PYRIDYL- AND PYRIMIDINYL-SUBSTITUTED PYRROLE-, THIOPHENE- AND FURANE-DERIVATIVES AS KINASE INHIBITORS

The present invention relates to heteropentacycles, a process for their preparation, pharmaceutical compositions comprising them and their use as therapeutic agents, particularly in the treatment of cancer and cell proliferation disorders.

The malfunctioning of protein kinases (PKs) is the hallmark of numerous diseases. A large share of the oncogenes and proto-oncogenes involved in human cancers code for PKs. The enhanced activities of PKs are also implicated in many non-malignant diseases. For a general reference to PKs malfunctioning or disregulation see, for instance, *Current Opinion in Chemical Biology* **1999**, *3*, 459 - 465.

Among the several protein kinases known in the art as being implicated in the growth of cancer cells is Cdc7, an evolutionary conserved serine-threonine kinase which plays a pivotal role in linking cell cycle regulation to genome duplication, being essential for the firing of DNA replication origins (see Montagnoli A. et al., *EMBO Journal*, **2002**, Vol. *21*, No.12, 3171; Montagnoli A. et al., *Cancer Research* **2004**, Vol. *64*, October 1, 7110).

Several heterocyclic compounds are known in the art as protein kinase inhibitors.

Among them are, for instance, pyrrolo-pyrazoles disclosed in WO2002/12242; tetrahydroindazoles disclosed in WO2000/69846; pyrrolo-pyridines disclosed in WO2001/98299; aminophthalazinones disclosed in WO2003/014090 and aminoindazoles disclosed in WO2003/028720. Pyrrole derivatives are disclosed in WO2001/001986, WO98/35944, thiazole derivatives are reported in WO2002/030358 and thiophenes are claimed to be kinase inhibitors in WO2005/095386. WO2006/012642 discloses pyrrole derivatives modulating the activity of one or more steroid nuclear receptors, and WO2003/068749 discloses furan derivatives modulating vanilloid receptors.

Pyridylfurans and pyridylthiophenes are described in EP853083 as inhibitors of TNFα biosynthesis and CAMs expression; pyridylpyrroles are diclosed in WO98/02430 as interleukin and tumor necrosis factor antagonists; pyrrole acids and esters are also therein disclosed. Piperazinylphenylcarboxamide derivatives containing a furane ring are diclosed in WO95/04729 as 5-HT1D receptor antagonists. In WO2005/100342 there are disclosed and claimed pyrimidine/pyridine substituted pyrroles having

antiproliferative and Erk2 kinase inhibition activities. In WO2000/006085 there are disclosed and claimed heterocyclecarboxamides as CCR5 receptor modulators.

The present inventors have now discovered some compounds useful, in therapy, as agents against a host of diseases caused by and/or associated to a disregulated protein kinase activity and, more particularly, Cdc7 or Cdc7/Cdks activity.

It is another object of the present invention to provide compounds endowed with protein kinase inhibiting activity and, more particularly, Cdc7 or Cdc7/Cdks inhibiting activity.

In particular, the present invention provides heteropentacycles that are endowed with protein kinase inhibiting activity, especially Cdc7 or Cdc7/Cdks inhibiting activity.

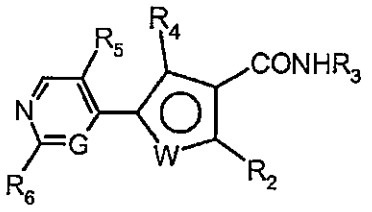
More specifically, the compounds of this invention are useful in the treatment of a variety of cancers including, but not limited to: carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocitic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkitt's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of PKs, and, in particular, of Cdc7 and Cdks like Cdk2 in the regulation of cellular proliferation, these heteropentacycles are also useful in the treatment of a variety of cell proliferative disorders such as, for instance, benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

The compounds of the invention can be also active as inhibitors of other protein kinases such as, for instance, protein kinase C in different isoforms, Met, PAK-4, PAK-5, ZC-1, STLK-2, DDR-2, Aurora 1, Aurora 2, Bub-1, PLK, Chk1, Chk2, HER2, raf1, MEK1,

MAPK, EGF-R, PDGF-R, FGF-R, IGF-R, VEGF-R, PI3K, weel kinase, Src, Abl, Akt, ILK, MK-2, IKK-2, Nek, CK2, GSK3, SULU, PKA, PKC, PDK, RET, KIT, LCK, TRKA and thus be effective in the treatment of diseases associated with other protein kinases.

Accordingly, in a first embodiment, the present invention provides a compound of the formula (I):



(I)

wherein

G is CH or nitrogen atom;

W is an oxygen atom, NR_1 or $S(O)_n$; **n** is 0, 1 or 2;

R_1 and R_3 independently represent hydrogen atom or an optionally substituted group selected from alkyl, cycloalkyl, alkenyl, alkynyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heterocyclyloxy-alkyl and alkoxycarbonyl group;

R_2 is hydrogen or halogen atom, or an optionally substituted group selected from aryl, cycloalkyl and heterocyclyl group;

R_4 is hydrogen or halogen atom, or an optionally substituted alkyl or alkenyl group;

R_5 is hydrogen or halogen atom;

R_6 is hydrogen atom or NHR_7;

R_7 is hydrogen atom, an optionally substituted group selected from alkyl, aryl, cycloalkyl and heterocyclyl group or -CO-R_1 wherein R_1 is as defined above;

or a pharmaceutically acceptable salt thereof, with the proviso that the following compounds are excluded:

2, 5-di(pyridin-4-yl)-thiophene-3-carboxylic acid amide,

2, 5-di(pyridin-4-yl)-thiophene-3-carboxylic acid methylamide,

2, 5-di(pyridin-4-yl)-4-methyl-pyrrole-3-carboxylic acid amide,

5-pyridin-4-yl-furan-3-carboxylic acid [4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide,

5-pyridin-4-yl-furan-3-carboxylic acid (1-methyl-1,2,3,4-tetrahydro-quinolin-7-yl)-amide and

N-[2-amino-1-(2,4-dichlorobenzyl)ethyl]-5-[2-(methylamino)pyrimidin-4-yl] thiophene-3-carboxamide.

The compounds of formula (I), object of the invention, are obtainable through a synthetic process comprising well known reactions carried out according to conventional techniques, as well as through an extremely versatile solid-phase and/or combinatorial process, being all comprised within the scope of the invention.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) as defined above and at least one pharmaceutically acceptable excipient, carrier or diluent.

Preferably, a compound of the formula (I) is characterized in that **W** is NR_1, R_1 and R_3 independently represent hydrogen atom or an optionally substituted alkyl group, and R_6 is NHR_7 wherein R_7 is hydrogen atom or an optionally substituted aryl group.

More preferably, a compound of the formula (I) is characterized in that **W** is NR_1; R_1 represent hydrogen atom or an optionally substituted alkyl group; R_3 and R_4 represent hydrogen atoms, R_2 is an optionally substituted aryl or heterocyclyl group; and R_6 is NH_2.

Even more preferred are the compounds of the formula (I) wherein **W** is **NH** or R_3 represents hydrogen atom. Specific, not limiting, preferred compounds of formula (I) of the invention, whenever appropriate in the form of pharmaceutically acceptable salts, are the following:

2-phenyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (**A1**),

2-(2-fluoro-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (**A2**),

2-(3-fluoro-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (**A3**),

2-(4-fluoro-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (**A4**),

5-pyridin-4-yl-2-o-tolyl-1H-pyrrole-3-carboxylic acid amide (**A7**),

5-pyridin-4-yl-2-m-tolyl-1H-pyrrole-3-carboxylic acid amide (**A8**),

5-pyridin-4-yl-2-p-tolyl-1H-pyrrole-3-carboxylic acid amide (**A9**),

2-(3-methoxy-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (**A11**),

2-(4-methoxy-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (**A12**),

2-(2-nitro-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (**A13**),

2-(3-nitro-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (**A14**),
2-(2,3-dimethyl-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (**A20**),
5-pyridin-4-yl-2-thiophen-3-yl-1H-pyrrole-3-carboxylic acid amide (**C1**),
2-furan-3-yl-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (**C2**),
5-(3-fluoro-pyridin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid amide (**E1**),
5-(3-fluoro-pyridin-4-yl)-2-o-tolyl-1H-pyrrole-3-carboxylic acid amide (**E2**),
5-(2-amino-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid amide (**F1**),
5-(2-amino-pyrimidin-4-yl)-2-o-tolyl-1H-pyrrole-3-carboxylic acid amide (**F2**),
5-(2-amino-pyrimidin-4-yl)-2-(2-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F4**),
5-(2-amino-pyrimidin-4-yl)-2-(4-fluoro-2-methyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F13**),
5-(2-amino-pyrimidin-4-yl)-2-(5-fluoro-2-methyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F14**),
5-(2-amino-pyrimidin-4-yl)-2-(2,3-dimethyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F15**),
5-(2-amino-pyrimidin-4-yl)-2-(2,3-difluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F16**),
5-(2-amino-pyrimidin-4-yl)-2-(2,4-difluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F17**),
5-(2-amino-pyrimidin-4-yl)-2-(2,5-difluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F18**),
5-(2-amino-pyrimidin-4-yl)-2-(2-chloro-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F19**),
5-(2-amino-pyrimidin-4-yl)-2-(2-chloro-4-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F23**),
5-(2-amino-pyrimidin-4-yl)-2-(2,4-dichloro-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F26**),
5-(2-amino-pyrimidin-4-yl)-2-(2-fluoro-4-methyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F28**),
5-(2-amino-pyrimidin-4-yl)-2-(2-fluoro-3-methyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F30**),

5-(2-amino-pyrimidin-4-yl)-2-(2-chloro-5-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F31**),

5-(2-amino-pyrimidin-4-yl)-2-(3-chloro-2-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F33**),

5-(2-amino-pyrimidin-4-yl)-2-(2,3-dichloro-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F34**),

5-(2-amino-pyrimidin-4-yl)-2-(2-fluoro-3-methoxy-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F35**),

5-(2-amino-pyrimidin-4-yl)-2-(4-chloro-2-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F36**),

5-(2-amino-pyrimidin-4-yl)-2-(2-bromo-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F38**),

5-(2-amino-pyrimidin-4-yl)-2-(2-chloro-3-methoxy-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F39**),

5-(2-amino-pyrimidin-4-yl)-2-(3-methoxy-2-methyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F40**),

5-(2-amino-pyrimidin-4-yl)-2-(2-chloro-3-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F41**),

5-(2-amino-pyrimidin-4-yl)-2-(3-bromo-2-chloro-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F42**),

5-(2-amino-pyrimidin-4-yl)-2-(2-bromo-3-chloro-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F43**),

5-(2-amino-pyrimidin-4-yl)-2-(2,3-dibromo-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F44**),

5-(2-amino-pyrimidin-4-yl)-2-(3-bromo-2-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F45**),

5-(2-amino-pyrimidin-4-yl)-2-(3-bromo-2-methyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F46**),

5-(2-amino-pyrimidin-4-yl)-2-(2-bromo-3-methyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F47**),

5-(2-amino-pyrimidin-4-yl)-2-(4-methoxy-3-methyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F48**),

5-(2-amino-pyrimidin-4-yl)-2-(3,4-dimethoxy-phenyl)-1H-pyrrole-3-carboxylic acid amide **(F49)**,

5-(2-amino-pyrimidin-4-yl)-2-(2-fluoro-4-methoxy-phenyl)-1H-pyrrole-3-carboxylic acid amide **(F50)**,

5-(2-amino-pyrimidin-4-yl)-2-(2-chloro-4-methoxy-phenyl)-1H-pyrrole-3-carboxylic acid amide **(F51)**,

5-(2-amino-pyrimidin-4-yl)-2-(2-bromo-4-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide **(F52)**,

5-(2-amino-pyrimidin-4-yl)-2-(4-methoxy-2-methyl-phenyl)-1H-pyrrole-3-carboxylic acid amide **(F53)**,

5-(2-amino-pyrimidin-4-yl)-2-thiophen-3-yl-1H-pyrrole-3-carboxylic acid amide **(G1)**,

5-(2-amino-pyrimidin-4-yl)-2-thiophen-2-yl-1H-pyrrole-3-carboxylic acid amide **(G2)**,

5-(2-amino-pyrimidin-4-yl)-2-(5-methyl-thiophen-2-yl)-1H-pyrrole-3-carboxylic acid amide **(G3)**,

5-(2-amino-pyrimidin-4-yl)-2-(5-chloro-thiophen-2-yl)-1H-pyrrole-3-carboxylic acid amide **(G4)**,

5-(2-amino-5-chloro-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid amide **(N1)**,

5-(2-amino-5-bromo-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid amide **(N2)**,

5-(2-amino-pyrimidin-4-yl)-4-iodo-2-phenyl-1H-pyrrole-3-carboxylic acid amide **(N3)**,

5-(2-amino-5-chloro-pyrimidin-4-yl)-2-(2-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide **(N7)**,

5-(2-amino-5-bromo-pyrimidin-4-yl)-2-(2-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide **(N8)**,

5-(2-amino-pyrimidin-4-yl)-2-phenyl-thiophene-3-carboxylic acid amide **(S1)**,

5-(2-amino-5-fluoro-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid amide **(V1)** and

5-(2-amino-pyrimidin-4-yl)-4-chloro-2-phenyl-1H-pyrrole-3-carboxylic acid amide **(Z1)**.

More preferred compounds according to the present inventions are:

5-(2-amino-pyrimidin-4-yl)-2-(2,3-dimethyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F15**),

5-(2-amino-pyrimidin-4-yl)-2-(2,4-dichloro-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F26**) and

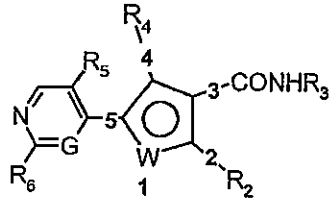
5-(2-amino-pyrimidin-4-yl)-2-(4-chloro-2-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (**F36**), or their pharmaceutically acceptable salt thereof.

A method of treating cell proliferative disorders caused by and/or associated with an altered Cdc7 kinase activity by administering to a mammal in need thereof an effective amount of a compound of formula I as defined above is also provided.

In a preferred embodiment of the method described above, the cell proliferative disorder is cancer.

Specific types of cancer that may be treated include carcinoma, squamous cell carcinoma, hematopoietic tumors of myeloid or lymphoid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer, and Kaposi's sarcoma.

The bonds of the heteropentacycle are aromatic; the numbering of said heteropentacycle is as shown hereinbelow:



(I)

In the present description, unless otherwise specified, the following terms have the following meanings.

Aryl, cycloalkyl and heterocyclyl groups sometimes will be collectively defined as "cyclyl" for convenience.

The term "alkyl" or "Alk" refers to straight or branched monovalent saturated aliphatic hydrocarbyl groups having from 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, n-hexyl, and the like. "Substituted alkyl" refers to an alkyl group having from

1 to 3 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogens, hydroxyl, nitro, carboxyl, carboxyl esters, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl.

"Cycloalkyl" refers to cyclic alkyl groups of from 3 to 10 carbon atoms having single or multiple cyclic rings including, by way of example, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl and the like.

"Substituted cycloalkyl" refers to a cycloalkyl, having from 1 to 5 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogen, hydroxyl, nitro, carboxyl, carboxyl esters, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl.

"Alkenyl" refers to alkenyl groups having from 2 to 6 carbon atoms. Such groups are exemplified by vinyl, allyl, but-3-en-1-yl, and the like.

"Substituted alkenyl" refers to alkenyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogen, hydroxyl, nitro, carboxyl, carboxyl esters, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl with the proviso that any hydroxyl substitution is not attached to a vinyl (unsaturated) carbon atom.

"Alkynyl" refers to alkynyl groups having from 2 to 6 carbon atoms. "Substituted alkynyl" refers to alkynyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogen, hydroxyl, nitro, carboxyl, carboxyl esters, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl with the proviso that any hydroxyl substitution is not attached to an acetylene (unsaturated) carbon atom.

"Alkoxy" refers to the group "alkyl-O-" which includes, by way of example, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, t-butoxy, sec- butoxy, n-pentoxy and the like.

"Substituted alkoxy" refers to the group "substituted alkyl-O-".

"Acyl" refers to the groups H-C(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heterocyclyl-C(O)-and substituted heterocyclyl-C(O)-, wherein alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclyl and substituted heterocyclyl are as defined herein.

"Acylamino" refers to the group -C(O)NR'R' where each R' is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl and where each R' can be joined to form together with the nitrogen atom a heterocyclyl or substituted heterocyclyl ring and wherein alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclyl and substituted heterocyclyl are as defined herein;

"Acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, aryl-C(O) O-, substituted aryl-C(O) O-, cycloalkyl- C(O) O-, substituted cycloalkyl-C(O)O-, heterocyclyl-C(O)O-, and substituted heterocyclyl-C(O)O- wherein alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclyl and substituted heterocyclyl are as defined herein.

"Substituted amino" refers to the group $-NR'R'$ wherein R' are as defined above provided that both R' are not hydrogen. When R' is hydrogen and the other R' is alkyl, the substituted amino group is sometimes referred to herein as alkylamino. When both of R' are alkyl, the substituted amino group is sometimes referred to herein as dialkylamino. When referring to a monosubstituted amino, it is meant that either R' is hydrogen but not both. When referring to a disubstituted amino, it is meant that neither R' is hydrogen.

"Aminoacyl" refers to the groups-NR'C(O)alkyl, - NR'C(O)substituted alkyl, -NR'C(O)cycloalkyl, -NR'C(O)substituted cycloalkyl, -NR'C(O)aryl, -NR'C(O) substituted aryl, -NR'C(O)heterocyclyl, and $-NR'C(O)$substituted heterocyclyl where R' is as defined above.

"Carboxyl" refers to -COOH or salts thereof.

"Carboxyl ester" refers to the groups -C(O)O-alkyl, -C(O)O- substituted alkyl, - C(O)O-aryl, and -C(O)O- substituted aryl wherein alkyl, substituted alkyl, aryl and substituted aryl are as deemed herein.

"Halo" or "halogen" or "X" refer to fluoro, chloro, bromo and iodo and preferably is fluoro, chloro or bromo.

"Aryl" or "Ar" refer to a monovalent aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g. phenyl) or multiple condensed rings (e.g. naphthyl or anthryl) which condensed rings may or may not be aromatic (e.g. 2-benzoxazolinone, 2H-1,4- benzoxazin- 3(4H)-one-7-yl, and the like) provided that the point of attachment is at an aromatic carbon atom. Preferred aryls include phenyl and naphthyl.

"Substituted aryl" refers to aryl groups which are substituted with from 1 to 3 substituents, selected from the group consisting of hydroxy, acyl, acylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, carboxyl, carboxyl esters, cyano, cycloalkyl, substituted cycloalkyl, halo, nitro, heterocyclyl, substituted heterocyclyl, heterocyclyloxy, substituted heterocyclyloxy, amino sulfonyl (NH_2-SO_2-), and substituted aminosulfonyl.

"Aryloxy" refers to the group aryl-O- that includes, by way of example, phenoxy, naphthoxy, and the like.

"Substituted aryloxy" refers to substituted aryl-O- groups.

