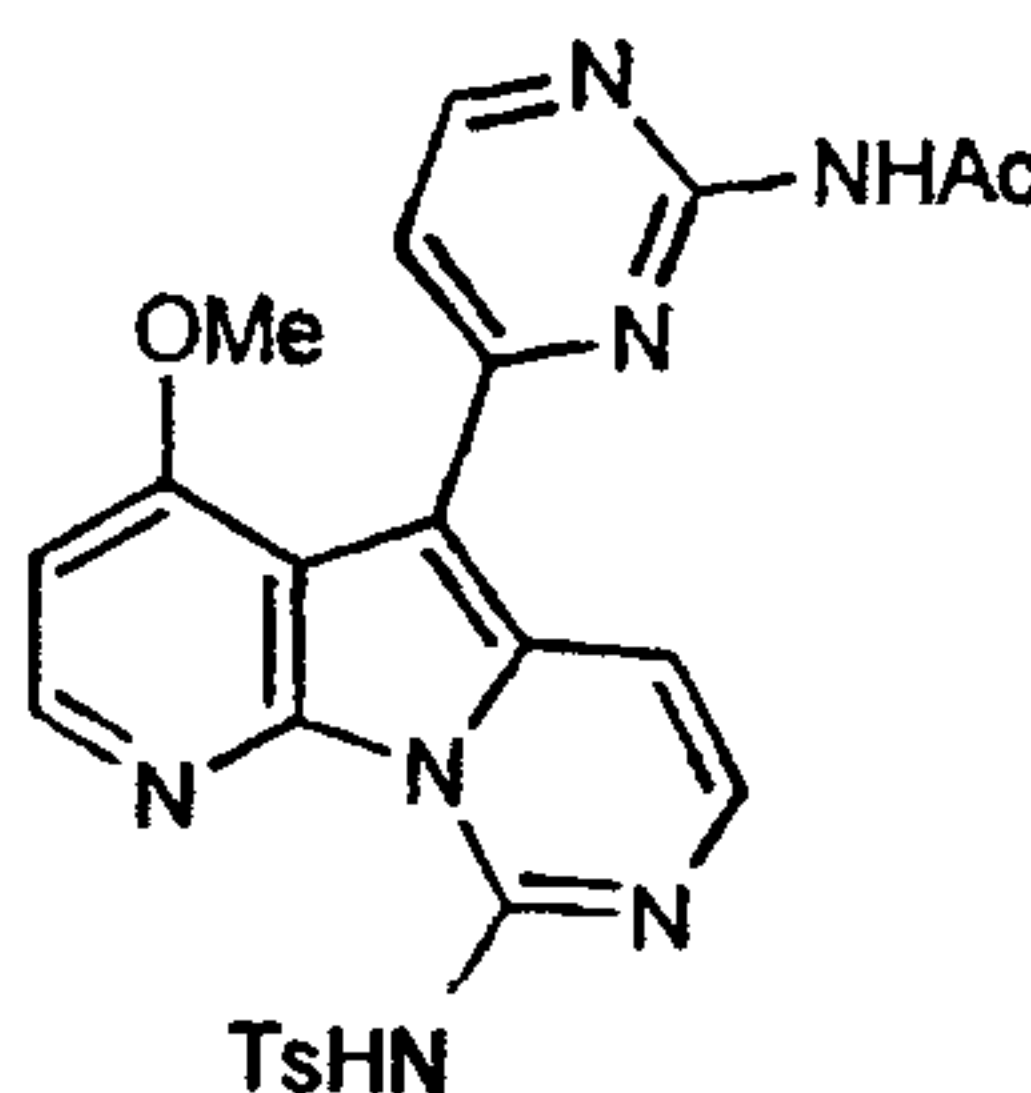
IR (KBr) ν 3259 (m, NH), 1592 (s, C=N), 1293 (m, SO₂), 1142.

¹H-NMR (DMSO-*d*⁶, 200 MHz) δ 2.33 (s, 3H, Me), 3.97 (s, 3H, Me), 6.62 (d, *J* 7.7, 1H, H6), 7.06 (d, *J* 5.6, 1H, H3), 7.18 (d, *J* 7.7, 1H, H7), 7.35 (d, *J* 8.2, 2H, Ts), 8.02 (d, *J* 8.2, 2H, Ts), 8.40 (d, *J* 5.6, 1H, H2), 11.15 (br, 1H, NH).

¹³C-NMR (DMSO-*d*⁶, 50 MHz) δ 21.0 (q, Me), 56.2 (q, Me), 102.1 (d, C3), 113.9 (s, C4a), 126.1 (d, Ts), 129.4 (d, C2 and Ts), 133.9 (s, C5a), 142.6 (s, C10a), 143.4 (s, C9), 145.1 (d, C7), 159.0 (s, C4).

MS (EI) *m/z* 494 (*M*⁺, 31), 429 (*M*-SO₂, 65), 368 (*M*-I, 12), 339 (*M*-Ts, 15), 303 (*M*-SO₂-I, 58), 212 (*M*-Ts-I, 100).

HRMS *m/z* calculated for C₁₈H₁₅IN₄O₅S: 493.9909; found: 493.9891.

Example 45**4-Methoxy-9-tosylamino-5-(2-acetylamino-4-yl) pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine (25)**

A solution of **24b** (295 mg, 0.60 mmol), **27** (258 mg, 0.9 mmol), Pd₂(dba)₃.CHCl₃ (120 mg, 0.12 mmol), PPh₃ (60 mg, 0.24 mmol), LiCl (74 mg, 1.8 mmol) and CuI (23 mg, 0.12 mmol) in dioxane (25 mL) was refluxed for one hour. The solvent was evaporated and the crude dissolved in CH₂Cl₂. The organic solution was extracted three times with 4N HCl solution. The aqueous solutions were basified together with solid NaHCO₃ and extracted with CH₂Cl₂. The organic solution was evaporated and the mixture was purified by flash column chromatography. Elution with CH₂Cl₂/MeOH (99/1) gave **23b** (66 mg, 28%) and with CH₂Cl₂/MeOH (9/1) gave **25** (209 mg, 71%) as a yellow solid.