"Heterocyclyl" or "heterocyclic" refer to a saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 10 carbon atoms and from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur or oxygen within the ring wherein, in fused ring systems, one or more the rings can be cycloalkyl, aryl or heteroaryl provided that the point of attachment is through the heterocyclic ring.

"Substituted heterocyclyl" refers to heterocyclyl groups that are substituted with from 1 to 3 of the same substituents as defined for substituted cycloalkyl.

Examples of heterocyclyls include, but are not limited to, pyridinyl, pyrrolyl, indolyl, thienyl, furyl, benzothienyl, benzofuranyl, imidazolyl, benzoimidazolyl, pyrazolyl, thiazolyl, benzothiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, isoindolyl, purinyl, quinolyl, isoquinolyl, dihydroquinolinyl, 2,3-dihydro-1H-indolyl, quinoxalinyl, benzodioxolyl, indanyl, indenyl, triazolyl, azetidinyl,

indolizinyl, dihydroindolyl, indazolyl, quinolizinyl, phthalazinyl, naphthylpyridinyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, carbolinyl, phenanthridinyl, acridinyl, phenanthrolinyl, phenazinyl, phenoxazinyl, phenothiazinyl, imidazolidinyl, imidazolinyl, piperidinyl, piperazinyl, indolinyl, phthalimidyl, 1,2,3,4- tetrahydro-isoquinolinyl, 4,5,6,7-tetrahydrobenzo[b]thiophenyl, thiazolidinyl, morpholinyl, thiomorpholinyl (also referred to as thiamorpholinyl), piperidinyl, pyrrolidinyl, pyrrolinyl, pyrazolinyl, pyrazolidinyl and tetrahydrofuranyl.

It should be noted that when referring to heterocyclyl and substituted heterocyclyl, any nitrogen or sulfur atoms that might be present may optionally be oxidized.

From all of the above, it is clear to the skilled man that any of the groups or substituents being defined, for instance, as haloalkyl, alkoxy, alkoxycarbonyl, aryloxy, heteroaryloxy, aminoalkyl, alkylamino, alkylaminoalkyl, dialkylaminoalkyl, and the like, have to be construed from the names of the groups from which they originate.

In this respect, as an example, any group which is identified as an arylalkyl or heterocycloalkyl has to be intended as an alkyl group which is further substituted by aryl or heterocycl, wherein aryl, heterocycl and alkyl are as above defined.

The compounds of formula (I) of the invention may have asymmetric carbon atoms and may therefore exist as individual optical isomers, as racemic admixtures or as any other admixture including a majority of one of the two optical isomers, which are all to be intended as comprised within the scope of the present invention.

In cases when compounds may exist in tautomeric forms, for instance keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

Likewise, the use as an antitumor agent of all the possible isomers and their admixtures and of both the metabolites and the pharmaceutically acceptable bio-precursors (otherwise referred to as pharmaceutically acceptable pro-drugs) of the compounds of formula (I) are also within the scope of the present invention.

As used herein, the term "pharmaceutically acceptable salts" refers to the nontoxic acid or alkaline earth metal salts of the compounds of formula I. These salts can be prepared in situ during the final isolation and purification of the compounds of formula I, or by separately reacting the base or acid functions with a suitable organic or inorganic acid or base, respectively. Representative salts include, but are not limited to, the following:

acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, nicotinate, 2-napthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides, dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids that may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, perchloric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, methanesulfonic acid, succinic acid and citric acid, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, lactic acid, malonic acid, malic acid, tartaric acid, benzoic acid, cinnamic acid, mandelic acid, isethionic acid and salicylic acid.

Basic addition salts can be prepared in situ during the final isolation and purification of the compounds of formula I, or separately by reacting carboxylic acid moieties with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

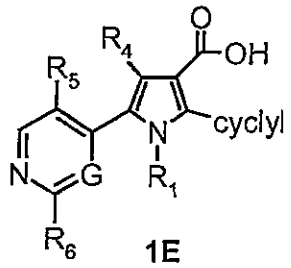
The terms "pharmaceutically acceptable prodrug" and "pharmaceutically acceptable bio-precursors" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the active parent drug, according to formula (I), in vivo, for example by hydrolysis in blood. A discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ea., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

As formerly indicated, it is a further object of the invention a process for preparing the compounds of formula (I) as above defined and pharmaceutically acceptable salts thereof.

The compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. Unless otherwise indicated, the starting materials are known compounds or may be prepared from known compounds according to well known procedures. It will be appreciated that, where typical or preferred process conditions (*i.e.*, reaction temperatures, times, mole ratios of reactants, solvents, pressures) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures. Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in T.W.Greene and P.G.M.Wuts, Protecting Groups in Organic Synthesis, Second Edition, Wiley, New York, 1991, and references cited therein.

In particular, the present invention provides a process comprising:

a) coupling a compound of formula **1E**



1E

wherein R_1, R_4, R_5, R_6 and G are as defined above and cyclyl is an optionally substituted group selected form aryl, cycloalkyl and heterocyclyl group as defined above,

either with an activated form of ammonia, optionally in the presence of a condensing agent, or with an amine of formula $\mathbf{R_3}$-NH_2, wherein R_3 is as defined above, thus obtaining a compound of formula (I) as defined above wherein W is $\mathbf{NR_1}$, wherein $\mathbf{R_1}$ is as defined above, and $\mathbf{R_2}$ is an optionally substituted group selected form aryl, cycloalkyl and heterocyclyl group;

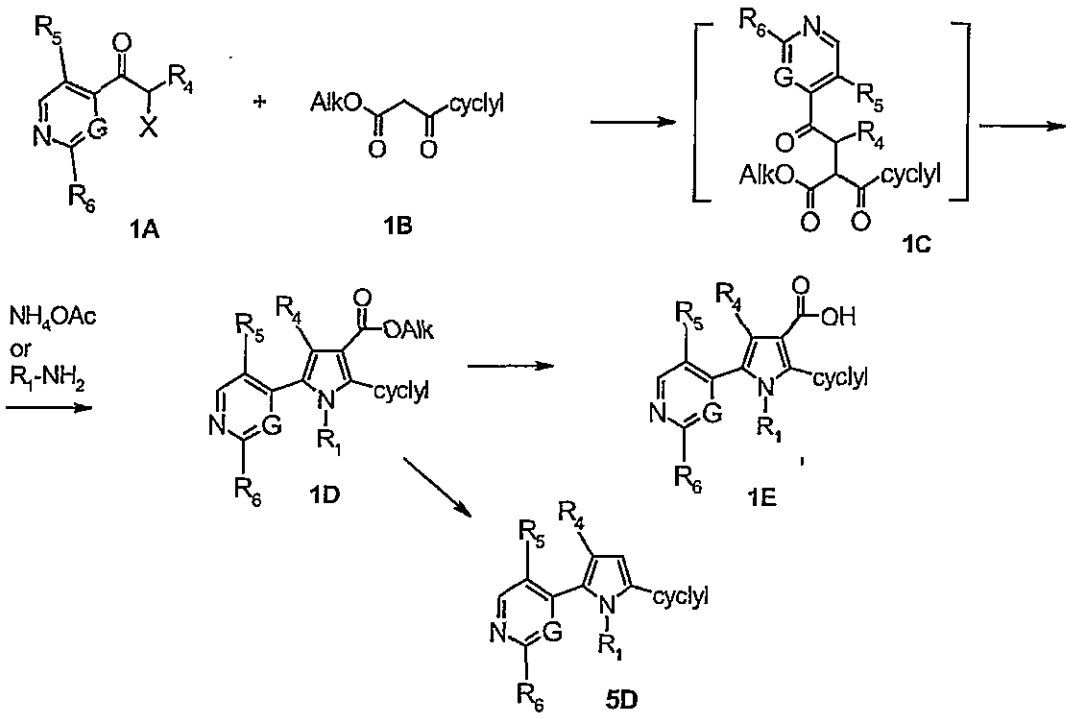
b) optionally converting a compound of formula (I) into another different compound of formula (I), and, if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt thereof or converting a salt into the free compound (I).

The coupling for converting **1E** into the desired compound of formula (I) may be carried out by well known primary amide-forming protocols [for example, 1-hydroxy-benzotriazole ammonium salt (HOBT·NH_3) in the presence of either 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) or CDI and ammonium carbonate]; the conversion into secondary amides may be carried out by coupling with an amine of formula $\mathbf{R_3}$-NH_2, wherein $\mathbf{R_3}$ is as defined above, under a variety of well known amide-forming conditions.

Likewise, the salification of a compound of formula (I) or the conversion of its salt into the free compound (I), carried out according to well-known procedures in the art, are still within the scope of the invention.

The preparation of the compounds of formula **1E** is depicted in the following **Scheme 1**.

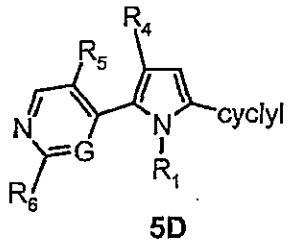
Scheme 1



wherein R_1, R_4, R_5, R_6, G and cyclyl are as defined above, X is a halogen atom such as bromine or chlorine and Alk is a C_1-C_5 alkyl goup.

Compound **1D** may be formed by coupling haloketone **1A** with beta-ketoester **1B** in the presence of a suitable base, such as sodium hydride in a solvent like tetrahydrofuran (THF) or dimethylformamide (DMF) at temperatures ranging from –20°C to 50°C and then by exposing intermediate **1C** to Hantzsch reaction conditions in the presence of ammonium acetate (when R_1=H) or of an amine of formula R_1-NH_2 in a suitable solvent such as ethanol or acetic acid or a mixture of the two, at temperatures ranging from rt to 150°C for a period of time from about 10 min to 16 h, optionally inside a microwave cavity. Ester **1D** may be then saponified in standard basic conditions to give the acid of formula **1E**.

In some instances, when R_4 is different from hydrogen atom, ester hydrolysis of **1D** may lead to the decarboxylated analog. Accordingly, another process for preparing a compound of formula I is provided which comprises the amidation of a compound formula **5D**:



5D

wherein R_1, R_5, R_6, G and cyclyl are as defined above and R_4 is not hydrogen atom, and b) optionally converting a compound of formula (I) into another different compound of formula (I), and, if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt thereof or converting a salt into the free compound (I). In this case amidation is accomplished as described, for example, in *Synthesis* **1978**, 374, by exposing compound **5D** to chlorosulfonylisocyanate in a suitable solvent, such as acetonitrile, dichloromethane or diethyl ether, and treating the obtained chlorosulfonylamide with alkali in order to achieve the corresponding sulfamic acid. The sulfamic acid is then hydrolyzed to the desired compound of formula (I) in acidic medium, such as, for example, concentrated hydrochloric acid.

The compounds of formula **1A** and **1B**, as well as any other reactant of the process, are known and, if not commercially available *per se*, can be easily prepared according to known methods. The compounds of formula **1A** may be prepared by halogenating, e.g. brominating or chlorinating, a suitable heteroaryl-ethanone derivative or an activated equivalent. The reaction occurs by working under conventional methods, for instance in the presence of bromine and in a suitable solvent such as aqueous hydrobromic acid or a mixture of acetic and hydrobromic acid, for a time varying between about 1 h and about 24 h. Alternatively, a suitably activated heteroaryl derivative, e.g. an alkylenolether or silylenolether, can be reacted with a halogen source, for instance N-bromo-succinimide (NBS), in a suitable solvent, such as tetrahydrofuran/water mixtures.

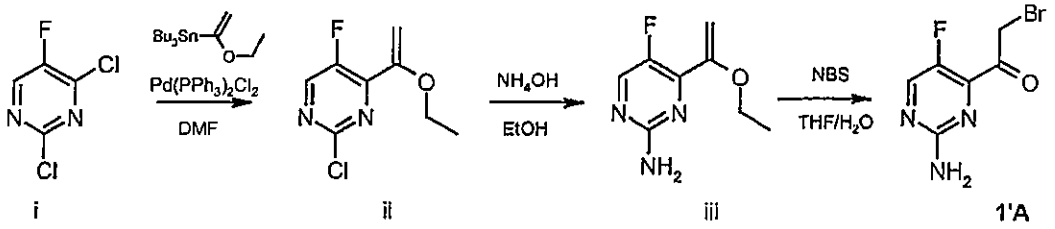
In particular, among the suitable haloderivatives of formula **1A**, we consider 2-bromo-1-pyridin-4-yl-ethanone (commercial), 2-bromo-1-(3-fluoro-pyridin-4-yl)-ethanone (reported in WO2005013986), 2-bromo-1-pyridin-4-yl-propan-1-one (commercial), 2-bromo-1-pyrimidin-4-yl-ethanone (reported in WO2005014572), 1-(2-amino-pyrimidin-4-yl)-2-bromo-ethanone (commercial), 2-bromo-1-(2-chloro-pyridin-4-yl)-ethanone (reported in WO2004058762), 2-bromo-1-(2-methylsulfanyl-pyrimidin-4-yl)-ethanone (reported in WO2003011838), 1-(2-amino-5-fluoro-pyrimidin-4-yl)-2-bromo-ethanone

1'A (Scheme 2.1.) and 2-bromo-1-(2-phenylamino-pyrimidin-4-yl)-ethanone **1''A** (Scheme 2.2.).

Among the suitable heteroaryl-ethanone derivatives subdued to halogenation we consider, for instance, 1-(3-fluoropyridin-4-yl)ethanone (commercial), 1-(2-chloropyridin-4-yl)ethanone (commercial), 1-(pyrimidin-4-yl)ethanone (commercial), 1-[2-(methylthio)pyrimidin-4-yl]ethanone (commercial) and 4-(1-ethoxy-vinyl)-5-fluoro-pyrimidin-2-ylamine **iii** (see Scheme 2.1.).

Intermediate 1-(2-amino-5-fluoro-pyrimidin-4-yl)-2-bromo-ethanone **1'A (1A,** wherein R_4=H, R_5=F, G=N, R_6=NH_2, X=Br) can be obtained according to the following reaction sequence **(Scheme 2.1.)**:

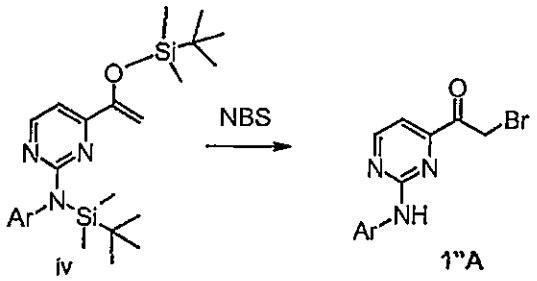
Scheme 2.1.



Commercially available 2,4-dichloro-5-fluoro-pyrimidine **i** is reacted with (1-ethoxyvinyl)-tributylstannane in standard conditions in the presence of a palladated catalyst (for example dichloroditriphenylphosphino palladium) in DMF, to afford the corresponding 4-vinyl ether **ii**. The amino group can be introduced at position 2 by direct treatment with aqueous concentrated ammonia in ethanol and heating with microwaves **(iii)**, while bromination of the vinyl ether to the α-bromo-ketone **(1'A)** is achieved with NBS in aqueous solvents.

Among the silylenolethers subdued to halogenation, we consider, for instance, (tert-butyl-dimethyl-silanyl)-{4-[1-(tert-butyl-dimethyl-silanyloxy)-vinyl]-pyrimidin-2-yl}-phenyl-amine **iv** (reported in WO2005014572), from which bromoketone **1''A (1A,** wherein R_4=R_5=H, G=N, R_6=NHAr, X=Br) can be obtained according to the reaction step shown in **Scheme 2.2.**

Scheme 2.2.

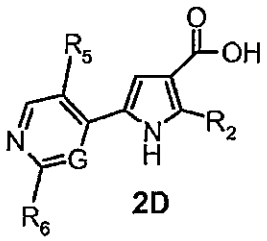


wherein Ar represents an aryl group as defined above.

Halogenation of the compound of formula (iv) may be promptly obtained with N-bromo succinimide in aqueous tetrahydrofuran at rt for about 20 h. The compounds of formula **1B**, when not commercially available, may be prepared with different methods according to references in the literature. For instance, acid homologation to beta-keto esters may be achieved from acyl chlorides or carboxylic acids by activation with 2,2-dimethyl-1,3-dioxane-4,6-dione (the Meldrum's acid) as described in *J.Med.Chem.* **2001**, *44*, 90, from acyl chlorides and ethyl hydrogenmalonate as reported in *J.Het.Chem.* **1990**, *27*, 1609, or from aryl ethanones with diethylcarbonate as shown in *Can.J.Chem.* **1992**, 1323.

Alternatively, a compound of formula (I) as defined above, may be obtained by

a') coupling a compound of formula **2D**



2D

wherein $\mathbf{R_2}$ is hydrogen or halogen atom, and R_5, R_6, and G are as defined above, either with an activated form of ammonia, optionally in the presence of a condensing agent, or with an amine of formula $\mathbf{R_3}$-NH_2, wherein R_3 is as defined above, thus obtaining a compound of formula (I) as defined above wherein W is N, $\mathbf{R_1}$ is hydrogen atom and $\mathbf{R_2}$ is hydrogen atom or halogen atom;

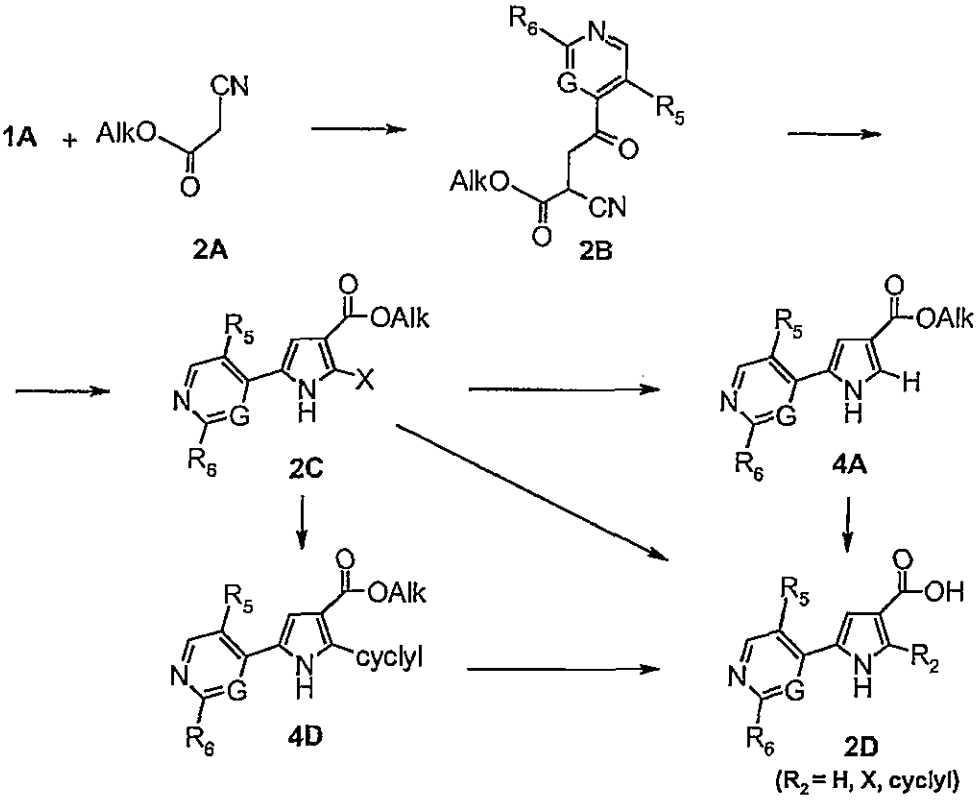
a'$_1$) optionally converting the resultant compound of formula (I) wherein $\mathbf{R_2}$ is halogen atom into another compound of formula (I) wherein $\mathbf{R_2}$ is hydrogen atom or an optionally substituted group selected form aryl, cycloalkyl and heterocyclyl group as defined above; and/or

a'$_2$) converting the resultant compound of formula (I) wherein $\mathbf{R_1}$ is hydrogen atom into another compound of formula (I) wherein $\mathbf{R_1}$ is an optionally substituted group selected from alkyl, cycloalkyl, alkenyl, alkynyl, heterocyclyl, aryl, heterocyclyloxy-alkyl and alkoxycarbonyl;

and, if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt thereof or converting a salt into the free compound (I).

The starting material of formula **2D** is prepared via a Pinner-like reaction as shown in the following **Scheme 3**, analogously or accordingly to methods reported in the literature (for instance *Il Farmaco* **1999**, *54*, 542 or *Tetrahedron Letters* **1994**, *35*, 5989).

Scheme 3



wherein R_5, R_6, X, G, cyclyl and Alk are as defined above.

Compound **2B** may be formed by treating haloketone **1A**, as defined above, with cyanoester **2A** in the presence of a suitable base, such as sodium ethoxide in ethanol, at temperatures ranging from rt to reflux, for periods of time from about 1 h to 16 h.

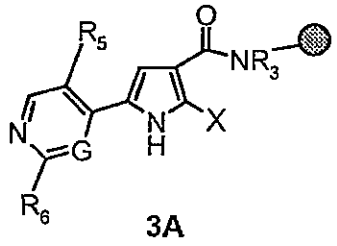
Halopyrrole **2C** may be obtained by exposing **2B** to halohydric acids, such as hydrochloric acid in dioxane or hydrobromic acid in acetic acid, in a solvent like

dichloromethane or diethylether or mixtures thereof at temperatures ranging from –20°C to reflux, most frequently at rt. Access to 2-unsubstituted pyrroles can be achieved by dehalogenation of halopyrrole **2C** that may be accomplished, for instance, by hydrogenolysis, to give **4A**.

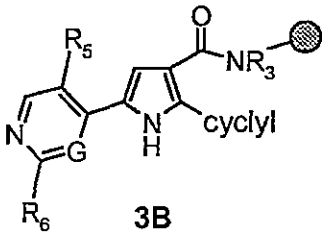
Alternatively, functionalization at position 2 may be accomplished on haloester **2C** to yield ester **4D**. Esters **2C**, **4A** and **4D** may be then saponified in standard basic conditions to the corresponding acids **2D**.

Alternatively, a compound of formula (I) as defined above, may be obtained by

a') cleaving a compound of formula **3A** or **3B**



3A



3B

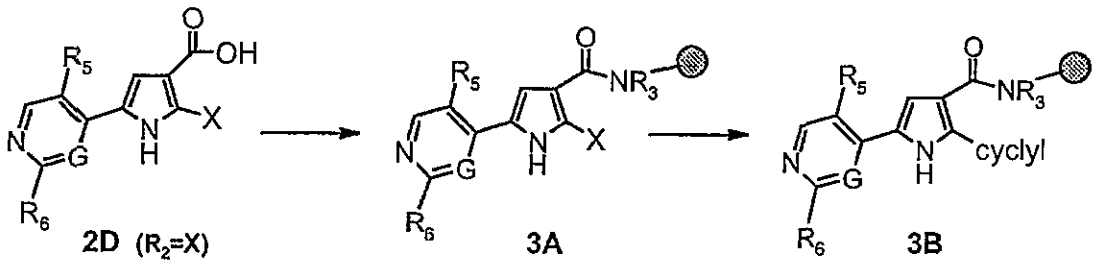
wherein R_3, R_5, R_6, cyclyl, X, G are as defined above and the symbol  represents a solid support to which the chemical molecule is linked,

and, if desired, converting the resultant compound of formula (I) wherein **W** is nitrogen atom and $\mathbf{R_2}$ is halogen or an optionally substituted group selected form aryl, cycloalkyl and heterocyclyl group, into a pharmaceutically acceptable salt thereof or converting a salt into the free compound (I).

The cleavage is preferably accomplished with TFA/DCM.

The above preparation is aimed at avoiding the formation of unwanted by-products. The preparation of compounds **3A** and **3B** is displayed in **Scheme 4**. Acid **2D** is loaded onto a solid support, such as a resin (for example a Rink amide MBHA resin, previously cleaved by shaking at rt in a 20% piperidine solution in DMF) by stirring at rt overnight in DMF in the presence of EDCI and HOBT to form amide **3A** on which a carbon-carbon bond forming reaction, for instance the Suzuki reaction, is successfully applied to give the compound of formula **3B**.

Scheme 4

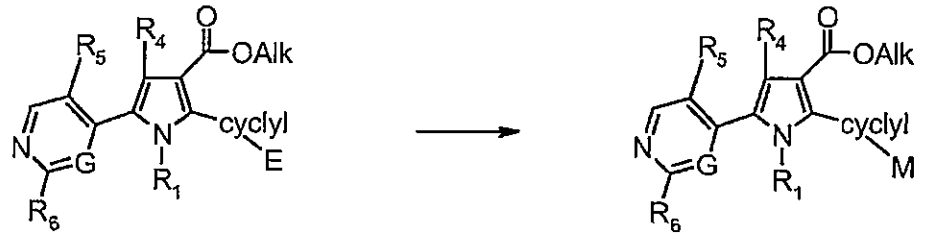


2D (R_2=X) **3A** **3B**

wherein R_3, R_5, R_6, X, G, and cyclyl are as defined above.

A particular compound of formula **1D**, named **6D**, wherein the cyclyl bears a substituent may be optionally converted into different compound of formula **1D**, named **7D**, as represented in **Scheme 5.**

Scheme 5



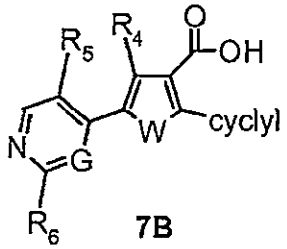
6D (1D, wherein R_2= cyclyl-E) **7D** (1D, wherein R_2= cyclyl-M)

wherein R_1, R_4, R_5, R_6, G, cyclyl and Alk are as defined above, E is halogen, triflate, mesilate or tosylate group, and M is aryl, heteroaryl, heterocyclyl, alkenyl, alkynyl, or optionally substituted amino moictics.

A particular cyclyl moiety, namely a suitably substituted aryl or heterocyclyl ring, bearing a substituent E as above defined, may be subdued to carbon-carbon or carbon-nitrogen bond formation with an array of well known methods from the literature, for example the Suzuki, Stille, Sonogashira or Buchwald protocols, able to produce the desired outcome **7D**, where the group M is as above defined.

Moreover, the present invention provides a process comprising:

a) coupling a compound of formula 7B



7B

wherein W is an oxygen or sulphur atom, R_4, R_5, R_6 and G are as defined above and cyclyl is an optionally substituted group selected form aryl, cycloalkyl and heterocyclyl group as defined above, either with an activated form of ammonia, optionally in the presence of a condensing agent, or with an amine of formula R_3-NH_2, wherein R_3 is as defined above, thus obtaining a compound of formula (I) as defined above, wherein W is an oxygen or sulphur atom, and $\mathbf{R_2}$ is an optionally substituted group selected form aryl, cycloalkyl and heterocyclyl group;

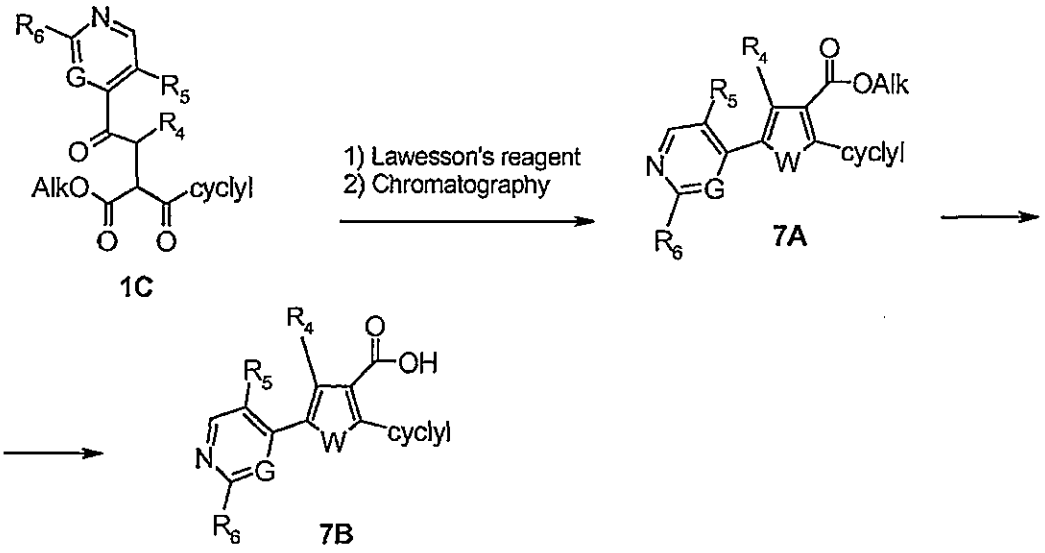
b) optionally converting a compound of formula (I) into another different compound of formula (I), and, if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt thereof or converting a salt into the free compound (I).

Under optional step b), when W is sulphur atom, thiophene ring may be oxidized to the corresponding 1-oxo or 1,1-dioxo thiophenes by well known procedures from the literature.

The esters of general formula **7A**, belonging to the thiophene and furan series, may be conveniently obtained in mixture from ketoesters **1C** by cyclization, for instance with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (the Lawesson's reagent).

After chromatographic separation the two esters may be independently subdued to standard basic hydrolysis providing the desired acids **7B** (**Scheme 6**).

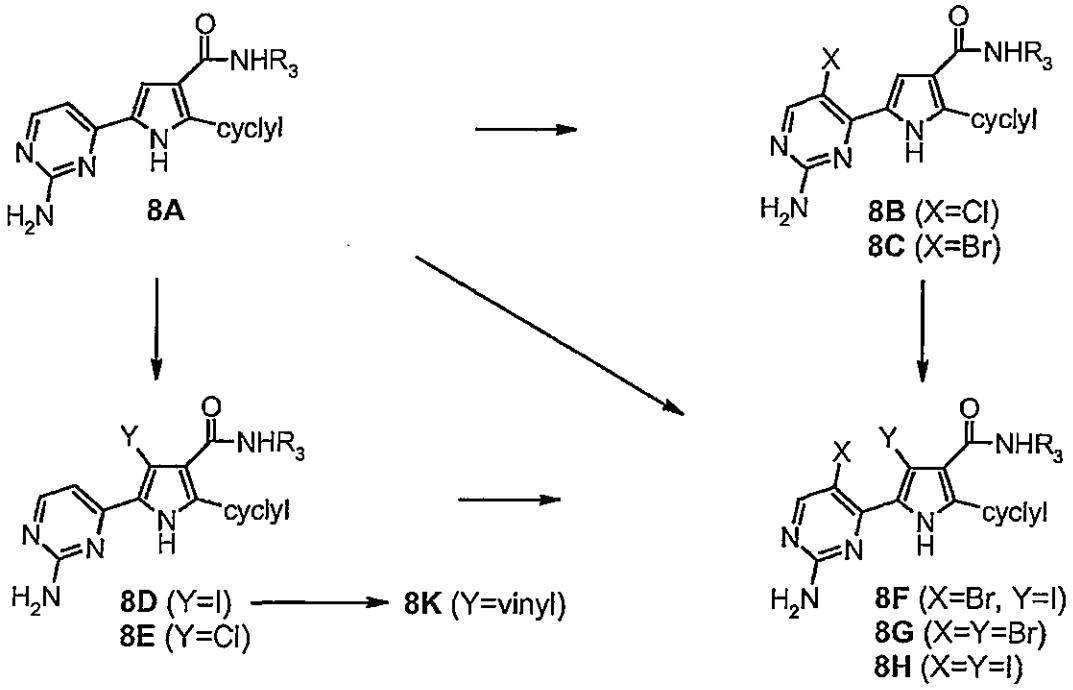
Scheme 6



wherein R_4, R_5, R_6, G, W, cyclyl and Alk are as defined above.

As stated above, optionally the compounds of formula (I) may be directly modified at either of their heteroaromatic component generating another derivative of formula (I). For instance the pyrimidine ring of pyrrole **8A** can be directly halogenated to yield amides **8B** and **8C**. This transformation is achieved respectively by treatment with NCS at about 100°C or with NBS at room temperature in a suitable solvent, like, for example, THF or DMF. Alternatively, NIS in the same conditions transforms amide **8A** into the corresponding amide **8D**, halogenated at position 4 of pyrrole. The same amide **8A**, if previously protected at the aminopyrimidine nucleus as Boc derivative, can be also transformed in chloro amide **8E** by treatment with NCS at 100°C in DMF and deprotection in standard acidic conditions. Both double sequential and double simultaneous halogenations can also be achieved, as shown in Scheme 7. Bromo amide **8C**, when treated with NIS, affords amide **8F** and the same result is obtained by treating iodo amide **8D** with NBS. Amide **8A** is simultaneously dihalogenated by two equivalents of halogenating agent to provide amides **8G** and **8H**, upon treatment with NBS and NIS respectively. Amide **8D** can be transformed into the 4-vinyl derivative **8K** by direct vinylation via the Stille cross-coupling reaction protocol, as described, for example, in *Tetr. Lett.* **1995**, *36*, 7043. The reaction occurs by treating **8D** with vinyltributylstannane in the presence of a palladated catalyst, such as palladium tetrakis or dichloroditriphenylphosphino palladium, in solvents like dioxane, DMF or their mixtures, at temperatures ranging from 25 to 200°C.

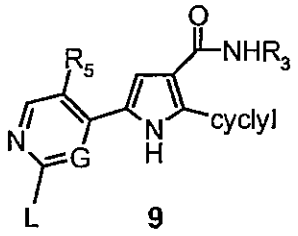
Scheme 7



wherein R_3, R_5, R_6, X, G and cyclyl are as defined above.

Another process for preparing a compound of formula (I) comprises:

a) reacting a compound of formula **9**



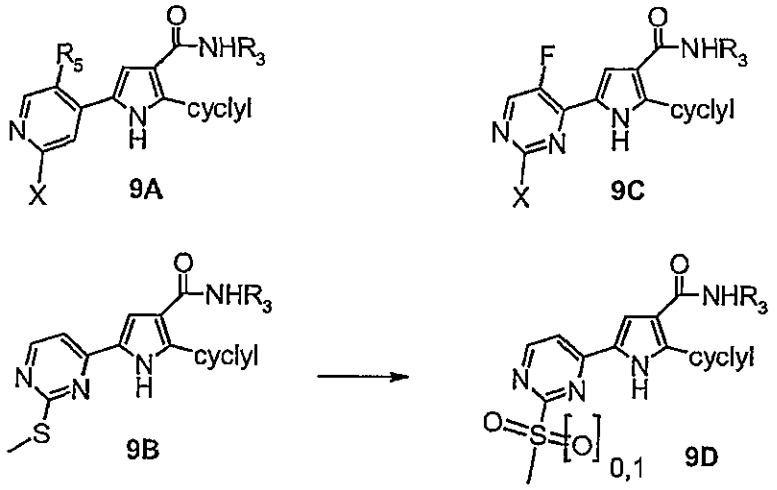
wherein L is a leaving group such as halogen, methansulphonyl or methansulfinyl and R_3, R_5, cyclyl and G are as defined above, either with an activated form of ammonia, like lithium bis(trimethylsilyl)amide, optionally in the presence of a condensing agent, or with hydrazine followed by reduction to amine, or with an amine of formula $\mathbf{R_7}$-NH_2, wherein R_7 is as defined above, in a Pd-catalyzed coupling, thus obtaining a compound of formula (I) as defined above wherein W is NR_1, $\mathbf{R_1}$ is hydrogen atom and $\mathbf{R_6}$ is NH-R_7;

and, if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt thereof or converting a salt into the free compound (I).

The starting compounds **9** of this process are shown in **Scheme 8.**

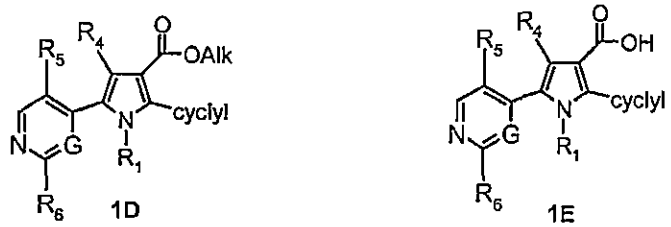
Halopyridine **9,** wherein L is halogen (**9A**) may be obtained, for example, from 2-bromo-1-(2-chloro-pyridin-4-yl)-ethanone prepared by halogenation of 1-(2-chloropyridin-4-yl)ethanone, obtainable from 2-chloro-4-cyano pyridine, as described in *J.Het.Chem.*, **1983,** *20,* 533. 1-[2-(Methylthio)pyrimidin-4-yl] derivative **9,** wherein L is CH_3-S- (**9B**), obtainable from 2-bromo-1-(2-methylsulfanyl-pyrimidin-4-yl)-ethanone (described in WO03/011838), may be activated to the corresponding sulfoxide or sulfone **9,** wherein L is CH_3-S(O)- or CH_3-$S(O)_2$- (**9D**), by oxidation, for example with oxone. Halopyrimidine derivative **9,** wherein L is halogen and R_5 is fluorine (**9C**), may be instead prepared from 2-bromo-1-(2-chloro-5-fluoropyrimidin-4-yl) ethanone, obtained by halogenation of 1-(2-chloro-5-fluoropyrimidin-4-yl) ethanone, in turn prepared as described in WO04/058762.

Scheme 8



wherein R_3, R_5, X and cyclyl are as defined above.