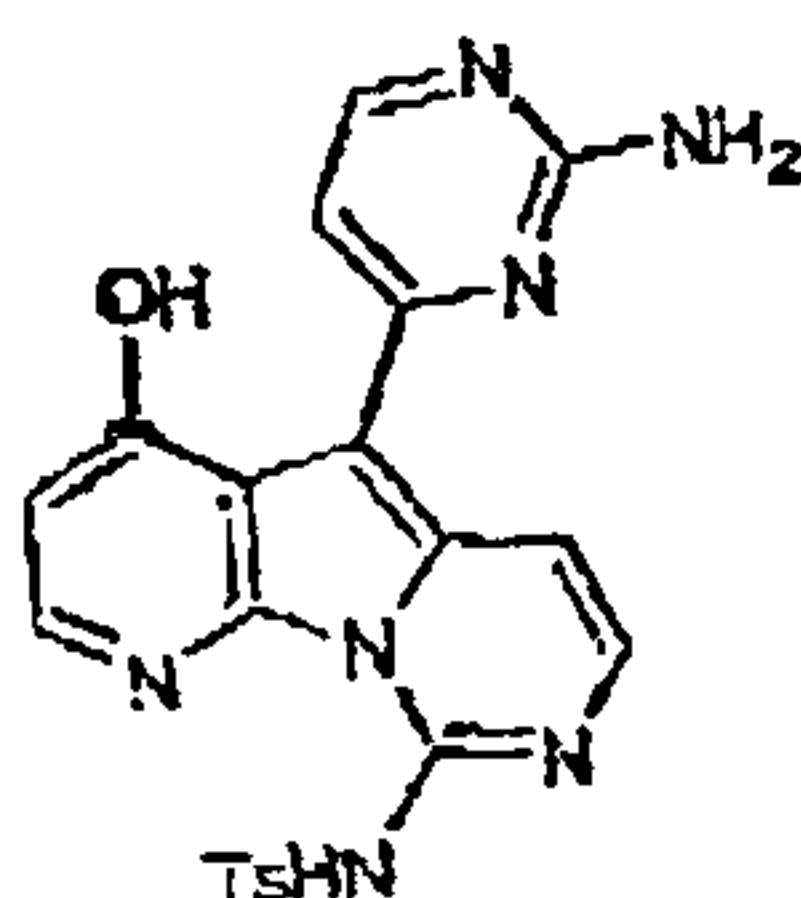
IR (KBr) ν 3379 (m, NH), 1592 (s, C=N), 1474, 1449, 1422, 1293 (SO₂), 1143.

¹H-NMR (CDCl₃, 200 MHz) δ 2.41 (s, 3H, Me), 2.47 (s, 3H, Me), 4.05 (s, 3H, Me), 6.92 (br, 1H, H3), 7.31 (d, *J* 8.4, 2H, Ts), 7.46 (brd, 1H, H6), 7.60 (d, *J* 6.6, 1H, H7), 7.98 (br, 1H, H5'), 8.12 (d, *J* 8.4, 2H, Ts), 8.38 (br, 1H, H2), 8.50 (br, 1H, H6').

MS (ES+) *m/z* 505 (M+2, 30), 504 (M+1, 100).

Example 46

4-Hydroxy-9-tosylamino-5-(2-aminopyrimidin-4-yl)pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine (26)



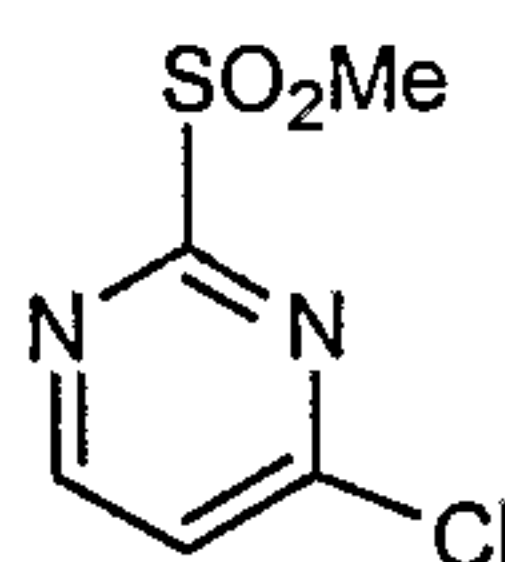
A solution of **25** (10 mg, 0.02 mmol) in HBr (48%) was refluxed for 10 min. The solution was basified with NaHCO₃ and extracted with CH₂Cl₂. The organic solution was dried, filtrated and evaporated to obtain **26** (7 mg, 78%) as a yellow solid.

¹H-NMR (CDCl₃+CD₃OD, 300 MHz) δ 2.34 (s, 3H, Me), 6.76 (d, *J* 6.6, 1H, H6), 7.03 (d, *J* 6.6, 1H, H5'), 7.06 (d, *J* 6.6, 1H, H5'), 7.23 (d, *J* 8.1, 2H, Ts), 7.65 (d, *J* 6.6, 1H, H7), 8.00 (d, *J* 8.1, 2H, Ts), 8.01 (d, *J* 6.6, 1H, H6'), 8.23 (brd, 1H, H2).

MS (ES+) *m/z* 449 (M+1, 10), 448 (M⁺, 100).