It is a further object of the present invention an intermediate of the formula 1D or 1E:



wherein G, Alk, cyclyl, R_1, R_4, R_5 and R_6 are as defined above, with the proviso that the following compounds are excluded:

1H-Pyrrole-3-carboxylic acid, 1-(methoxymethyl)-4-methyl-2,5-di-4-pyridinyl-, ethyl ester;
1H-pyrrole-3-carboxylic acid, 2,5-di-4-pyridinyl-, methyl ester, 1H-pyrrole-3-carboxylic acid, 4-methyl-2-phenyl-5-(4-pyridinyl)-, methyl ester,
1H-pyrrole-3-carboxylic acid, 4-methyl-2,5-di-4-pyridinyl-, compd. with morpholine (1:1) ,
1H-pyrrole-3-carboxylic acid, 4-methyl-2,5-di-4-pyridinyl,

1H-pyrrole-3-carboxylic acid, 4-(methoxymethyl)-2,5-di-4-pyridinyl-, methyl ester,
1H-pyrrole-3-carboxylic acid, 4-butyl-2,5-di-4-pyridinyl-, ethyl ester,
1H-pyrrole-3-carboxylic acid, 4-(1-methylethyl)-2,5-di-4-pyridinyl-, ethyl ester ,
1H-pyrrole-3-carboxylic acid, 4-propyl-2,5-di-4-pyridinyl-, ethyl ester,
1H-pyrrole-3-carboxylic acid, 4-methyl-2,5-di-4-pyridinyl-, 2-methoxyethyl ester,
1H-pyrrole-3-carboxylic acid, 4-methyl-2,5-di-4-pyridinyl-, butyl ester,
1H-pyrrole-3-carboxylic acid, 4-methyl-2,5-di-4-pyridinyl-, propyl ester,
1H-pyrrole-3-carboxylic acid, 4-methyl-2,5-di-4-pyridinyl-, 1,1-dimethylethyl ester,
1H-pyrrole-3-carboxylic acid, 4-methyl-2,5-di-4-pyridinyl-, 1-methylethyl ester,
1H-pyrrole-3-carboxylic acid, 4-methyl-2,5-di-4-pyridinyl-, 2-propenyl ester,
1H-pyrrole-3-carboxylic acid, 4-methyl-2,5-di-4-pyridinyl-, phenylmethyl ester,
1H-pyrrole-3-carboxylic acid, 4-methyl-2,5-di-4-pyridinyl-, methyl ester,
1H-pyrrole-3-carboxylic acid, 4-methyl-2,5-di-4-pyridinyl-, ethyl ester and
1H-pyrrole-3-carboxylic acid, 4-ethyl-2,5-di-4-pyridinyl-, ethyl ester.

PHARMACOLOGY

The compounds of formula (I) are active as protein kinase inhibitors and are therefore useful, for instance, to restrict the unregulated proliferation of tumor cells.
In therapy, they may be used in the treatment of various tumors, such as those formerly reported, as well as in the treatment of other cell proliferative disorders such as psoriasis, vascular smooth cell proliferation associated with atherosclerosis and post-surgical stenosis and restenosis and in the treatment of Alzheimer's disease.

Inhibition assay of Cdc7 activity

The inhibiting activity of putative Cdc7 inhibitors and the potency of selected compounds is determined through a method of assay based on the use of Dowex resin capture technology.

The assay consists of the transfer of radioactivity labeled phosphate moiety by the kinase to an acceptor substrate. The resulting 33P-labeled product is separated from unreacted tracer, transferred into a scintillation cocktail and light emitted is measured in a scintillation counter.

The inhibition assay of Cdc7/Dbf4 activity is performed according to the following protocol.

The MCM2 substrate is trans-phosphorylated by the Cdc7/Dbf4 complex in the presence of ATP traced with γ^{33}-ATP. The reaction is stopped by addition of Dowex resin in the presence of formic acid. Dowex resin particles capture unreacted γ^{33}-ATP and drag it to the bottom of the well while ^{33}P phosphorylated MCM2 substrate remains in solution. The supernatant is collected, transferred into Optiplate plates and the extent of substrate phosphorylation is evaluated by β counting.

The inhibition assay of Cdc7/Dbf4 activity was performed in 96 wells plate according to the following protocol.

To each well of the plate were added:

- 10 µl test compound (10 increasing concentrations in the nM to uM range to generate a dose-response curve). The solvent for test compounds contained 3% DMSO. (final concentration 1%)
- 10 µl substrate MCM2 (6 µM final concentration), a mixture of cold ATP (2 µM final concentration) and radioactive ATP (1/5000 molar ratio with cold ATP).
- 10 µl enzyme (Cdc7/Dbf4, 2 nM final concentration) that started the reaction. The buffer of the reaction consisted in 50 mM HEPES pH 7.9 containing 15 mM $MgCl_2$, 2 mM DTT, 3 uM $NaVO_3$, 2mM glycerophosphate and 0.2mg/ml BSA.
- After incubation for 60 minutes at room temperature, the reaction was stopped by adding to each well 150 µl of Dowex resin in the presence of 150 mM formic acid. After another 60 min incubation, 50 µL of suspension were withdrawn and transferred into 96-well OPTIPLATEs containing 150 µl of MicroScint 40 (Packard); after 5-10

minutes shaking the plates were read for 1 min in a Packard TOP-Count radioactivity reader.

IC50 determination: inhibitors were tested at different concentrations ranging from 0.0005 to 10 μM. Experimental data were analyzed by the computer program Assay Explorer using the four parameter logistic equation:

y = bottom+(top-bottom)/(1+10^((logIC50-x)*slope))

where x is the logarithm of the inhibitor concentration, y is the response; y starts at bottom and goes to top with a sigmoid shape.

The compounds of formula (I) of the present invention showed IC_{50} values on Cdc7/Dbf4 between 1 and 1000 nM. In particular, the compounds coded A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A20, C1, C2, E1, F1, G1, H1, L1, M2, M3, M4, here below, showed IC_{50} values on Cdc7/Dbf4 between 1 and 100 nM.

In addition the selected compounds have been characterized for specificity on a panel of many other kinases, among which Cdk2A, IGF1-R, Aurora-2, AKT1, PLK1, SULU1, ERK2, CK2, GSK3β, PKAα, PKCβ, VEGFR3, PDGFR.

Inhibition assay of Cdk2/Cyclin A activity

Kinase reaction: 1.5 μM histone H1 substrate, 25 μM ATP (0.2 μCi P33γ-ATP), 30 ng of baculovirus co-expressed Cdk2/Cyclin A, 10 μM inhibitor in a final volume of 100 μl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, 7.5 mM DTT) were added to each well of a 96 U bottom well plate. After 10 min at 37 °C incubation, reaction was stopped by 20 μl EDTA 120 mM.

Capture: 100 μl were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 μl/well PBS Ca^{++}/Mg^{++} free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 μl/well scintillant were added and 33P labeled histone H1 was detected by radioactivity counting in the Top-Count instrument.

Results: data were analyzed and expressed as % inhibition referred to total activity of enzyme (=100%).

All compounds showing inhibition ≥ 50 % were further analyzed in order to study and define potency (IC50) as well as the kinetic-profile of inhibitor through Ki calculation.

IC50 determination: the protocol used was the same described above, where inhibitors were tested at different concentrations ranging from 0.0045 to 10 μM. Experimental data were analyzed by the computer program GraphPad Prizm using the four parameter logistic equation: y = bottom+(top-bottom)/(1+10^((logIC50-x)*slope))

where x is the logarithm of the inhibitor concentration, y is the response; y starts at bottom and goes to top with a sigmoid shape.

Ki calculation: either the concentration of ATP and histone H1 substrate were varied: 4, 8, 12, 24, 48 μM for ATP (containing proportionally diluted $P^{33}\gamma$-ATP) and 0.4, 0.8, 1.2, 2.4, 4.8 μM for histone were used in absence and presence of two different, properly chosen inhibitor concentrations.

Experimental data were analyzed by the computer program "SigmaPlot" for Ki determination, using a random bireactant system equation:

$$v = \frac{Vmax \frac{(A)(B)}{aKAKB}}{1 + \frac{(A)}{KA} + \frac{(B)}{KB} + \frac{(A)(B)}{aKAKB}}$$

where A=ATP and B=histone H1.

The compounds of the present invention can be administered either as single agents or, alternatively, in combination with known anticancer treatments such as radiation therapy or chemotherapy regimen in combination with cytostatic or cytotoxic agents, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents, cyclooxygenase inhibitors (e.g. COX-2 inhibitors), matrixmetalloprotease inhibitors, telomerase inhibitors, tyrosine kinase inhibitors, anti-growth factor receptor agents, anti-HER agents, anti-EGFR agents, anti-angiogenesis agents (e.g. angiogenesis inhibitors), farnesyl transferase inhibitors, ras-raf signal transduction pathway inhibitors, cell cycle inhibitors, other cdks inhibitors, tubulin binding agents, topoisomerase I inhibitors, topoisomerase II inhibitors, and the like.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent within the approved dosage range.

Compounds of formula (I) may be used sequentially with known anticancer agents when a combination formulation is inappropriate.

The compounds of formula (I) of the present invention, suitable for administration to a mammal, e.g., to humans, can be administered by the usual routes and the dosage level depends upon the age, weight, conditions of the patient and administration route.

For example, a suitable dosage adopted for oral administration of a compound of formula (I) may range from about 10 to about 1000 mg per dose, from 1 to 10 times daily. The compounds of the invention can be administered in a variety of dosage forms, e.g., orally, in the form tablets, capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally in the form suppositories; parenterally, e.g., intramuscularly, or through intravenous and/or intrathecal and/or intraspinal injection or infusion.

The present invention also includes pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient, which may be a carrier or a diluent.

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a suitable pharmaceutical form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g., lactose, dextrose saccharose, sucrose, cellulose, corn starch or potato starch; lubricants, e.g., silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g., starches, arabic gum, gelatine methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disintegrating agents, e.g., starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. These pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may be, e.g., syrups, emulsions and suspensions.

As an example, the syrups may contain, as carrier, saccharose or saccharose with glycerine and/or mannitol and sorbitol.

The suspensions and the emulsions may contain, as examples of carriers, natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g., sterile water, olive oil, ethyl oleate, glycols, e.g., propylene glycol and, if desired, a suitable amount of lidocaine hydrochloride.

The solutions for intravenous injections or infusions may contain, as a carrier, sterile water or preferably they may be in the form of sterile, aqueous, isotonic, saline solutions or they may contain propylene glycol as a carrier.

The suppositories may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g., cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

With the aim to better illustrate the present invention, without posing any limitation to it, the following examples are now given.

EXAMPLES

For a reference to any specific compound of formula (I) of the invention, optionally in the form of a pharmaceutically acceptable salt, see the experimental section and claims.

Referring to the examples that follow, compounds of the present invention were synthesized using the methods described herein, or other methods, which are well known in the art.

General methods

Flash Chromatography was performed on silica gel (Merck grade 9395, 60A). Where specified, chromatographic separations have been performed on a Biotage Horizon system. Microwave-assisted reactions were performed using Biotage/PersonalChemistry SmithCreator™.

HPLC was performed on Waters X Terra RP 18 (4,6 x 50 mm, 3.5 μm) column using a Waters 2790 HPLC system equipped with a 996 Waters PDA detector and Micromass mod. ZQ single quadrupole mass spectrometer, equipped with an electrospray (ESI) ion source. Mobile phase A was ammonium acetate 5 mM buffer (pH 5.5 with acetic acid/acetonitrile 95:5), and Mobile phase B was H_2O/acetonitrile (5:95). Gradient from 10 to 90% B in 8 minutes, hold 90% B 2 minutes. UV detection at 220 nm and 254 nm.

Flow rate 1 mL/min. Injection volume 10 µL. Full scan, mass range from 100 to 800 amu. Capillary voltage was 2.5 KV; source temp. was 120°C; cone was 10 V. Retention times (HPLC r.t.) are given in minutes at 220 nm or at 254 nm. Mass are given as m/z ratio.

When necessary, compounds have been purified by preparative HPLC:

- on a Waters Symmetry C18 (19 x 50 mm, 5 µm) column using a Waters preparative HPLC 600 equipped with a 996 Waters PDA detector and a Micromass mod. ZMD single quadrupole mass spectrometer, electron spray ionization, positive mode. Mobile phase A was water 0.01% TFA, and Mobile phase B was acetonitrile. Gradient from 10 to 90% B in 8 min, hold 90% B 2 min. Flow rate 20 mL/min.
- on a Waters X Terra Prep RP18 (19 x 100 mm, 5 µm) column using a Waters FractionLynx System (FL2) equipped with a Waters 2996 PDA UV-VIS detector and a Waters ZQ single quadrupole mass spectrometer. Mobile phase A was 0.05% NH_4OH in H_2O pH10/Acetonitrile 95/5, and Mobile phase B was acetonitrile. Gradient from 0 to 80% B in 8 min, hold 100% B 2 min. Flow rate 20 mL/min.

Low-resolution mass spectral (MS) data were determined on a Finnigan MAT LCQ ion trap instrument, equipped with an electrospray (ESI) ion source. High-resolution mass spectra (HRMS) were obtained on a Waters Q-TOF Ultima instrument, equipped with an electrospray (ESI) ion source, and using Reserpine (MW 609.28065) for Lock Mass correction. Unless differently reported, ^{1}H-NMR spectrometry was performed on a Mercury VX 400 operating at 400.45 MHz equipped with a 5 mm double resonance probe [1H (15N-31P) ID_PFG Varian]. Chemical shifts are expressed as δ (ppm).

In these examples and elsewhere, abbreviations have the following meanings:

AcOH = acetic acid

$AcONH_4$ = ammonium acetate

aq = aqueous

Boc = tert-butoxycarbonyl

^{t}BuONa = sodium tert-butoxide

CDI = N,N'- carbonyldiimidazole

CH_3CN = acetonitrile

$ClSO_2NCO$ = chlorosulfonyl isocyanate

conc = concentrated

Cs_2CO_3 = cesium carbonate

DCM = dichloromethane

DIEA = diisopropylethylamine

DMAP = dimethylaminopyridine

DMF = N,N'- dimethylformamide

DMSO-D6 = deuterated dimethylsulfoxide

EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

eq = equivalents

ESI = electrospray ionization

EtI = ethyl iodide

$EtNH_2$ = ethylamine

EtOAc = ethyl acetate

EtOH = ethanol

Et_2O = diethylether

g = grams

h = hour(s)

HBr = hydrobromic acid

HCl = hydrochloric acid

HCOOH = 88% formic acid

$HCOONH_4$ = ammonium formate

HOBT = hydroxybenzotriazole

$HOBT{\cdot}NH_3$ = hydroxybenzotriazole ammonium salt

HPLC = high performance liquid chromatography

KOH = potassium hydroxide

Lawesson's reagent = 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide

LiCl = lithium chloride

M = molar

MBHA resin = 4-methylbenzhydrylamine-resin hydrochloride

Meldrum's acid = 2,2-dimethyl-1,3-dioxane-4,6-dione

$MeNH_2$ = methylamine

MeOH = methanol

mg = milligrams

min = minutes

mL = milliliters

mmol = millimoles

mol = moles

N = normal

Na_2CO_3 = sodium carbonate

NaH = sodium hydride, 60% in mineral oil

$NaHCO_3$ = sodium hydrogen carbonate

NaH_2PO_4 = sodium dihydrogen phosphate

$NaNO_2$ = sodium nitrite

NaOH = sodium hydroxyde

Na_2SO_4 = anhydrous sodium sulphate

NBS = N-bromo-succinimide

NCS= N-chloro-succinimide

NIS= N-iodo-succinimide

NH_3 = ammonia

$Pd(OAc)_2$ = palladium acetate

$(Ph_3P)_2PdCl_2$ = dichlorobis(triphenylphosphine)palladium(II)

rt = room temperature

TBTU = O-benzotriazol-1-yl- N,N,N',N'-tetramethyluronium tetrafluoroborate

TEA = triethylamine

TFA = trifluoroacetic acid

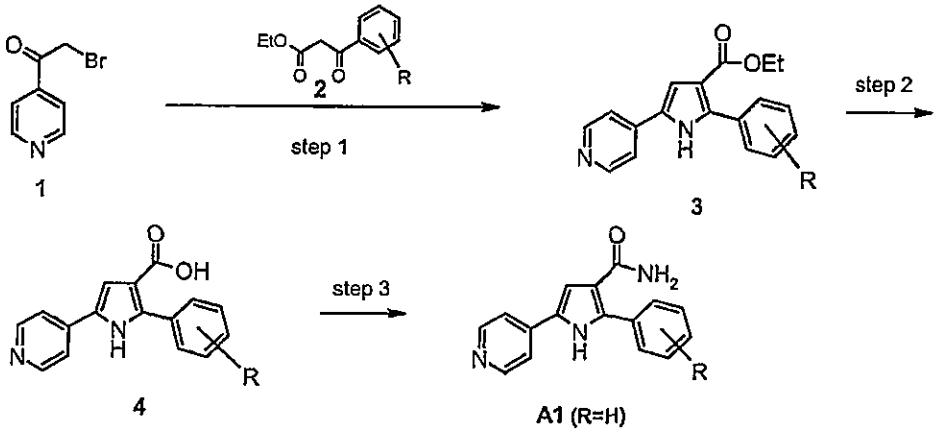
THF = tetrahydrofuran

Xantphos = 9,9-dimethyl-9H-xanthene-4,5-diyl)bis[diphenylphosphine]

µL = microliters

Example 1

2-Phenyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A1)



Step 1: Formation of pyrrole ring (3)

2-Bromo-1-pyridin-4-ylethanone hydrobromide **1** (1.7 g, 6.2 mmol) was added to a mixture of 3-oxo-3-phenyl-propionic acid ethyl ester **2** (R=H, 1 g, 5.2 mmol) in 100 mL of dry THF and NaH (0.5 g, 13.0 mmol) at 0 °C. The solution was left at 0°C for 1 h and then stirred at rt for 3 h. The solvent was removed and the residue was dissolved in 60 mL of EtOH, ammonium acetate (1.4 g, 18.7 mmol) was added and the reaction mixture was left overnight at rt. The crude material was purified by flash chromatography (DCM/MeOH 98:2) affording 920 mg (60%) of 2-phenyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid ethyl ester as a solid.

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 1.20 (t, *J*=7.08 Hz, 3H), 4.16 (q, *J*=7.08 Hz, 2H), 7.30 (d, *J*=2.81 Hz, 1H), 7.43 (m, 3H), 7.64 (m, 2H), 7.79 (m, 2H), 8.53 (m, 2H), 12.12 (s, 1H); ESI (+) MS: m/z 293 (MH^+).

Step 2: Saponification to carboxylic acids (4)

Ester **3** (440 mg, 1.5 mmol) in 3 mL of EtOH and 3 mL of 4M aq NaOH was heated at 100°C for 3 h. The reaction mixture was cooled at 0 °C and acidified with conc HCl observing precipitation of the product which was filtered, washed with a little amount of water and acetone and dried leading to 400 mg (88%) of 2-phenyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid as a solid that was used in the next step without further purification.

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 7.51 (m, 3H), 7.68 (m, 2H), 7.75 (d, *J*=2.44 Hz, 1H), 8.28 (d, *J*=6.65 Hz, 2H), 8.74 (d, *J*=6.65 Hz, 2H), 12.51 (s, 1H); MS: m/z 263 [M-H].

Step 3: Condensation to amides (A1)

Acid **4** (380 mg, 1.44 mmol) was dissolved in 10 mL of dry THF in the presence of DIEA (0.5 mL, 2.90 mmol). To the solution, cooled at 0°C, EDCI (414 mg, 2.16 mmol) and HOBT·NH_3 (330 mg, 2.16 mmol) were added. The reaction mixture was left overnight at rt. The solvent was removed, water was added and the slurry was extracted with DCM. The organic layer was dried (Na_2SO_4), the solvent was evaporated and the crude was purified by flash chromatography (DCM/MeOH 95:5) to give 150 mg (40%) of 2-phenyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide as a pale yellow solid.

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 6.90 (bs, 2H), 7.27 (d, *J*=2.56 Hz, 1H), 7.37 (m, 1H), 7.44 (m, 2H), 7.67-7.71 (m, 4H), 8.53 (m, 2H), 11.82 (s, 1H); ESI (+) MS: m/z 264 (MH^+).

The above procedure was employed to synthesize the following compounds:

Example 2, step-1

2-(2-Fluoro-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 1.11 (t, *J*=7.07 Hz, 3H) 4.09 (t, *J*=7.07 Hz, 2H) 7.28 - 7.34 (m, 5H) 7.75 (dd, *J*=1.46, 4.63 Hz, 2H) 8.52 (m, 2H) 12.31 (s, 1H); ESI (+) MS: m/z 311 (MH^+).

Example 2, step-2

2-(2-Fluoro-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 7.33 (m, 4H) 7.72 (d, *J*=2.56 Hz, 1H) 8.22 (d, *J*=6.40 Hz, 2H) 8.72 (m, 2H) 12.73 (s, 1H); MS: m/z 281 [M-H].

Example 2, step-3

2-(2-Fluoro-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide hydrochloride (A2)

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 7.00 (bs, 2H), 7.29-7.36 (m, 4H), 7.73 (d, *J*=2.43 Hz, 1H), 8.11 (d, *J*=6.59 Hz, 2H), 8.74 (d, *J*=6.59 Hz, 2H), 12.56 (s, 1H); ESI (+) MS: m/z 282 (MH^+).

Example 3, step-1

2-(3-Fluoro-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 1.20 (t, *J*=7.10 Hz, 3H) 4.15 (q, *J*=7.10 Hz, 2H) 7.27 (m, 1H) 7.30 (d, *J*=2.81 Hz, 1H), 7.49 - 7.53 (m, 3H) 7.78 (m, 2H) 8.53 (d, *J*=5.13 Hz), 12.17 (s, 1H); ESI (+) MS: m/z 311 (MH^+).

Example 3, step-2

2-(3-Fluoro-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm .25 (m, 1H) 7.31 (d, *J*=2.9 Hz, 1H) 7.40 (m, 3H) 7.80 (m, 2H) 8.50 (m, 2H); MS: m/z 281 [M-H].

Example 3, step-3

2-(3-Fluoro-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A3)

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 7.16 (bs, 2H), 7.29 (m, 2H), 7.52 (m, 2H), 7.74 (s, 1H), 8.23 (d, *J*=5.80 Hz, 2H), 8.78 (d, *J*=5.80 Hz, 2H), 12.42 (s, 1H); ESI (+) MS: m/z 282 (MH^+).

Example 4, step-1

2-(4-Fluoro-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 1.21 (t, *J*=7.08 Hz, 3H) 4.16 (q, *J*=7.08 Hz, 2H) 7.29 - 7.34 (m, 3H) 7.69 (m, 2H) 7.78 (dd, *J*=1.60, 4.63 Hz, 2H) 8.53 (dd, *J*=1.60, 4.63 Hz, 2H) 12.13 (s, 1H); ESI (+) MS: m/z 311 (MH^+).

Example 4, step-2

2-(4-Fluoro-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 7.62 - 7.76 (m, 5H) 8.30 (bd, *J*=5.61 Hz, 2H) 8.75 (d, *J*=6.71 Hz, 2H) 12.58 (bs, 1H); MS: m/z 281 [M-H].

Example 4, step-3

2-(4-Fluoro-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide hydrochloride (A4)

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 7.12 (bs, 2H), 7.32-7.39 (m, 4H), 7.70 (d, *J*=2.43 Hz, 1H), 8.15 (d, *J*=6.59 Hz, 2H), 8.72 (d, *J*=6.59 Hz, 2H), 12.52 (s, 1H); ESI (+) MS: m/z 282 (MH^+).

Example 5, step-1

2-(3-Bromo-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 1.22 (t, *J*=7.07 Hz, 3H) 4.17 (q, *J*=7.11 Hz, 2H) 7.31 (d, *J*=2.80 Hz, 1H) 7.44 (t, *J*=7.86 Hz, 1H) 7.62 - 7.69 (m, 2H) 7.80 (d, *J*=6.22 Hz, 2H) 7.86 (t, *J*=1.77 Hz, 1H) 8.55 (d, *J*=6.22 Hz, 2H) 12.20 (s, 1H); ESI (+) MS: m/z 316 (MH^+).

Example 5, step-2

2-(3-Bromo-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 7.46 (t, *J*=7.93 Hz, 1H) 7.65 - 7.74 (m, 3H) 7.90 (s, 1H) 8.26 (d, *J*=5.73 Hz, 2H) 8.75 (d, *J*=6.46 Hz, 2H) 12.29 (bs, 1H) 12.54 (bs, 1H); MS: m/z 342 [M-H]. ESI (+) MS: m/z 343 (MH^+).

Example 5, step-3

2-(3-Bromo-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide hydrochloride (A5)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 7.14 (bs, 1H) 7.44 (t, *J*=7.93 Hz, 1H) 7.51 (bs, 1H) 7.60-7.65 (m, *J*=9.02 Hz, 1H) 7.69 (d, *J*=2.56 Hz, 1H) 7.71-7.75 (m, 1H) 7.93 (t, *J*=1,83 Hz, 1H) 8.18 (d, *J*=5.85 Hz, 2H) 8.76 (d, *J*=6.83 Hz, 2H) 12.38 (bs, 1H); ESI (+) MS: m/z 342 (MH^+).

Example 6, step-1

2-(4-Bromo-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 1.22 (t, *J*=7.07 Hz, 3H) 4.16 (q, *J*=7.07 Hz, 2H) 7.30 (d, *J*=2.80 Hz, 1H) 7.61 (d, *J*=8.54 Hz, 2H) 7.68 (d, *J*=8.54 Hz, 2H) 7.79 (d, *J*=6.22 Hz, 2H) 8.55 (d, *J*=5.98 Hz, 2H) 12.17 (bs, 1H); ESI (+) MS: m/z 316 (MH^+).

Example 6, step-2

2-(4-Bromo-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 7.62 - 7.76 (m, 5H) 8.30 (bd, *J*=5.61 Hz, 2H) 8.75 (d, *J*=6.71 Hz, 2H) 12.58 (bs, 1H); MS: m/z 342 [M-H].

Example 6, step-3

2-(4-Bromo-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide hydrochloride (A6)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.93 (bs, 1H) 7.28 (d, *J*=2.68 Hz, 1H) 7.37 (bs, 1H) 7.62-7.67 (m, 4H) 7.69 (d, *J*=6.22 Hz, 2H) 8.54 (d, *J*=6.22 Hz, 2H) 11.86 (s, 1H); ESI (+) MS: m/z 342 (MH^+).

Example 7, step-1

7-(3-Ethoxycarbonyl-5-pyridin-4-yl-1H-pyrrol-2-yl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J*=7.07 Hz, 3H) 1.44 (s, 9H) 2.84 (t, *J*=5.85 Hz, 2H) 3.60 (t, *J*=5.91 Hz, 2H) 4.14 (q, *J*=7.07 Hz, 2H) 4.56 (bs, 2H) 7.24 (d, 1H) 7.27 (d, 1H) 7.41 - 7.47 (m, 2H) 7.76 (d, *J*=6.22 Hz, 2H) 8.52 (d, *J*=6.10 Hz, 2H) 12.02 (bs, 1H); ESI (+) MS: m/z 448 (MH^+).

Example 7, step-2

7-(3-Carboxy-5-pyridin-4-yl-1H-pyrrol-2-yl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

MS: m/z 418 [M-H].

Example 7, step-3

7-(3-Carbamoyl-5-pyridin-4-yl-1H-pyrrol-2-yl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (A27)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.44 (s, 9H) 2.82 (t, *J*=5.79 Hz, 2H) 3.59 (t, *J*=5.85 Hz, 2H) 4.54 (bs, 2H) 6.86 (bs, 2H) 7.20 (d, *J*=7.93 Hz, 1H) 7.24 (d, *J*=2.68 Hz, 1H) 7.44 (m, 1H) 7.47 (m, 1H) 7.67 (d, *J*=6.22 Hz, 2H) 8.51 (d, *J*=6.10 Hz, 2H) 11.72 (bs, 1H); ESI (+) MS: m/z 419 (MH^+).

By treatment with acids (for instance trifluoroacetic acid at room temperature for 24 h) the corresponding deprotected analog was obtained:

Example 8

5-Pyridin-4-yl-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-1H-pyrrole-3-carboxylic acid amide (A28)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 3.07 (t, *J*=6.10 Hz, 2H) 3.38-3.45 (m, 2H) 4.30 (t, *J*=4.33 Hz, 2H) 7.05 (bs, 1H) 7.30 (d, *J*=7.93 Hz, 1H) 7.42 (bs, 1H) 7.58 (d, *J*=8.50 Hz, 1H) 7.57 (s, 1H) 7.69 (d, *J*=2.32 Hz, 1H) 8.18 (d, *J*=6.22 Hz, 2H) 8.73 (d, *J*=6.83 Hz, 2H) 9.38 (bs, 2H) 12.41 (bs, 1H); ESI (+) MS: m/z 319 (MH^+).

Example 9

2-(2-Methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A29)

By reductive amination, performed with formaldehyde and sodium cyanoborohydride, on the tetrahydro-isoquinoline nucleus of compound **A28**, the title compound **A29** was obtained.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.94 (s, 3H) 3.09 (d, *J*=16.90 Hz, 1H) 3.69 (d, *J*=7.44 Hz, 1H) 4.31 (dd, *J*=14.90, 6.60 Hz, 1H) 4.50 (d, *J*=14.88 Hz, 1H) 7.05 (bs, 1H) 7.33 (d, *J*=8.05 Hz, 1H) 7.44 (bs, 1H) 7.54 (d, *J*=1.10 Hz, 1H) 7.61 (dd, *J*=7.93, 1.71 Hz, 1H) 7.69 (d, *J*=2.56 Hz, 1H) 8.17 (d, *J*=6.71 Hz, 2H) 8.73 (d, *J*=6.83 Hz, 2H) 10.77 (bs, 1H) 12.42 (s, 1H); ESI (+) MS: m/z 333 (MH^+).

Example 10, step-1

2,5-Di-pyridin-4-yl-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.23 (t, *J*=7.07 Hz, 3H) 4.18 (q, *J*=7.07 Hz, 2H) 7.33 (d, *J*=2.8 Hz, 1H) 7.65(dd, *J*=1.60, 4.51 Hz, 2H) 7.80 (dd, *J*=1.71, 4.63 Hz, 2H) 8.55 (dd, *J*=1.60, 4.51 Hz, 2H) 8.65 (dd, *J*=1.71, 4.61 Hz, 2H) 12.30 (bs, 1H); ESI (+) MS: m/z 294 (MH^+).

Example 10, step-2

2,5-Di-pyridin-4-yl-1H-pyrrole-3-carboxylic acid

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.02 (bs, 1H) 7.73 (m, 2H) 8.01 (m, 2H) 8.47 (m, 4H) 11.40 (bs, 1H); MS: m/z 264 [M-H].

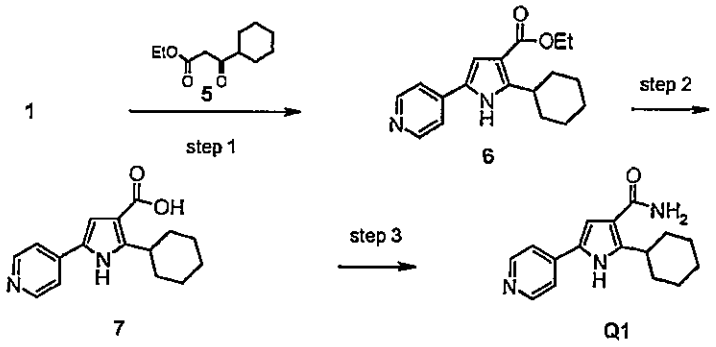
Example 10, step-3

2,5-Di-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (C3)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 7.02 (bs, 2H), 7.29 (s, 1H), 7.71 (m, 4H), 8.56 (m, 4H), 12.01 (bs, 1H); ESI (+) MS: m/z 265(MH^+).

Example 11

2-Cyclohexyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (Q1)



Step 1: Formation of pyrrole ring (6)

To a solution of 3-cyclohexyl-3-oxo-propionic acid ethyl ester **5** (1.6 g, 8.3 mmol) in anhydrous THF (200 mL), cooled at 0°C, NaH (900 mg, 21 mmol) was added. After 15 min 2-bromo-1-pyridin-4-yl-ethanone hydrobromide **1** (3 g, 10.8 mmol) was added and the mixture was stirred 5 h at 0°C. The solvent was removed and the residue was dissolved in EtOH (120 mL). Ammonium acetate (1.9 g, 25 mmol) was added and the solution was stirred overnight at rt. After solvent removal the residue was dissolved in EtOAc and the organic phase was washed with a saturated aqueous solution of Na_2CO_3, then with water, dried (Na_2SO_4) and concentrated. The crude material was purified by silica gel chromatography (eluant: EtOAc) to yield 2-cyclohexyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid ethyl ester as a white solid (1.1 g, 43%).

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.33 (m, 1H) 1.30 (t, *J*=7.13 Hz, 3H) 1.70-1.88 (m, 7H) 3.44-3.56 (m, 1H) 4.20 (q, *J*=7.15 Hz, 2H) 7.06 (d, *J*=2.68 Hz, 1H) 7.71 (d, *J*=6.22 Hz, 2H) 8.50 (d, *J*=6.22 Hz, 2H) 11.37 (bs, 1H); ESI (+) MS: m/z 299 (MH^+).

Step 2: Saponification to carboxylic acid (7)

A solution of ester **6** (0.58 g, 1.95 mmol) in 4M aq NaOH and EtOH (1:1, 20 mL) was refluxed for 3 h, cooled in ice and acidified with 2N HCl. The precipitate was filtered, washed with little water and dried. 2-Cyclohexyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid hydrochloride was obtained as a white solid (0.55 g, 90%).

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.22-1.42 (m, 3H) 1.69-1.89 (m, 7H) 3.50-3.64 (m, 1H) 7.56 (d, *J*=2.56 Hz, 1H) 8.26 (d, *J*=6.71 Hz, 2H) 8.69 (d, *J*=6.71 Hz, 2H) 11.85 (s, 1H) 12.17 (bs, 1H); MS: m/z 269 [M-H].

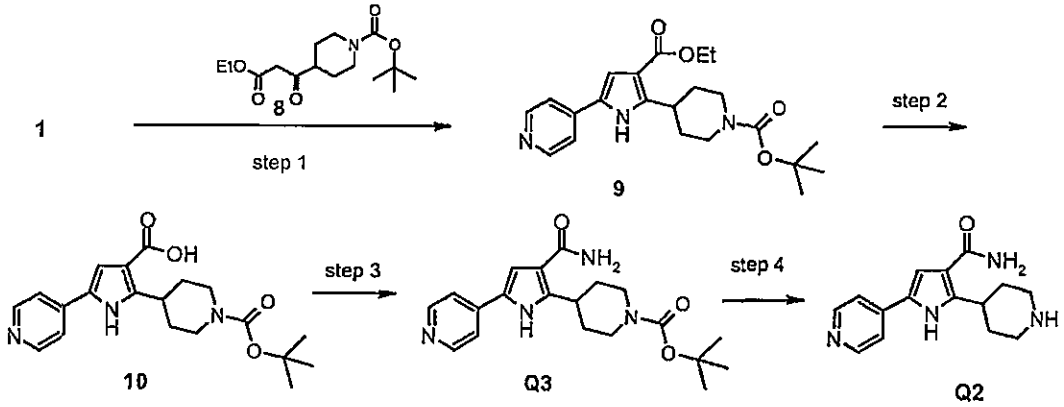
Step 3: Condensation to amide (Q1)

A solution of acid **7** (0.3 g, 1 mmol), HOBT·NH_3 (0.3 g, 2 mmol), TBTU (0.64 g, 2 mmol), DIEA (1 mL, 6 mmol) in DMF (4 mL) was stirred at rt for 6 h. The reaction mixture was poured into water and the aqueous phase was extracted (x 3) with EtOAc. The organic phase was washed with 1N NaOH, then with water, brine, dried (Na_2SO_4) and concentrated. The crude material was purified by silica gel chromatography (DCM/MeOH 12:1) to yield 2-cyclohexyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (0.12 g, 43%) as a white solid.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.62-1.84 (m, 10H) 3.59-3.71 (m, 1H) 6.67 (bs, 1H) 7.13 (d, *J*=2.68 Hz, 1H) 7.21 (bs, 1H) 7.58 (d, *J*=6.22 Hz, 2H) 8.48 (d, *J*=6.10 Hz, 2H) 11.13 (bs, 1H); ESI (+) MS: m/z 270 (MH^+).

Example 12

4-(3-Carbamoyl-5-pyridin-4-yl-1H-pyrrol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester (Q3) and 2-piperidin-4-yl-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (Q2)



Step 1: Formation of pyrrole ring (9)

To a solution of 4-(2-ethoxycarbonyl-acetyl)-piperidine-1-carboxylic acid tert-butyl ester **8** (2.5 g, 8.3 mmol) in anhydrous THF (200 mL), cooled at 0°C, NaH (900 mg, 21 mmol) was added. After 15 min 2-bromo-1-pyridin-4-yl-ethanone hydrobromide **1** (3 g, 10.8 mmol) was added and the mixture was stirred 5 h at 0°C. The solvent was removed under reduced pressure and the residue was dissolved in EtOH (120 mL). Ammonium acetate (1.9 g, 25 mmol) was added and the solution was stirred overnight at rt. After solvent removal the residue was dissolved in EtOAc and the organic phase was washed with a saturated aq solution of Na_2CO_3, then with water, dried (Na_2SO_4) and

concentrated. The crude material was purified by silica gel chromatography (eluant: EtOAc) to yield 4-(3-ethoxycarbonyl-5-pyridin-4-yl-1H-pyrrol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester as a pink solid (1.55 g, 47%).

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.30 (t, *J*=7.07 Hz, 3H) 1.45 (s, 9H) 1.71 (bd, 2H) 1.80-1.92 (m, 2H) 2.79 (bs, 2H) 3.64-3.74 (m, 1H) 4.15 (bd, *J*=11.46 Hz, 2H) 4.21 (q, *J*=7.07 Hz, 2H) 7.08 (d, *J*=2.68 Hz, 1H) 7.71 (d, *J*=6.22 Hz, 2H) 8.50 (d, *J*=6.10 Hz, 2H) 11.45 (bs, 1H); ESI (+) MS: m/z 400 (MH^+).

Step 2: Saponification to carboxylic acid (10)

A solution of ester **9** (0.8 g, 2 mmol) in 4M aq NaOH and EtOH (1:1, 20 mL) was refluxed for 2 h, cooled in ice and acidified with 2N HCl. The precipitate was filtered, washed with little water and dried. 4-(3-Carboxy-5-pyridin-4-yl-1H-pyrrol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester hydrochloride was obtained as a white solid (0.54 g, 66%).