Example 47

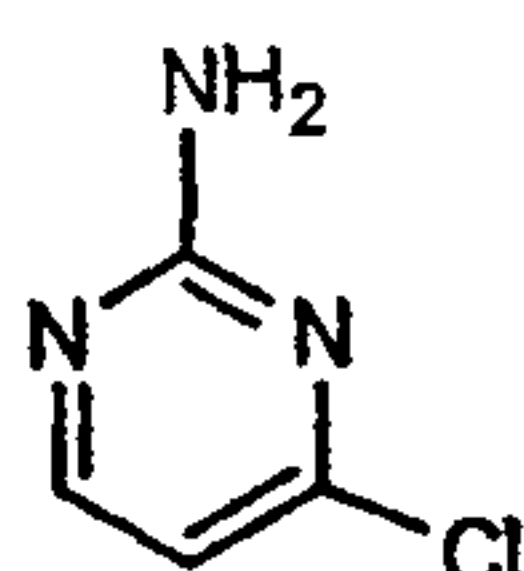
4-Chloro-2-methanesulfonylpyrimidine



See *Heterocycles*, **1977**, 8, 299. To a solution of 4-chloro-2-methanesulfonylpyrimidine (5 g, 31 mmol) in CH₂Cl₂ (100 ml) *m*CPBA (16.12 g, 94 mmol) was added and stirred for 2h. at room temperature. The mixture was washed with saturated aq. Na₂S₂O₃ and the aqueous solution basified with saturated aq. Na₂CO₃. The organic layer was separated and the aqueous solution extracted with CH₂Cl₂. The organic layers were evaporated together to obtain 4-chloro-2-methanesulfonylpyrimidine (5.5 g, 92%) as a white solid.

¹H-NMR (CDCl₃, 200 MHz) δ 3.39 (s, 3H, Me), 7.61 (d, *J* 5.4, 1H, H5), 8.83 (d, *J* 5.4, 1H, H6).

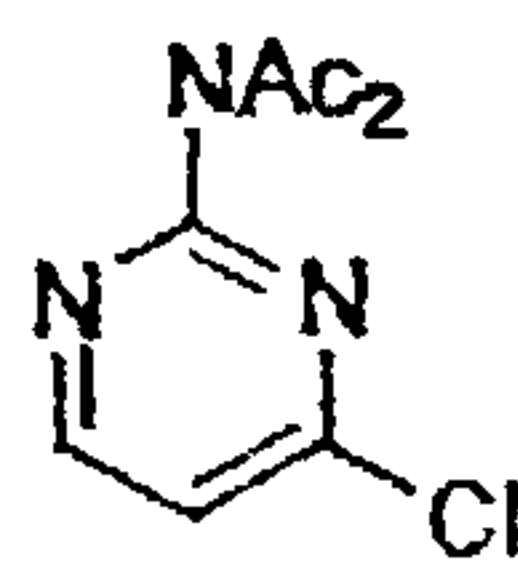
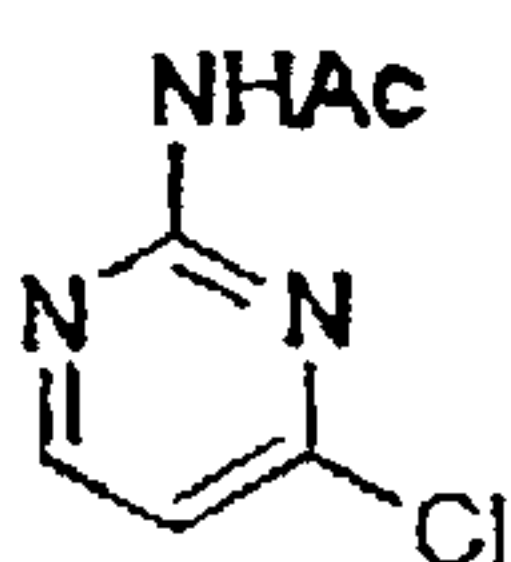
MS (CI, CH₄) *m/z* 192 (M³⁵Cl⁺, 1), 157 (M-Cl, 1), 97 (100).

Example 48**2-Amino-4-chloropyrimidine**

To a solution of 4-chloro-2-methanesulfonylpyrimidine (5 g, 26 mmol) in *i*-PrOH (20 ml) 20% aq. NH₃ (20 ml) was added and the mixture stirred for 20 min. at room temperature. The mixture was extracted with CH₂Cl₂ four times and the organic solvent removed under vacuum. 2-Amino-4-chloropyrimidine (3.3 g, 100%) was obtained as a white solid.

¹H-NMR (CDCl₃, 200 MHz) δ 5.26 (br, 2H, NH₂), 6.67 (d, *J* 5.2, 1H, H5), 8.17 (d, *J* 5.2, 1H, H6).

MS (CI, CH₄) *m/z* 132 (³⁷ClM+1, 33), 131 (³⁷ClM⁺, 2), 130 (³⁵ClM+1, 87), 129 (³⁵ClM, 8), 97 (100), 94 (M-Cl, 53).

Example 49**2-Acetylamino-4-chloropyrimidine and 4-Chloro-2-diacetylamino-2,3-dihydropyrimidin-4(1H)-one**

A solution of 2-amino-4-chloropyrimidine (500 mg, 3.9 mmol) in acetic anhydride (20 ml) was refluxed for 30 min. The solvent was removed under vacuum and the remaining oil was dissolved in saturated aq. Na_2CO_3 . The aqueous solution was extracted with CH_2Cl_2 . The organic solution was dried and evaporated to give an oil which was purified by flash column chromatography. Elution with CH_2Cl_2 /hexane (2/1) gave 4-Chloro-2-diacetylaminopyrimidine (122 mg, 16%) as a white solid and with CH_2Cl_2 yielded 2-Acetylamino-4-chloropyrimidine (270 mg, 45%) as a white solid.

2-Acetylamino-4-chloropyrimidine

^1H -NMR (CDCl_3 , 200 MHz) δ 2.51 (s, 3H, Me), 7.04 (d, J 5.3, 1H, H5), 8.17 (d, J 5.3, 1H, H6).

^{13}C -NMR (CDCl_3 , 50 MHz) δ 25.3 (q, Me), 116.0 (d, C5), 157.5 (s, C4), 159.2 (d, C6), 161.8 (s, C2).

MS (EI) m/z 173 (^{37}ClM , 5), 171 (^{35}ClM , 16), 131 ($^{37}\text{ClM-Ac}$, 32), 129 ($^{35}\text{ClM-Ac}$, 100).

4-Chloro-2-diacetylaminopyrimidine

^1H -NMR (CDCl_3 , 200 MHz) δ 3.32 (s, 6H, 2Me), 7.45 (d, J 5.2, 1H, H5), 8.76 (d, J 5.2, 1H, H6).

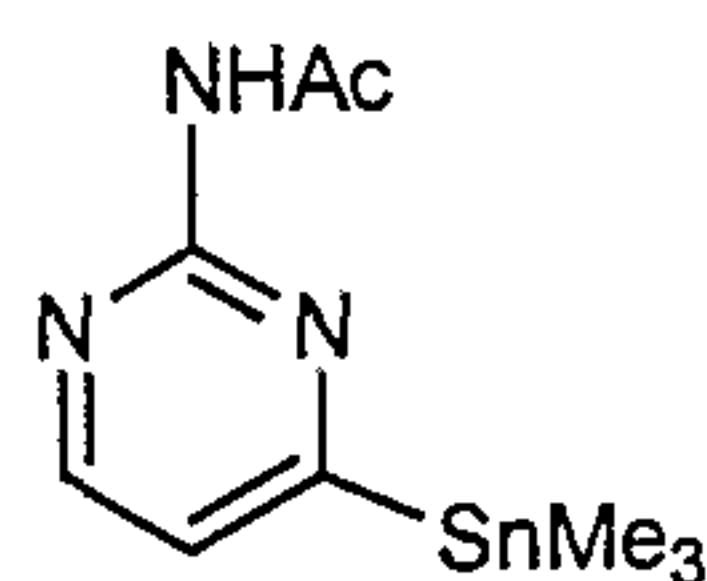
^{13}C -NMR (CDCl_3 , 50 MHz) δ 26.3 (q, Me), 121.2 (d, C5), 160.0 (d, C6), 163.1 (s, C4), 171.6 (s, C2).

MS (CI, CH_4) m/z 215 (^{37}ClM , 1), 214 ($^{37}\text{ClM-1}$, 3), 213 (^{35}ClM , 1), 212 ($^{35}\text{ClM-1}$, 5), 174 ($^{37}\text{ClM-Ac}$, 32), 172 ($^{35}\text{ClM-Ac}$, 100).

Example 50

2-Acetylamino-4-trimethylstannylpyrimidine (27)

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A solution of 2-Acetylamino-4-chloropyrimidine (170 mg, 1.0 mmol), hexamethylditin (400 μ l, 1.8 mmol) and Pd(PPh₃)₄ (40 mg, 0.03 mmol) in dioxane (6 ml), was refluxed for 1 h. The solvent was removed under vacuum and the residue purified by neutral alumina column chromatography. Elution with hexane/AcOEt (7/3) gave **27** (240 mg, 80%) as a white solid.

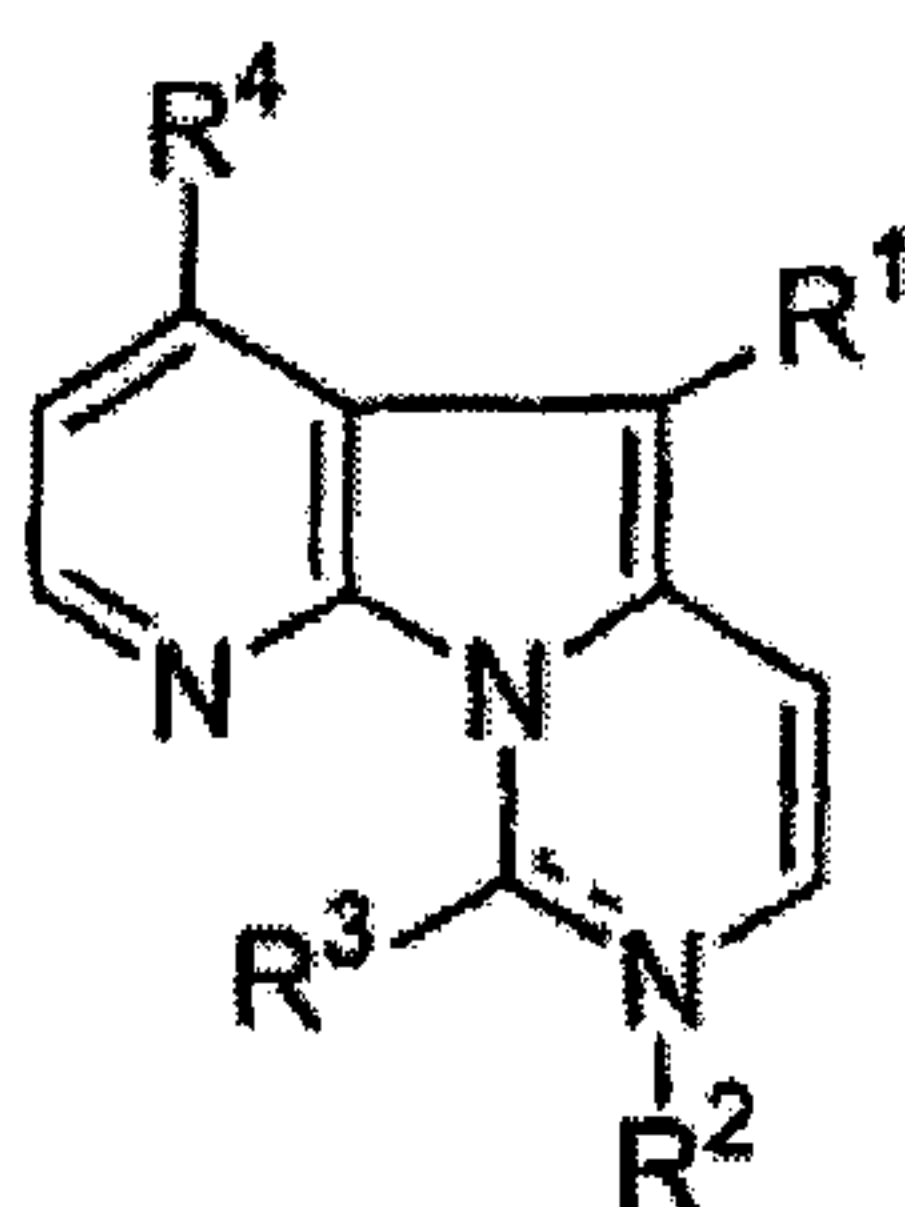
¹H-NMR (CDCl₃, 300 MHz) δ 0.36 (s, 9H, 3Me), 2.53 (s, 3H, Me), 7.13 (d, *J* 4.8, 1H, H5), 7.98 (br, 1H, NH), 8.35 (d, *J* 4.8, 1H, H6).