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.43 (s, 9H) 1.67-1.92 (m, 4H) 2.79 (bs, 2H) 3.68-3.79 (m, 1H) 4.13 (bd, *J*=11.58 Hz, 2H) 7.57 (d, *J*=2.56 Hz, 1H) 8.22 (d, *J*=6.83 Hz, 2H) 8.69 (d, *J*=6.83 Hz, 2H) 11.82 (bs, 1H); MS: m/z 370 [M-H].

Step 3: Condensation to protected amide (Q3)

A solution of acid **10** (0.53 g, 1.4 mmol), HOBT·NH_3 (0.43 g, 2.8 mmol), TBTU (0.9 g, 2.8 mmol), DIEA (1.4 mL) in DMF (4 mL) was stirred at rt for 15 h. The reaction mixture was poured into water and the aqueous phase was extracted (x 3) with EtOAc. The organic phase was washed with 1N NaOH, then with water, brine, dried (Na_2SO_4) and concentrated. Upon solvent evaporation the crude material precipitated. It was filtered, washed with EtOAc, then with Et_2O. 4-(3-Carbamoyl-5-pyridin-4-yl-1H-pyrrol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester was obtained as a white solid (0.25g, 47%).

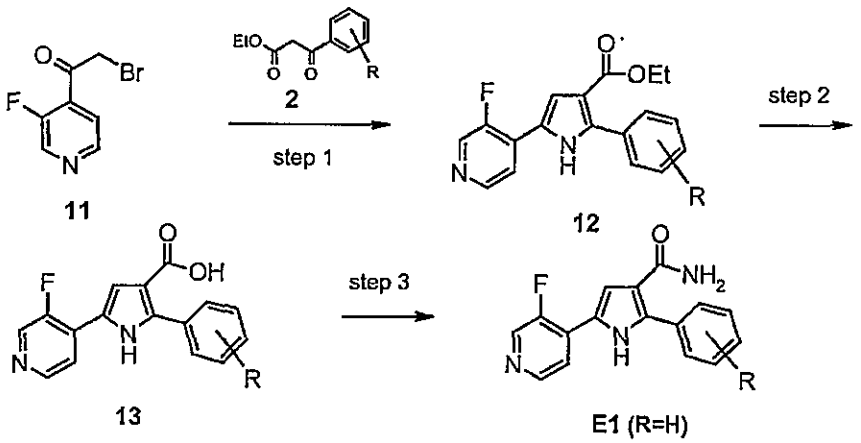
^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.45 (s, 9H) 1.67 (bd, *J*=12.32 Hz, 2H) 1.76-1.89 (m, 2H) 2.71 (bs, 2H) 3.81-3.91 (m, 1H) 4.12 (bd, *J*=11.10 Hz, 2H) 6.76 (bs, 1H) 7.18 (d, *J*=2.56 Hz, 1H) 7.29 (bs, 1H) 7.59 (d, *J*=6.22 Hz, 2H) 8.50 (d, *J*=6.10 Hz, 2H) 11.22 (bs, 1H); ESI (+) MS: m/z 371 (MH^+).

Step 4: Deprotection to amide (Q2)

Amide **Q3** (30 mg, 0.08 mmol) was dissolved in MeOH (5 mL), 2N HCl (1 mL) was added and the clear solution was warmed at 50°C under stirring for 5 h. The precipitate was filtered and washed with MeOH. 2-Piperidin-4-yl-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide dihydrochloride was obtained as a white solid (25 mg, 90%). ^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.96 (d, *J*=13.05 Hz, 2H) 2.09-2.24 (m, 2H) 2.92-3.07 (m, 2H) 3.74-3.87 (m, 1H) 7.01 (bs, 1H) 7.49 (bs, 1H) 7.66 (s, 1H) 8.10 (bs, 2H) 8.56 (bs, 1H) 8.71 (d, *J*=6.34 Hz, 2H) 8.83 (bs, 1H) 11.97 (bs, 1H); ESI (+) MS: m/z 271 (MH^+).

Example 13

5-(3-Fluoro-pyridin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid amide (E1)



Step 1: Formation of pyrrole ring (12)

Bromoacetylfluoropyridine hydrobromide **11** (3.6 g, 12.0 mmol) was added to a mixture of 3-oxo-3-phenyl-propionic acid ethyl ester **2** (R=H, 2.0 g, 10.0 mmol) in 200 mL of anhydrous THF and NaH (0.5 g, 13.0 mmol) at 0 °C. The solution was left at 0°C for 1 h and then stirred to rt for 3 h. The solvent was removed and the residue was dissolved in 120 mL of EtOH, ammonium acetate (2.7 g, 36.0 mmol) was added, the reaction mixture was left overnight at rt and then warmed at 50°C for 2 h. The crude material was purified by flash chromatography (DCM/MeOH 98:2) affording 1.88 g (60%) of 5-(3-fluoro-pyridin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid ethyl ester as a yellow solid.

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 1.25 (t, *J*=7.09 Hz, 3H), 4.23 (q, *J*=7.09 Hz, 2H), 7.30-7.60 (m, 7H), 8.40 (m, 1H), 8.53 (m, 1H), 11.80 (s, 1H); ESI (+) MS: m/z 311 (MH^+).

Step 2: Saponification to carboxylic acids (13)

Ester **12** (1.8 g, 5.8 mmol) in 10 mL of EtOH and 12 mL of 4M aq NaOH was heated at 100 °C for 4 h. The reaction mixture was cooled at 0°C and acidified with conc HCl observing precipitation of the product which was filtered, washed with a little amount of water and acetone and dried, leading to 5-(3-fluoro-pyridin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid (1.7 g, 92%) as a solid that was used without further purification.

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 7.30-7.70 (m, 7H), 8.35 (m, 1H), 8.51 (m, 1H); MS: m/z 281 [*M*-H].

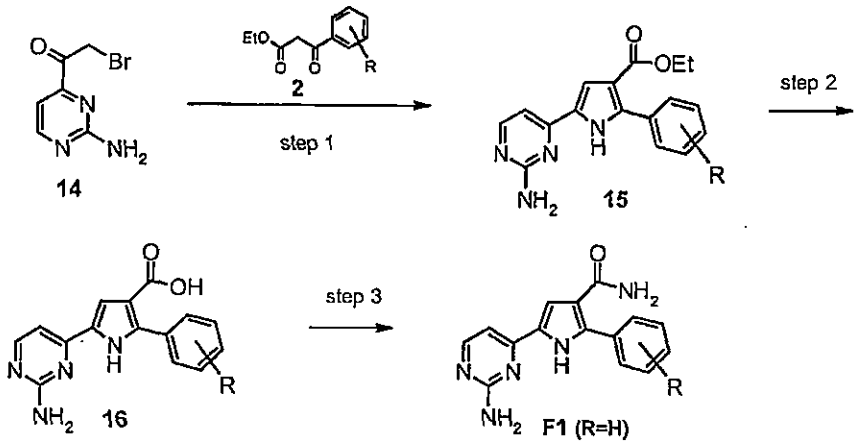
Step 3: Condensation to amides (E1)

Acid **13** (1.0 g, 3.1 mmol) was dissolved in 40 mL of dry THF in the presence of DIEA (1.1 mL, 6.2 mmol). The solution was cooled at 0°C and EDCI (0.9 g, 4.6 mmol) and HOBT·NH_3 (0.7 g, 4.6 mmol) were added. The reaction mixture was left overnight at rt. The solvent was removed, water was added and the mixture was extracted with DCM. The organic layer was dried (Na_2SO_4), the solvent was evaporated and the crude material was purified by flash chromatography (DCM/MeOH 95:5) to give 350 mg (40%) of 5-(3-fluoro-pyridin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid amide as a white solid.

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 6.86 (bs, 2H), 7.24 (t, *J*=3.05 Hz, 1H), 7.36-7.45 (m, 3H), 7.65 (m, 2H), 7.94 (m, 1H), 8.39 (d, *J*=5.12 Hz, 1H), 8.56 (d, *J*=3.41 Hz, 1H), 11.84 (s, 1H); ESI (+) MS: m/z 282 (MH^+).

Example 14

5-(2-Amino-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid amide (F1)



Step 1: Formation of pyrrole ring (15)

To a solution of ester **2** (R=H, 1.34 g, 7 mmol) in anhydrous THF (100 mL) at 0°C, NaH (0.7 g, 17.5 mmol) was added under argon with stirring. After 5 min bromoketone **14** (2.5 g, 8.4 mmol) was added and the mixture was stirred at rt for 3 h. Solvent was evaporated, the residue was dissolved in EtOH (65 mL), ammonium acetate (1.6 g, 21 mmol) was added and the solution was stirred at rt overnight. Solvent was evaporated to dryness and the residue was purified by flash chromatography (EtOAc/n-hexane 7:3). Obtained 5-(2-amino-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid ethyl ester (0.99 g, 3.2 mmol, 46%).

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.20 (t, *J*=7.13 Hz, 3H) 4.14 (q, *J*=7.07 Hz, 2H) 6.45 (s, 2H) 7.10 (d, *J*=5.24 Hz, 1H) 7.33 (d, *J*=2.56 Hz, 1H) 7.40-7.49 (m, 3H) 7.61-7.65 (m, 2H) 8.23 (d, *J*=5.24 Hz, 1H) 12.01 (bs, 1H); ESI (+) MS: m/z 309 (MH^+).

Step 2: Saponification to carboxylic acids (16)

To a suspension of ester **15** (3.65 g, 11.85 mmol) in 95% EtOH (45 mL), 4M aq NaOH (45 mL) was added and the mixture was refluxed for 5 h. Most solvent was evaporated and the residue, cooled in ice bath, was acidified to pH 5 with conc HCl, observing precipitation of the product. The precipitate was filtered, washed with little cold water, and dried. 5-(2-Amino-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid, obtained as a white solid (3.5 g), was used in the next step without further purifications.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 7.35-7.69 (m, 6H) 7.76 (bs, 2H) 8.31 (d, *J*=5.73 Hz, 1H) 12.37 (bs, 1H); MS: m/z 279 [M-H].

Step 3: Condensation to amides (F1)

To a suspension of acid **16** (4 g, 14.3 mmol) in anhydrous THF (80 mL), DIEA (5.5 g, 42.9 mmol) and anhydrous DMF (8 mL), cooled in ice bath and under stirring, HOBT·NH_3 (3.26 g, 21.4 mmol) and EDCI (4.1 g, 21.4 mmol) were added. The reaction mixture was stirred at rt overnight then it was poured into a stirred 1:1 mixture of water and EtOAc. The organic phase was washed with water, the aqueous layer was extracted with EtOAc and the combined organic layers were washed with water, dried (Na_2SO_4) and concentrated, affording the title compound as a precipitate that was filtered and washed with little cold MeOH. The mother liquor was purified by flash chromatography (DCM/MeOH/acetone 9:1:1), affording the desired amide. The two product batches were combined, suspended in MeOH and acidified to pH 1 with 1.25M HCl in MeOH. Solvent was removed and the residue was treated with diethyl ether. The resulting solid was filtered, washed with Et_2O and dried (Na_2SO_4), affording 5-(2-amino-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid amide hydrochloride as a white solid (1.6 g, 5.1 mmol, 43%).

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 7.37-7.49 (m, 4H) 7.49-7.52 (m, 2H) 7.61 (d, *J*=2.44 Hz, 1H) 7.65-7.71 (m, 2H) 8.01 (bs, 3H) 8.31 (d, *J*=6.58 Hz, 1H) 12.28 (s, 1H); ESI (+) MS: m/z 280 (MH^+).

The above procedure was employed to synthesize the following compounds:

Example 15, step-1

5-(2-Amino-pyrimidin-4-yl)-2-o-tolyl-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 (t, *J*= 7.07 Hz, 3H) 2.14 (s, 3H) 4.02 (q, *J*=7.07 Hz, 2H) 6.54 (bs, 2H) 7.04 (d, *J*=5.37 Hz, 1H) 7.22 - 7.37 (m, 5H) 8.20 (d, *J*= 5.37, 1H) 12.12 (bs, 1H); ESI (+) MS: m/z 323 (MH^+).

Example 15, step-2

5-(2-Amino-pyrimidin-4-yl)-2-o-tolyl-1H-pyrrole-3-carboxylic acid

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.34 (bs, 2H) 6.98 (d, *J*=5.24 Hz, 1H) 7.18 - 7.33 (m, 5H) 8.15 (d, *J*=5.24 Hz, 1H) 11.75 (bs, 1H); MS: m/z 293 [M-H].

Example 15, step-3

5-(2-Amino-pyrimidin-4-yl)-2-o-tolyl-1H-pyrrole-3-carboxylic acid amide (F2)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.16 (s, 3H), 6.87 (bs, 2H), 7.21-7.34 (m, 5H), 7.62 (s, 1H), 7.74 (bs, 2H), 8.25 (d, *J*=6.47 Hz, 1H), 12.20 (bs, 1H); ESI (+) MS: m/z 294 (MH^+).

Example 16, step-1

5-(2-Amino-pyrimidin-4-yl)-2-(2-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.11 (t, *J*=7.07 Hz, 3H) 4.06 (q, *J*= 7.07 Hz, 2H) 6.43 (bs, 2H) 7.03 (d, *J*=5.24 Hz, 1H) 7.28 (m, 3H) 7.50 (m, 2H) 8.21 (d, *J*=5.24 Hz, 1H) 12.23 (bs, 1H); ESI (+) MS: m/z 327 (MH^+).

Example 16, step-2

5-(2-Amino-pyrimidin-4-yl)-2-(2-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.36 (bs, 2H) 6.97 (d, *J*=5.24 Hz, 1H) 7.23 (m, 3H) 7.39 (m, 1H) 7.58 (m, 1H) 8.17 (d, *J*=5.24 Hz, 1H) 11.69 (bs, 1H); MS: m/z 297 [M-H].

Example 16, step-3

5-(2-Amino-pyrimidin-4-yl)-2-(2-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (F4)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.92 (bs, 2H), 7.27 (m, 3H), 7.45-7.54 (m, 2H), 7.62 (bs, 1H), 7.84 (bs, 2H), 8.28 (d, *J*=6.58 Hz, 1H), 12.41 (bs, 1H); ESI (+) MS: m/z 298 (MH^+).

Example 17, step-1

5-(2-Amino-pyrimidin-4-yl)-2-(2,3-dimethyl-phenyl)-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.06 (t, *J*=7.07 Hz, 3H) 2.02 (s, 3H) 2.29 (s, 3H) 4.01 (q, *J*=7.07 Hz, 2H) 6.40 (bs, 2H) 7.01 (d, *J*=5.24 Hz, 1H) 7.07 - 7.16 (m, 2H) 7.23 (d, *J*=6.83 Hz, 1H) 7.29 (d, *J*=2.68 Hz, 1H) 8.18 (d, *J*=5.24 Hz, 1H) 12.03 (bs, 1H); ESI (+) MS: m/z 337 (MH^+).

Example 17, step-2

5-(2-Amino-pyrimidin-4-yl)-2-(2,3-dimethyl-phenyl)-1H-pyrrole-3-carboxylic acid

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.04 (s, 3H) 2.30 (s, 3H) 6.37 (bs, 2H) 7.00 (d, *J*=5.24 Hz, 1H) 7.08 - 7.17 (m, 2H) 7.23 (d, *J*=6.71 Hz, 1H) 7.27 (d, *J*=2.68 Hz, 1H) 8.18 (d, *J*=5.24 Hz, 1H) 11.64 (bs, 1H) 11.89 (bs, 1H); MS: m/z 307 [M-H].

Example 17, step-3

5-(2-Amino-pyrimidin-4-yl)-2-(2,3-dimethyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (F15)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.03 (s, 3H), 2.29 (s, 3H), 6.31 (bs, 2H), 6.69 (bs, 2H), 6.94 (d, *J*=5.24 Hz, 1H), 7.08-7.17 (m, 2H), 7.23 (d, *J*=6.95 Hz, 1H), 7.31 (d, *J*=2.68 Hz, 1H), 8.16 (d, *J*=5.24 Hz, 1H), 10.70 (bs, 1H); ESI (+) MS: m/z 308 (MH^+).

Example 18, step-1

5-(2-Amino-pyrimidin-4-yl)-2-(2-chloro-4-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 (t, *J*=7.07 Hz, 3H) 4.03 (q, *J*=7.07 Hz, 2H) 6.41 (bs, 2H) 7.00 (d, *J*=5.24 Hz, 1H) 7.25 - 7.34 (m, 2H) 7.48 - 7.59 (m, 2H), 8.21 (d, *J*=5.24 Hz, 1H) 12.27 (bs, 1H); ESI (+) MS: m/z 361 (MH^+).

Example 18, step-2

5-(2-Amino-pyrimidin-4-yl)-2-(2-chloro-4-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.38 (bs, 2H) 6.99 (d, *J*=5.24 Hz, 1H) 7.22 - 7.30 (m, 2H) 7.50 - 7.57 (m, 2H) 8.20 (d, *J*=5.24 Hz, 1H) 11.49 (bs, 1H) 12.10 (bs, 1H); MS: m/z 331 [M-H].

Example 18, step-3

5-(2-Amino-pyrimidin-4-yl)-2-(2-chloro-4-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (F23)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.38 (bs, 2H), 6.72 (bs, 1H), 6.92 (d, *J*=5.24 Hz, 1H), 7.22-7.33 (m, 2H), 7.35 (d, *J*=2.56 Hz, 1H), 7.45-7.54 (m, 2H), 8.22 (d, *J*=5.24 Hz, 1H), 11.95 (bs, 1H); ESI (+) MS: m/z 332 (MH^+).

Example 19, step-1

5-(2-Amino-pyrimidin-4-yl)-2-(2,4-dichloro-phenyl)-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 1.08 (t, *J*=7.07 Hz, 3H) 4.04 (q, *J*=7.07 Hz, 2H) 6.42 (bs, 2H) 7.01 (d, *J*=5.24 Hz, 1H) 7.29 (d, *J*=2.19 Hz, 1H) 7.49 (m, 2H) 7.73 (t, *J*=1.22 Hz, 1H) 8.22 (d, *J*=5.24 Hz, 1H) 12.30 (bs, 1H); ESI (+) MS: m/z 377 (MH^+).

Example 19, step-2

5-(2-Amino-pyrimidin-4-yl)-2-(2,4-dichloro-phenyl)-1H-pyrrole-3-carboxylic acid

MS: m/z 347 [M-H].

Example 19, step-3

5-(2-Amino-pyrimidin-4-yl)-2-(2,4-dichloro-phenyl)-1H-pyrrole-3-carboxylic acid amide (F26)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.81 (bs, 1H) 6.95 (bs, 2H) 7.01 (d, *J*=5.73 Hz, 1H) 7.37 (bs, 1H) 7.46 (d, *J*=2.68 Hz, 1H) 7.68 (dd, *J*=1.77, 0.55 Hz, 1H) 8.23 (d, *J*=5.73 Hz, 1H) 12.17 (bs, 1H); ESI (+) MS: m/z 348 (MH^+).

Example 20, step-1

5-(2-Amino-pyrimidin-4-yl)-2-(2-fluoro-4-methyl-phenyl)-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 1.13 (t, *J*=7.07 Hz, 3H) 2.38 (s, 3H) 4.07 (q, *J*=7.07 Hz, 2H) 6.43 (bs, 2H) 7.03 (d, *J*=5.24 Hz, 1H) 7.06 - 7.15 (m, 2H) 7.29 (d, *J*=2.44 Hz, 1H) 7.38 (t, *J*=8.17 Hz, 1H) 8.22 (d, *J*=5.24 Hz, 1H) 12.15 (bs, 1H); ESI (+) MS: m/z 341 (MH^+).

Example 20, step-2

5-(2-Amino-pyrimidin-4-yl)-2-(2-fluoro-4-methyl-phenyl)-1H-pyrrole-3-carboxylic acid

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 2.58 (s, 3H) 6.39 (bs, 2H) 7.00 (d, *J*=5.24 Hz, 1H) 7.04 - 7.13 (m, 2H) 7.26 (d, *J*=2.44 Hz, 1H) 7.37 (t, *J*=8.17 Hz, 1H) 8.21 (d, *J*=5.24 Hz, 1H) 11.78 (bs, 1H) 12.03 (bs, 1H); MS: m/z 311 [M-H].

Example 20, step-3

5-(2-Amino-pyrimidin-4-yl)-2-(2-fluoro-4-methyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (F28)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.37 (s, 3H), 6.37 (bs, 2H), 6.73 (bs, 1H), 6.95 (d, *J*=5.24 Hz, 1H), 7.02-7.09 (m, 2H), 7.26 (bs, 1H), 7.30 (d, *J*=2.56 Hz, 1H), 7.37 (t, *J*=7.90 Hz, 1H), 8.20 (d, *J*=5.24 Hz, 1H), 11.78 (bs, 1H); ESI (+) MS: m/z 312 (MH^+).

Example 21, step-1

5-(2-Amino-pyrimidin-4-yl)-2-(2-chloro-5-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 1.07 (t, *J*=7.07 Hz, 3H) 4.05 (q, *J*=7.07 Hz, 2H) 6.42 (bs, 2H) 7.01 (d, *J*=5.24 Hz, 1H) 7.30 (d, *J*=2.44 Hz, 1H) 7.32 - 7.39 (m, 1H) 7.41 (dd, *J*=8.90, 3.05 Hz, 1H) 8.60 (dd, *J*=8.90, 5.24 Hz, 1H) 8.23 (d, *J*=5.24 Hz, 1H) 12.32 (bs, 1H); ESI (+) MS: m/z 361 (MH^+).

Example 21, step-2

5-(2-Amino-pyrimidin-4-yl)-2-(2-chloro-5-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 6.40 (bs, 2H) 7.00 (d, *J*=5.24 Hz, 1H) 7.26 (d, *J*=2.32 Hz, 1H) 7.30 - 7.37 (m, 1H) 7.40 (dd, *J*=8.90, 3.05 Hz, 1H) 8.59 (dd, *J*=8.90, 5.24 Hz, 1H) 8.22 (d, *J*=5.24 Hz, 1H) 11.85 (bs, 1H) 12.20 (bs, 1H); MS: m/z 331 [M-H].

Example 21, step-3

5-(2-Amino-pyrimidin-4-yl)-2-(2-chloro-5-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (F31)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.35 (bs, 2H), 6.75 (bs, 1H), 6.92 (d, *J*=5.24 Hz, 1H), 7.26-7.34 (m, 3H), 7.35 (d, *J*=2.56 Hz, 1H), 7.55 (dd, *J*=8.72, 5.30 Hz, 1H), 8.22 (d, *J*=5.24 Hz, 1H), 11.98 (bs, 1H); ESI (+) MS: m/z 332 (MH^+).

Example 22, step-1

5-(2-Amino-pyrimidin-4-yl)-2-(4-chloro-2-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 4.10 (q, *J*=7.07 Hz, 2H) 6.48 (bs, 2H) 7.04 (d, *J*=5.24 Hz, 1H) 7.32 (bs, 1H) 7.38 (m, 1H) 7.54 (m, 2H) 8.24 (d, *J*=5.24 Hz, 1H) 12.32 (bs, 1H); ESI (+) MS: m/z 361 (MH^+).

Example 22, step-2

5-(2-Amino-pyrimidin-4-yl)-2-(4-chloro-2-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 6.32 (bs, 2H) 6.93 (d, *J*=5.24 Hz, 1H) 7.14 (s, 1H) 7.25 (m, 2H) 7.65 (t, *J*=8.17 Hz, 1H) 8.15 (d, *J*=5.25 Hz, 1H) 12.20 (bs, 1H); MS: m/z 331 [M-H].

Example 22, step-3

5-(2-Amino-pyrimidin-4-yl)-2-(4-chloro-2-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (F36)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.37 (bs, 2H), 6.80 (bs, 1H), 6.93 (d, *J*=5.24 Hz, 1H), 7.31-7.37 (m, 2H), 7.41 (bs, 1H), 7.46 (dd, *J*=9.76, 1.95 Hz, 1H), 7.49-7.56 (m, 1H), 8.23 (d, *J*=5.24, 1H), 11.95 (bs, 1H); ESI (+) MS: m/z 332 (MH^+).

Example 23, step-1

5-(2-Amino-pyrimidin-4-yl)-2-(2,6-difluoro-phenyl)-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 1.09 (t, *J*=7.07 Hz, 3H) 4.06 (q, *J*=7.07 Hz, 2H) 6.46 (bs, 2H) 7.01 (d, *J*=5.24 Hz, 1H) 7.14 - 7.26 (m, 2H) 7.34 (d, *J*=2.32 Hz, 1H) 7.49 - 7.60 (m, 1H) 8.24 (d, *J*=5.24 Hz, 1H) 12.44 (bs, 1H); ESI (+) MS: m/z 345 (MH^+).

Example 23, step-2

5-(2-Amino-pyrimidin-4-yl)-2-(2,6-difluoro-phenyl)-1H-pyrrole-3-carboxylic acid

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 6.42 (bs, 2H) 6.99 (d, *J*=5.24 Hz, 1H) 7.12 - 7.23 (m, 2H) 7.30 (d, *J*=1.95 Hz, 1H) 7.48 - 7.56 (m, 1H) 8.22 (d, *J*=5.24 Hz, 1H) 11.92 (bs, 1H) 12.32 (bs, 1H); MS: m/z 315 [M-H].

Example 23, step-3

5-(2-Amino-pyrimidin-4-yl)-2-(2,6-difluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (F37)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.40 (bs, 2H), 6.75 (bs, 1H), 6.89 (d, *J*=5.24 Hz, 1H), 7.09-7.16 (m, 2H), 7.38 (d, *J*=2.44 Hz, 1H), 7.41 (bs, 1H), 7.43-7.52 (m, 1H), 8.22 (d, *J*=5.24 Hz, 1H), 12.10 (bs, 1H); ESI (+) MS: m/z 316 (MH^+).

Example 24, step-1

5-(2-Amino-pyrimidin-4-yl)-2-thiophen-2-yl-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 1.26 (t, *J*=7.07 Hz, 3H) 4.19 (q, *J*=7.07 Hz, 2H) 6.47 (bs, 2H) 7.11 (d, *J*=5.12 Hz, 1H) 7.15 (dd, *J*=5.06, 3.72 Hz, 1H) 7.30 (d, *J*=2.07 Hz, 1H) 7.64 (dd, *J*=3.66, 1.22 Hz, 1H) 7.67 (dd, *J*=5.06, 1.16 Hz, 1H) 8.23 (d, *J*=5.24 Hz, 1H) 11.92 (bs, 1H); ESI (+) MS: m/z 315 (MH^+).

Example 24, step-2

5-(2-Amino-pyrimidin-4-yl)-2-thiophen-2-yl-1H-pyrrole-3-carboxylic acid

MS: m/z 285 [M-H].

Example 24, step-3

5-(2-Amino-pyrimidin-4-yl)-2-thiophen-2-yl-1H-pyrrole-3-carboxylic acid amide (G2)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.46 (bs, 2H) 6.91 (bs, 1H) 7.04 (d, *J*=5.37 Hz, 1H) 7.11 (dd, *J*=5.12, 3.66 Hz, 1H) 7.30 (d, *J*=1.95 Hz, 1H) 7.44 (bs, 1H) 7.57 (dd, *J*=5.12, 1.22 Hz, 1H) 7.66 (dd, *J*=3.66, 1.22 Hz, 1H) 8.23 (d, *J*=5.24 Hz, 1H) 11.60 (bs, 1H); ESI (+) MS: m/z 286 (MH^+).

Example 25, step-1

5-(2-Amino-pyrimidin-4-yl)-2-(5-methyl-thiophen-2-yl)-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 1.26 (t, *J*=7.07 Hz, 3H) 2.50 (s, 3H) 4.19 (q, *J*=7.07 Hz, 2H) 6.46 (bs, 2H) 6.84 (dd, *J*=3.54, 0.98 Hz, 1H) 7.10 (d, *J*=5.24 Hz, 1H) 7.27 (d, *J*=2.07 Hz, 1H) 7.45 (d, *J*=3.54 Hz, 1H) 8.22 (d, *J*=5.12 Hz, 1H) 11.92 (bs, 1H); ESI (+) MS: m/z 329 (MH^+).

Example 25, step-2

5-(2-Amino-pyrimidin-4-yl)-2-(5-methyl-thiophen-2-yl)-1H-pyrrole-3-carboxylic acid

MS: m/z 299 [M-H].

Example 25, step-3

5-(2-Amino-pyrimidin-4-yl)-2-(5-methyl-thiophen-2-yl)-1H-pyrrole-3-carboxylic acid amide (G3)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.46 (d, *J*=0.73 Hz, 3H) 6.40 (bs, 2H) 6.79 (dd, *J*=3.54, 1.10 Hz, 1H) 6.85 (bs, 1H) 7.01 (d, *J*=5.24 Hz, 1H) 7.25 (d, *J*=2.07 Hz, 1H) 7.38 (bs, 1H) 7.44 (d, *J*=3.29 Hz, 1H) 8.21 (d, *J*=5.24 Hz, 1H) 11.45 (bs, 1H); ESI (+) MS: m/z 300 (MH^+).

Example 26, step-1

5-[5-(2-Amino-pyrimidin-4-yl)-3-ethoxycarbonyl-1H-pyrrol-2-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 1.08 (t, *J*=7.01 Hz, 3H) 1.44 (s, 9H) 2.51 - 2.59 (m, 2H) 3.42 - 3.53 (m, 2H) 4.03 (q, *J*=7.03 Hz, 2H) 4.58 (bs, 2H) 6.45 (bs, 2H) 7.03 (d, *J*=5.24 Hz, 1H) 7.16 - 7.35 (m, 4H) 8.21 (d, *J*=5.00 Hz, 1H) 12.11 (bs, 1H); ESI (+) MS: m/z 464 (MH^+).

Example 26, step-2

5-[5-(2-Amino-pyrimidin-4-yl)-3-carboxy-1H-pyrrol-2-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

MS: m/z 434 [M-H].

Example 26, step-3

5-[5-(2-Amino-pyrimidin-4-yl)-3-carbamoyl-1H-pyrrol-2-yl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (G7)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.44 (s, 9H) 2.58 (t, *J*=5.79 Hz, 2H) 3.48 (t, *J*=6.10 Hz, 2H) 4.58 (bs, 2H) 6.89 (bs, 1H) 7.11-7.39 (m, 5H) 7.64 (d, *J*=2.19 Hz, 1H) 7.75 (bs, 2H) 8.27 (d, *J*=6.34 Hz, 1H) 12.28 (bs, 1H); ESI (+) MS: m/z 435 (MH^+).

Example 27

5-(2-Amino-pyrimidin-4-yl)-2-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-1H-pyrrole-3-carboxylic acid amide (G8)

By treatment of compound G7 prepared in Example 26 with acids, for instance trifluoroacetic acid at room temperature for 24 h, the corresponding deprotected analog G8 was obtained.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.78 (t, *J*=5.91 Hz, 2H) 4.35 (t, *J*=4.51 Hz, 2H) 6.90 (bs, 1H) 7.25 (d, *J*=6.58 Hz, 1H) 7.27-7.30 (m, 1H) 7.31-7.39 (m, 3H) 7.70 (d, *J*=2.44 Hz, 1H) 7.86 (bs, 3H) 8.30 (d, *J*=6.46 Hz, 1H) 9.32 (bs, 2H) 12.44 (bs, 1H); ESI (+) MS: m/z 335 (MH^+).

Example 28, step-1

5-(2-Amino-pyrimidin-4-yl)-2-pyridin-2-yl-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 1.29 (t, 3H, *J*=7.1 Hz) 4.25(q, 2H, *J*=7.07 Hz) 6.64 (bs, 2H) 7.16 (d, 1H, *J*=5.12 Hz) 7.4 (m, 2H) 7.9 (td, 1H, *J*=7.8, 1.83 Hz) 8.2 (d,

1H, *J*=5.12 Hz) 8.4 (dt, 1H, *J*=8.05, 0.98 Hz) 8.7 (ddd, 1H, *J*=4.82, 1.77, 0.98 Hz) 11.5 (bs, 1H); ESI (+) MS: m/z 310 (MH^+).

Example 28, step-2

5-(2-Amino-pyrimidin-4-yl)-2-pyridin-2-yl-1H-pyrrole-3-carboxylic acid

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 6.46 (bs, 2H) 7.08 (d, 1H, *J*=5.12 Hz) 7.31 (m, 2H) 7.91 (t, 1H, *J*=7.87 Hz) 8.17 (d, 1H, *J*=5.12 Hz) 8.55 (d, 1H, *J*=3.90 Hz) 8.80 (bs, 1H); MS: m/z 280 [M-H].

Example 28, step-3

5-(2-Amino-pyrimidin-4-yl)-2-pyridin-2-yl-1H-pyrrole-3-carboxylic acid amide (G12)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.62 (bs, 2H), 7.03 (d, *J*=5.12 Hz, 1H), 7.16 (bs, 1H), 7.33-7.40 (m, 2H) 7.86-7.93 (m, 1H), 8.25 (d, *J*=5.12 Hz, 1H), 8.28 (bs, 1H), 8.43 (d, *J*=8.17 Hz, 1H), 8.62-8.67 (m, 1H), 11.29 (s, 1H); ESI (+) MS: m/z 281 (MH^+).

Example 29, step-1

5-(2-Amino-pyrimidin-4-yl)-2-(1-methyl-1H-indol-3-yl)-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 1.12 (t, *J*=7.07 Hz, 3H) 3.87 (s, 3H) 4.08 (q, *J*=7.07 Hz, 2H) 6.41 (bs, 2H) 7.05 (d, *J*=5.24 Hz, 1H) 7.08 - 7.14 (m, 1H) 7.19 - 7.25 (m, 1H) 7.33 (d, *J*=2.68 Hz, 1H) 7.47 - 7.53 (m, 2H) 7.77 (s, 1H) 8.18 (d, *J*=5.24 Hz, 1H) 11.65 (bs, 1H); ESI (+) MS: m/z 362 (MH^+).

Example 29, step-2

5-(2-Amino-pyrimidin-4-yl)-2-(1-methyl-1H-indol-3-yl)-1H-pyrrole-3-carboxylic acid

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 3.87 (s, 3H) 6.40 (bs, 2H) 7.03 (d, *J*=5.24 Hz, 1H) 7.11 (t, *J*=7.80 Hz, 1H) 7.22 (t, *J*=7.80 Hz, 1H) 7.32 (d, *J*=2.56 Hz, 1H) 7.49 - 7.54 (m, 2H) 7.77 (s, 1H) 8.18 (d, *J*=5.24 Hz, 1H) 11.50 (bs, 1H); MS: m/z 332 [M-H].

Example 29, step-3

5-(2-Amino-pyrimidin-4-yl)-2-(1-methyl-1H-indol-3-yl)-1H-pyrrole-3-carboxylic acid amide (G13)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 3.87 (s, 3H), 6.35 (bs, 2H), 6.73 (bs, 1H), 6.91 (bs, 1H), 6.98 (d, *J*=5.24 Hz, 1H), 7.11 (t, *J*=7.07 Hz, 1H), 7.22 (t, *J*=7.07 Hz, 1H), 7.32

(d, *J*=2.68 Hz, 1H), 7.48-7.53 (m, 2H), 7.80 (s, 1H), 8.17 (d, *J*=5.24 Hz, 1H), 11.36 (bs, 1H); ESI (+) MS: m/z 333 (MH^+).

Example 30, step-1

5-(2-Amino-pyrimidin-4-yl)-2-(1-methyl-1H-indol-2-yl)-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 1.10 (t, *J*=7.07 Hz, 3H), 3.59 (s, 3H), 4.09 (q, *J*=7.07 Hz, 2H), 6.47 (bs, 2H), 6.66 (d, *J*=0.73 Hz, 1H), 7.10 (d, *J*=5.24 Hz, 1H), 7.10 - 7.12 (m, 1H), 7.19 - 7.27 (m, 1H), 7.38 (d, *J*=2.68 Hz, 1H), 7.51 (d, 7.32 Hz, 1H), 7.62 (d, *J*=7.80 Hz, 1H) 8.24 (d, *J*=5.24 Hz, 1H) 12.33 (bs, 1H); ESI (+) MS: m/z 362 (MH^+).

Example 30, step-2

5-(2-Amino-pyrimidin-4-yl)-2-(1-methyl-1H-indol-2-yl)-1H-pyrrole-3-carboxylic acid

MS: m/z 332 [M-H].

Example 30, step-3

5-(2-Amino-pyrimidin-4-yl)-2-(1-methyl-1H-indol-2-yl)-1H-pyrrole-3-carboxylic acid amide (G14)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 3.58 (s, 3H), 6.38 (bs, 2H), 6.61 (d, *J*=0.61 Hz, 1H), 6.88 (bs, 1H), 7.00 (d, *J*=5.24 Hz, 1H), 7.08 (t, *J*=7.70 Hz, 1H), 7.20 (t, *J*=7.70 Hz, 1H), 7.25 (bs, 1H), 7.41 (d, *J*=2.44 Hz, 1H), 7.47 (d, *J*=7.70 Hz, 1H), 7.59 (d, *J*=7.70 Hz, 1H), 8.22 (d, *J*=5.24 Hz, 1H), 11.98 (bs, 1H); ESI (+) MS: m/z 333 (MH^+).

Example 31, step-1

5-(2-Amino-pyrimidin-4-yl)-2-benzo[b]thiophen-5-yl-1H-pyrrole-3-carboxylic acid ethyl ester

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 1.18 (t, *J*=7.07 Hz, 3H) 4.13 (q, *J*=7.07 Hz, 2H) 6.45 (s, 2H) 7.10 (d, *J*=5.24 Hz, 1H) 7.35 (d, *J*=2.56 Hz, 1H) 7.53 (d, *J*=5.12 Hz, 1H) 7.60 (dd, *J*=8.41, 1.59 Hz, 1H) 7.82 (d, *J*=5.49 Hz, 1H) 8.06 (d, *J*=8.41 Hz, 1H) 8.13 (d, *J*=1.34 Hz, 1H) 8.22 (d, *J*=5.24 Hz, 1H) 12.06 (bs, 1H); ESI (+) MS: m/z 365 (MH^+).