¹³C-NMR (CDCl₃, 75 MHz) δ -9.5 (q, 3Me), 25.3 (q, Me), 124.4 (d, C5), 154.7 (d, C6).

MS (EI) *m/z* 300 (¹²⁰SnM⁺, 1), 285 (¹²⁰SnM-Me, 34) 270 (¹²⁰SnM-2Me, 1), 255 (¹²⁰SnM-3Me, 6), 244 (¹²⁰SnM-3Me-Ac, 30), 136 (M-SnMe₃, 100).

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A compound of the formula (I):



wherein:

R^1 is an aromatic substituent of 4 to 10 ring atoms, which is optionally substituted with one or more groups chosen from alkyl, alkoxy, thioalkyl, halo, amino, N-acylamino, haloalkyl, alkoxyalkyl, aryl, hydroxy, carboxy, or alkoxycarbonyl;

R^2 is hydrogen or a nitrogen protecting group when the dotted line is absent, or R^2 is absent when the dotted line represents a bond to give a double bond between the nitrogen which bears R^2 and the carbon which bears R^3 ;

R^3 is an oxo group $=O$ when the dotted line is absent, or is an amino group or a N-acylamino group when the dotted line represents a bond to give a double bond between the nitrogen bearing R^2 and the carbon bearing R^3 ;

R^4 is hydrogen;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R^1 is a 4-pyrimidyl group.
3. A compound according to claim 2, wherein the 4-pyrimidyl group is substituted.
4. A compound according to any one of claims 1 to 3, wherein R^2 when present is hydrogen.
5. A compound according to any one of claims 1 to 4, wherein R^3 is an oxo group.

6. A compound according to any one of claims 1 to 5, wherein the dotted line represents a bond.

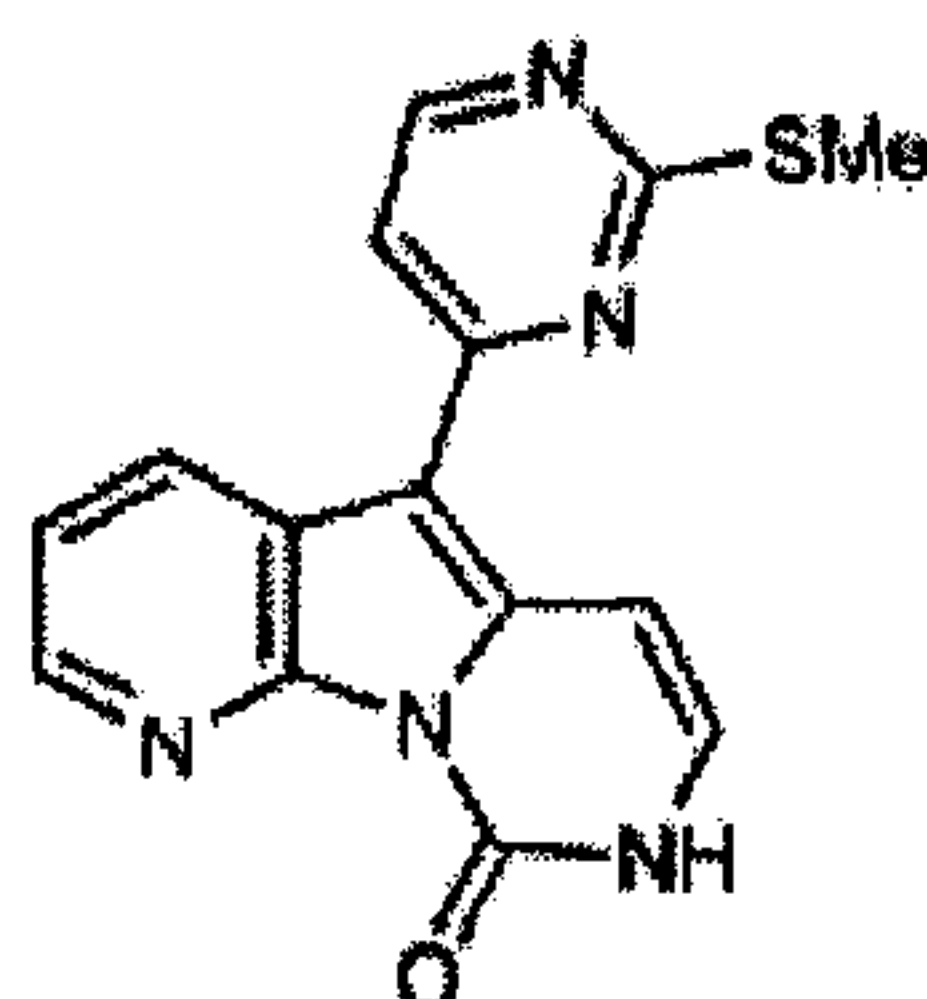
7. A compound according to any one of claims 1 to 6, wherein:

R^1 is a 4-pyrimidyl group substituted at the 2-position with amino, N-acylamino, or methylthio;

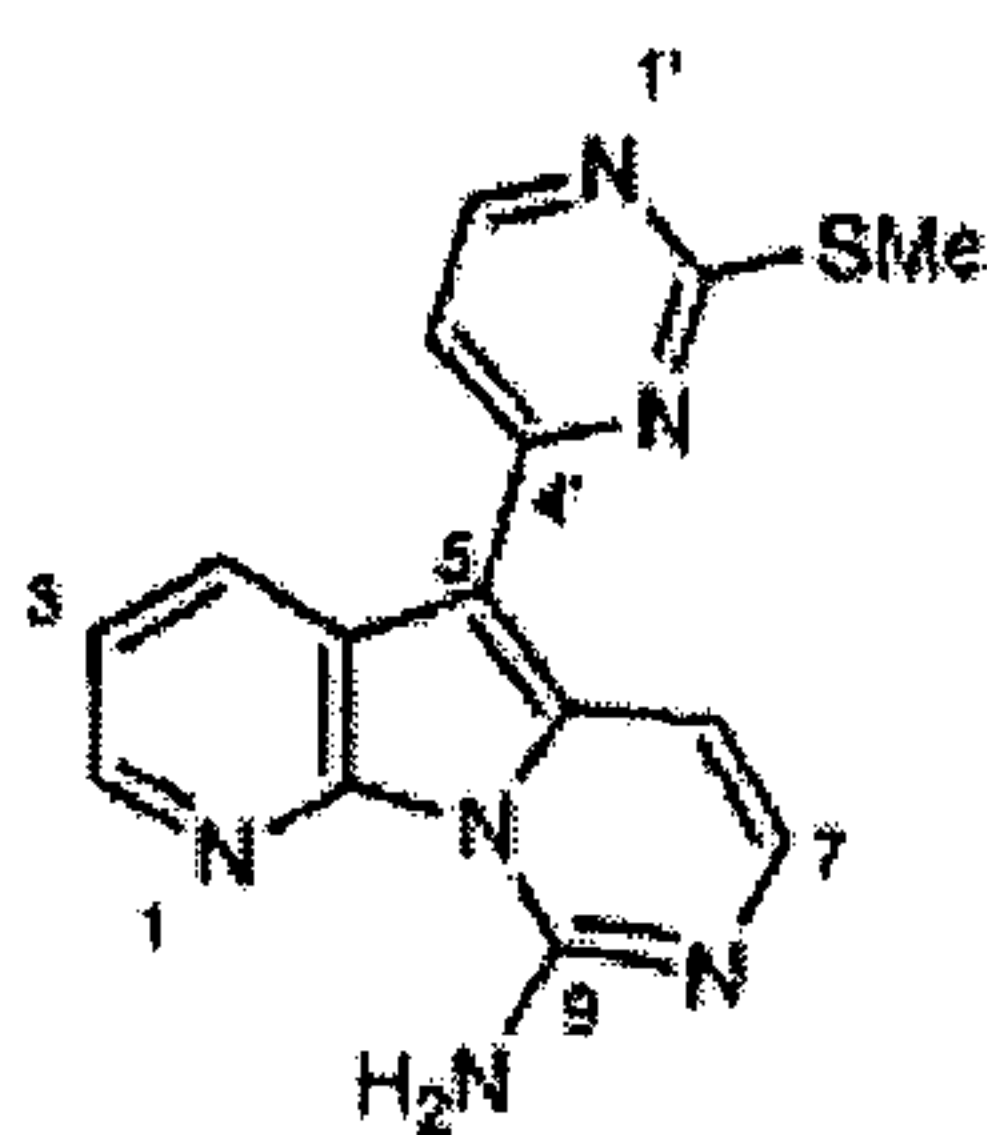
R^2 is absent; and

R^3 is an amino group or an N-acylamino group.

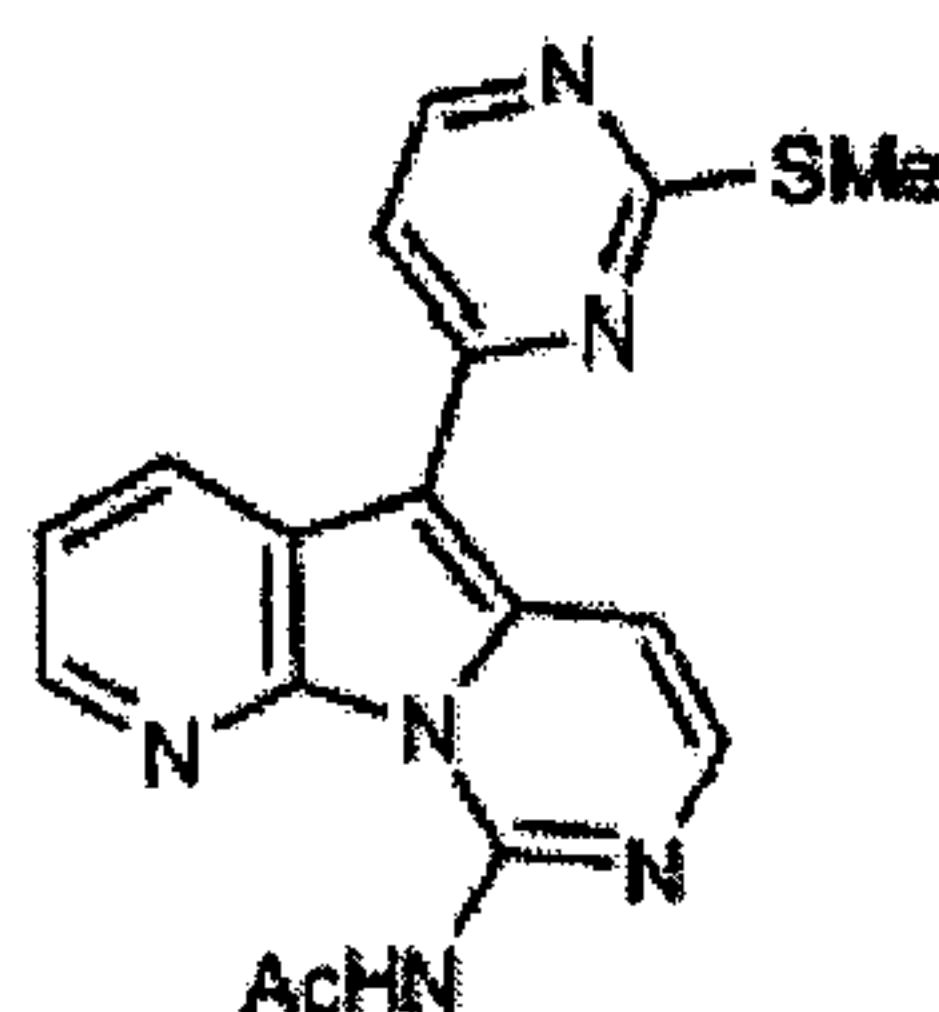
8. A compound according to claim 1, which is 8,9-dihydro-5-(2-methanesulfanylpurin-4-yl)pyrido[3',2':4,5]pyrrolo[1,2-c]-pyrimidin-9-one of formula:



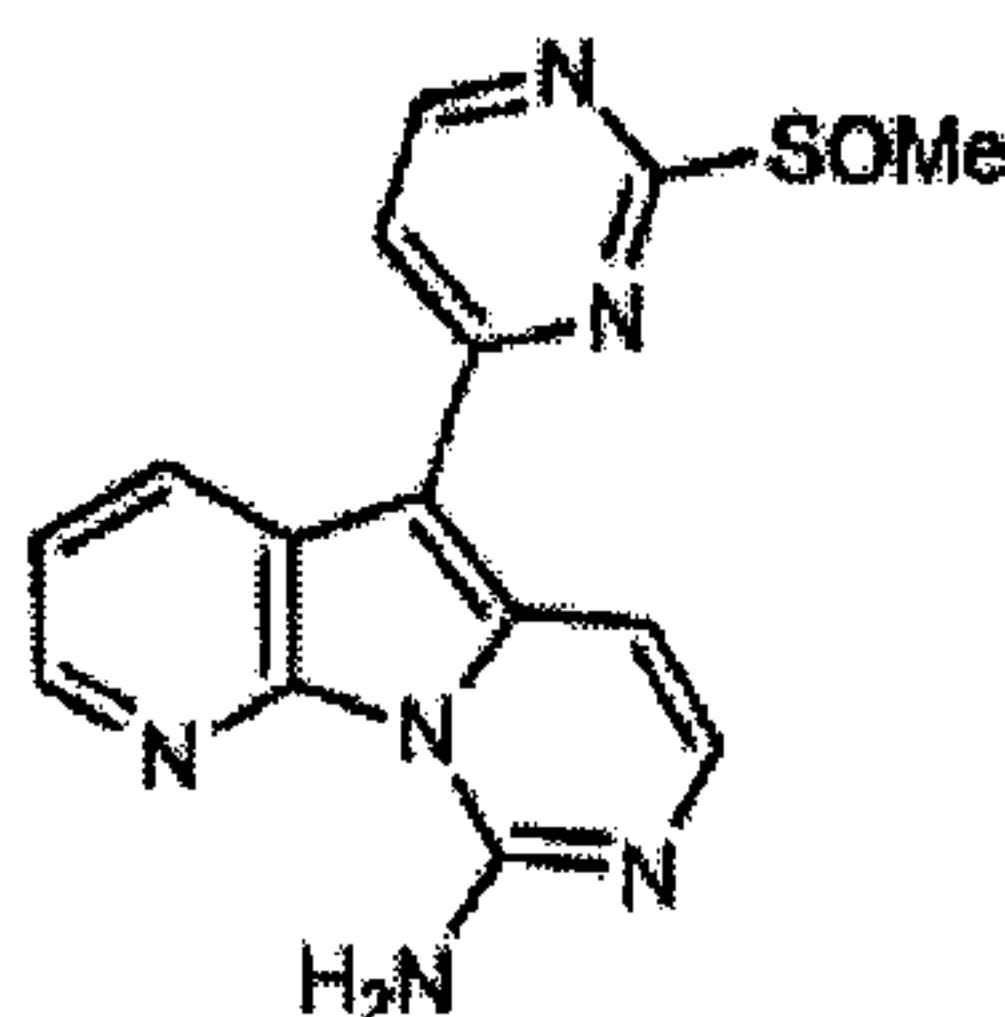
9. A compound according to claim 1, which is 9-amino-5-(2-methanesulfanylpurin-4-yl)pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine of formula:



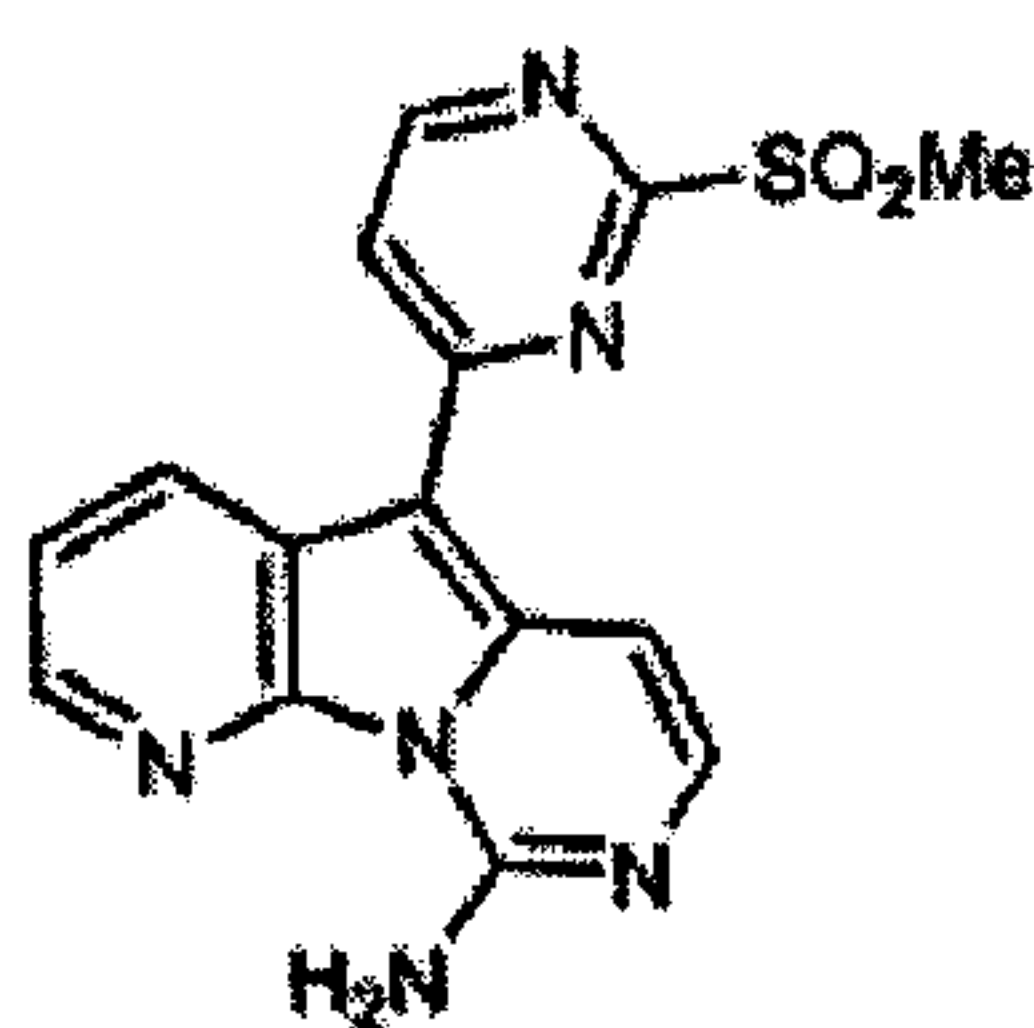
10. A compound according to claim 1, which is 9-acetylamino-5-(2-methanesulfanylpurin-4-yl)pyrido[3',2':4,5]-pyrrolo-[1,2-c]pyrimidine of formula:



11. A compound according to claim 1, which is 9-amino-5-(2-methanesulfinylpyrimidin-4-yl)pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine of formula:

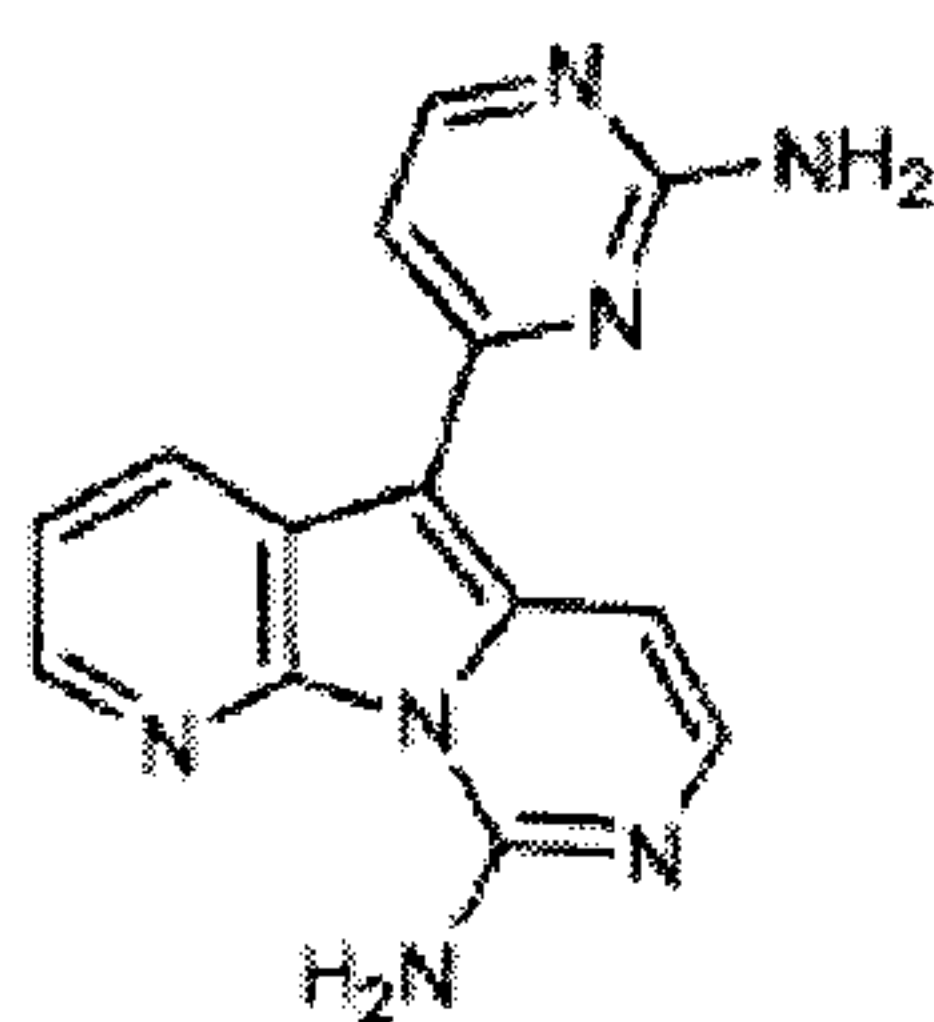


12. A compound according to claim 1, which is 9-amino-5-(2-methanesulfonylpyrimidin-4-yl)pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine of formula:



13. A compound according to claim 1, which is 9-amino-5-(2-aminopyrimidin-4-yl)pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine of formula:

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14. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 13 and a pharmaceutically acceptable carrier.
15. A pharmaceutical formulation for combination therapy, comprising a compound as defined in any one of claims 1 to 13, and at least one other therapeutically active compound.
16. Use of a compound as defined in any one of claims 1 to 13 in the preparation of a medicament for treatment of a cancer.
17. Use of variolin B or a pharmaceutically acceptable salt thereof for the treatment of non-small cell lung cancer.