Example 31, step-2

5-(2-Amino-pyrimidin-4-yl)-2-benzo[b]thiophen-5-yl-1H-pyrrole-3-carboxylic acid

MS: m/z 335 [M-H].

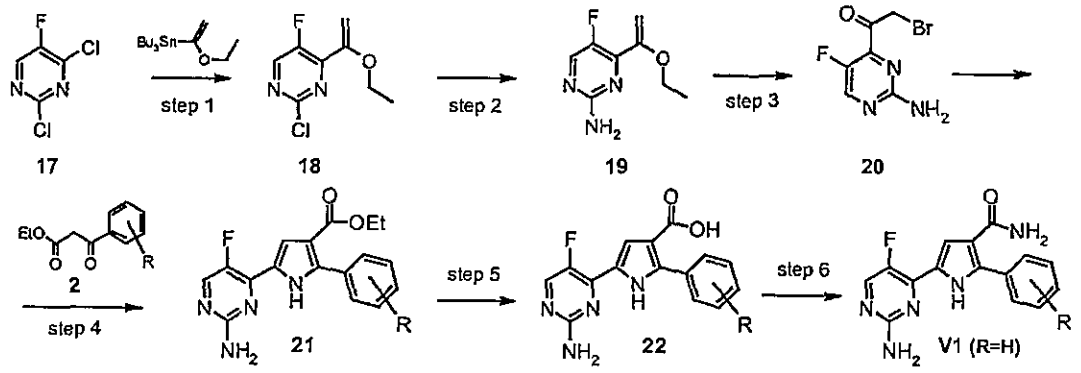
Example 31, step-3

5-(2-Amino-pyrimidin-4-yl)-2-benzo[b]thiophen-5-yl-1H-pyrrole-3-carboxylic acid amide (G15)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.43 (bs, 2H) 6.84 (bs, 1H) 7.04 (d, *J*=5.37 Hz, 1H) 7.31 (d, *J*=2.44 Hz, 1H) 7.34 (bs, 1H) 7.50 (dd, *J*=5.49, 0.49 Hz, 1H) 7.62 (dd, *J*=8.41, 1.71 Hz, 1H) 7.80 (d, *J*=5.49 Hz, 1H) 8.01 (d, *J*=8.41 Hz, 1H) 8.13 (d, *J*=1.34 Hz, 1H) 8.21 (d, *J*=5.37 Hz, 1H) 11.75 (bs, 1H); ESI (+) MS: m/z 336 (MH^+).

Example 32

5-(2-Amino-5-fluoro-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid amide (V1)



Step 1: Alkylation of pyrimidine ring (18)

To a solution of 2,4-dichloro-5-fluoro-pyrimidine **17** (1.2 g, 7.24 mmol) in DMF (14 mL), tributyl-(1-ethoxy-vinyl)-stannane (2.7 mL, 7.9 mmol) was added, followed by dichlorobis(triphenylphosphine) palladium(II) (100 mg, 0.145 mmol). The mixture was warmed at 70°C for 1 hour, cooled, a saturated solution of potassium fluoride (aq) was added and the mixture was stirred at room temperature for 18 hours. After dilution with water/diethylether and filtration through celite the organic phases were washed thoroughly with water and concentrated. The crude material was purified with the Horizon system (25 mm column), eluting with n-hexane/EtOAc 95:5. Obtained 2-chloro-4-(1-ethoxy-vinyl)-5-fluoro-pyrimidine (1.24 g, 84%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=6.95 Hz, 3H) 3.95 (q, *J*=6.99 Hz, 2H) 4.88 (d, *J*=2.80 Hz, 1H) 5.20 (d, *J*=2.93 Hz, 1H) 8.90 (d, *J*=3.17 Hz, 1H); ESI (+) MS: m/z 203 (MH^+).

Step 2: Amination of pyrimidine ring (19)

A solution of enolether **18** (15.5 g, 76.73 mmol) in absolute ethanol (25 mL) and 30% aqueous ammonia (50 mL) was warmed under shaking at 100°C for 1.5 hours in a Parr apparatus. After cooling, ethanol was removed and the compound was extracted with dichloromethane. The crude material was purified with the Horizon system, eluting with n-hexane/EtOAc 1:1. Obtained 4-(1-ethoxy-vinyl)-5-fluoro-pyrimidin-2-ylamine (9 g, 49.2 mmol, 64%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (t, J=7.01 Hz, 3H) 3.87 (q, J=6.95 Hz, 2H) 4.62 (d, J=2.44 Hz, 1H) 4.91 (dd, J=2.38, 0.55 Hz, 1H) 6.64 (bs, 2H) 8.28 (d, J=3.54 Hz, 1H); ESI (+) MS: m/z 184 (MH^+).

Step 3: Bromination to bromoketone (20)

To a solution of enolether **19** (510 mg, 2.78 mmol) in THF (25 mL), water (1.7 mL) was added followed by NBS (515 mg, 2.78 mmol). The mixture was stirred at room temperature for 1.5 hours. Solvent was evaporated, the residue was stirred thoroughly in methanol and filtered. Obtained 1-(2-amino-5-fluoro-pyrimidin-4-yl)-2-bromo-ethanone (500 mg, 77%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.70 (s, 2H) 6.94 (bs, 2H) 8.50 (d, J=2.93 Hz, 1H); ESI (+) MS: m/z 235 (MH^+).

Step 4: Formation of pyrrole ring (21)

To a solution of ketoester 2 (192 mg, 1 mmol) in THF (5 mL), cooled at 0°C, sodium hydride (80 mg, 2 mmol) was added under stirring. After 5 minutes a solution of bromoketone **20** (234 mg, 1 mmol) in DMF (2 mL) was added and the reaction mixture was stirred at 50°C for 8 hours. After removal of THF, ethanol (10 mL) and ammonium acetate (240 mg, 3 mmol) were added and the mixture was stirred at room temperature for 20 hours. After removal of the solvent, ethylacetate was added, the organic phase was washed with water and the crude material was purified through an Horizon system , eluting with n-hexane/EtOAc 1:1. Obtained 5-(2-amino-5-fluoro-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid ethyl ester (50 mg, 16%). ESI (+) MS: m/z 327 (MH^+).

Step 5: Hydrolysis to acids (22)

To a suspension of ester **21** (25 mg, 0.077 mmol) in 95% EtOH (0.5 mL), 4M aq NaOH (0.5 mL) was added and the mixture was refluxed for 2 h. The mixture was acidified to pH 5 with conc HCl, observing precipitation of the product. The precipitate was filtered,

washed with little cold water and dried. 5-(2-Amino-5-fluoro-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid, obtained as a white solid (16 mg, 64%), was used in the next step without further purifications.

ESI (+) MS: m/z 299 (MH^+).

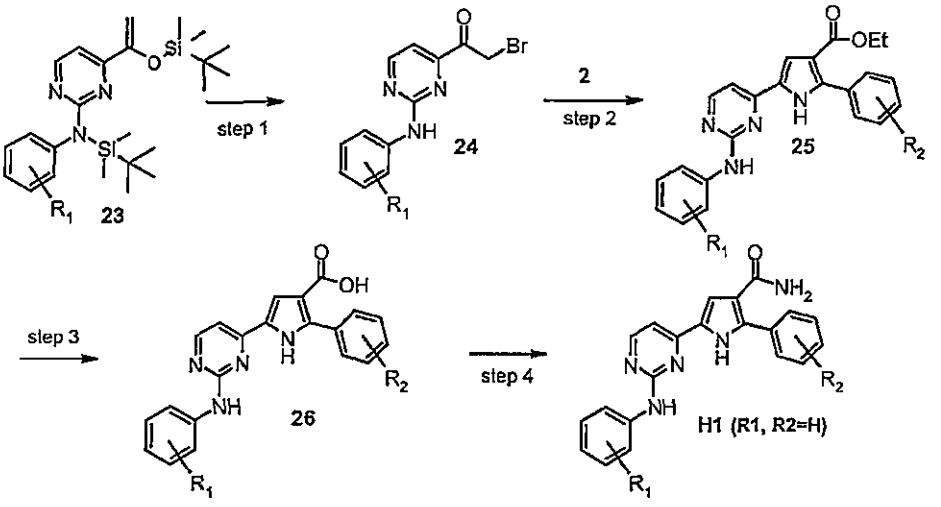
Step 6: Condensation to amides (V1)

To a solution of acid **22** (16 mg, 0.054 mmol) in DMF (0.5 mL) and DIEA (0.03 mL) stirred at 0°C, HOBT.NH_3 (13 mg, 0.08 mmol) and EDCI (16 mg, 0.08 mmol) were added. The mixture was stirred at room temperature for 20 hours. After dilution with ethyl acetate the organic phase was washed with water, with sat. aq. solution of sodium bicarbonate, dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (eluant: AcOEt/n-hexane 9:1). Obtained the title compound in 74% yield.

^1H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.34 (s, 2H) 6.87 (bs, 1H) 7.27 (t, *J*=2.80 Hz, 1H) 7.33-7.43 (m, 3H) 7.40 (s, 1H) 7.62-7.66 (m, 2H) 8.27 (d, *J*=3.41 Hz, 1H) 11.49 (bs, 1H). ESI (+) MS: m/z 298 (MH^+).

Example 33

2-Phenyl-5-(2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-3-carboxylic acid amide (H1)



Step 1: Bromination to bromoketone (24)

To a solution of enolsilylether **23** (1 g, 2.27 mmol) in THF (40 mL) and water (5 mL) at room temperature, solid NBS (0.43 g, 62.4 mmol) was added and the mixture was stirred for 20 hours. After solvent evaporation and aqueous work-up with ethyl acetate,

the crude material was purified by flash chromatography (eluant: n-hexane/EtOAc 4:1), yielding 2-bromo-1-(2-phenylamino-pyrimidin-4-yl)-ethanone as a yellow solid (0.27 g, 40%).

^{1}H NMR (DMSO-d_6 / 300 MHz) δ ppm 4.65 (s, 2H), 6.7 (m, 1H), 6.9 (d, 1H), 7.0 (m, 2H), 7.4 (d, 2H), 8.4 (d, 1H), 9.6 (s, 1H); ESI (+) MS: m/z 293 (MH^+).

Step 2: Pyrrole ring formation (25)

To a solution of ester **2** (150 µL, 0.87 mmol) in anhydrous THF (40 mL) at 0°C, NaH (50 mg, 1.2 mmol) was added under argon with stirring. After 40 min bromoketone **24** (260 mg, 0.89 mmol, prepared as described in WO2005014572) was added and the mixture was stirred at rt for 3 h. Solvent was evaporated to dryness, the residue was dissolved in EtOH (10 mL), ammonium acetate (343 g, 4.45 mmol) was added and the solution was stirred at rt overnight. Solvent was evaporated to dryness and EtOAc and water were added to the crude material and the organic layer was separated, washed with water, dried (Na_2SO_4) and concentrated. The residue was taken up with Et_2O/EtOAc/n-hexane (1:1:1) and filtered. Obtained 2-phenyl-5-(2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-3-carboxylic acid ethyl ester (120 mg, 36%).

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.20 (t, 3H) 4.14 (q, 2H) 6.90-7.85 (m, 11H) 7.35 (d, *J*=5.27 Hz, 1H) 8.46 (d, *J*=5.27 Hz, 1H) 9.45 (s, 1H) 12.10 (s, 1H); ESI (+) MS: m/z 385 (MH^+).

Step 3: Saponification to carboxylic acids (26)

To a suspension of ester **25** (120 mg, 0.31 mmol) in 95% EtOH (3 mL), 4M aq NaOH (4 mL) was added and the mixture was refluxed for 4 h. Most solvent was evaporated and the residue, cooled in ice bath, was acidified to pH 5 with conc. AcOH, observing precipitation of the product. The precipitate was filtered, washed with little cold water, and dried. 2-Phenyl-5-(2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-3-carboxylic acid, obtained as a white solid (100 mg), was used in the next step without further purifications. MS: m/z 355 [M-H].

Step 3: Condensation to amides (H1)

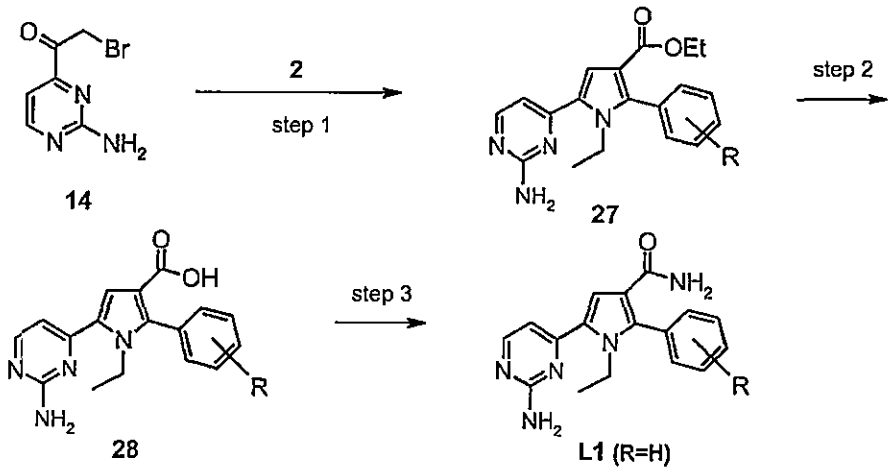
To a suspension of acid **26** (90 mg, 0.25 mmol) in DMF (3 mL), DIEA (120 µL, 0.67 mmol), EDCI (100 mg, 0.52 mmol) and HOBT·NH_3 (79 mg, 0.52 mmol) were added. The reaction mixture was stirred at rt overnight then it was poured into a stirred 1:1 mixture of water and EtOAc. The organic phase was washed with water, the aqueous

layer was extracted with EtOAc and the combined organic layers were washed with water, dried (Na_2SO_4) and concentrated, affording a crude material that was purified by flash chromatography (DCM/MeOH 96:4), affording 2-phenyl-5-(2-phenylamino-pyrimidin-4-yl)-1H-pyrrole-3-carboxylic acid amide as a white solid (35 mg, 30% two steps).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 6.90 (s, 1H) 6.95 (t, J=7.33 Hz, 1H) 7.25-7.50 (m, 7H) 7.29 (d, J=5.57 Hz, 1H) 7.60 (d, 2H) 7.85 (d, J=7.62 Hz, 2H) 8.43 (d, J=5.27 Hz, 1H) 9.40 (s, 1H) 11.75 (s, 1H); ESI (+) MS: m/z 356 (MH^+).

Example 34

5-(2-Amino-pyrimidin-4-yl)-1-ethyl-2-phenyl-1H-pyrrole-3-carboxylic acid amide (L1)



Step 1: Formation of pyrrole ring (27)

To a solution of ester **2** (1.34 g, 7 mmol) in anhydrous THF (100 mL) at 0°C, NaH (0.7 g, 17.5 mmol) was added under argon with stirring. After 5 min bromoketone **14** (2.5 g, 8.4 mmol) was added and the mixture was stirred at rt for 3 h. Solvent was evaporated, the residue was dissolved in AcOH (30 mL) and 2M $EtNH_2$ in THF (8.7 mL, 17.5 mmol). The mixture was treated with microwaves at 170°C for 5 min then it was diluted with EtOAc and washed with $NaHCO_3$ aq saturated solution. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (DCM/EtOH/acetone 96:2:2), thus affording 0.7 g of 5-(2-amino-pyrimidin-4-yl)-1-ethyl-2-phenyl-1H-pyrrole-3-carboxylic acid ethyl ester (29% yield). ESI (+) MS: m/z 337 (MH^+).

Step 2: Saponification to carboxylic acids (28)

To a suspension of ester **27** (0.7 g, 2.08 mmol) in 95% EtOH (8 mL), 4M aq NaOH (8 mL) was added and the mixture was stirred for 1 h at 100 °C. The solvent was removed under vacuum and the aqueous residue was acidified with conc HCl to pH 5, observing precipitation of the product. The mixture was filtered, the solid was washed with little cold water and dried thus affording 0.66 g of 5-(2-amino-pyrimidin-4-yl)-1-ethyl-2-phenyl-1H-pyrrole-3-carboxylic acid that was used in the next step without further purification. MS: m/z 307 [M-H].

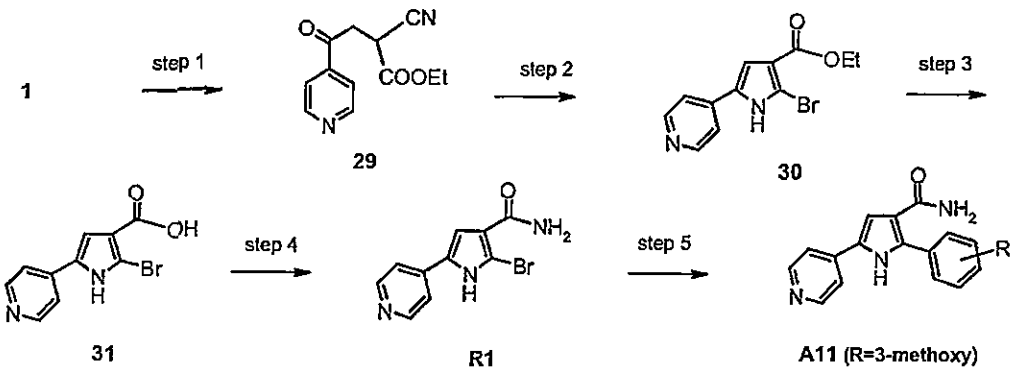
Step 3: Condensation to amides (L1)

To a suspension of acid **28** (400 mg, 1.31 mmol) in 10 mL of THF and 600 µL of DIEA (3.52 mmol), cooled in ice bath, 336 mg of EDCI (1.75 mmol) and 267 mg of HOBT·NH_3 (1.75 mmol) were added and the mixture was stirred overnight at rt. EtOAc and water were added, the layers were separated, the aqueous layer was extracted with EtOAc and the combined organic layers were washed with 1M aq NaOH and water. They were then dried (Na_2SO_4) and concentrated. The residue was filtered and washed with little cold MeOH. The mother liquor was purified by flash chromatography (DCM/MeOH/acetone 90:5:5), affording the desired amide. The two product batches were combined, suspended in MeOH and acidified to pH 1 with 1.25M HCl in MeOH. The solvent was removed and the residue was treated with Et_2O: the resulting solid was filtered, washed with Et_2O and concentrated, affording 380 mg of the hydrochloric salt of 5-(2-amino-pyrimidin-4-yl)-1-ethyl-2-phenyl-1H-pyrrole-3-carboxylic acid amide (1.1 mmol, 83% yield).

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.08 (t, *J*=6.89 Hz, 3H) 4.37 (q, *J*=6.91 Hz, 2H) 6.87 (bd, *J*=21.95 Hz, 2H) 7.18 (d, *J*=6.58 Hz, 1H) 7.38-7.43 (m, 2H) 7.50-7.55 (m, 3H) 7.81 (s, 1H) 8.00 (bs, 3H) 8.23 (d, *J*=6.71 Hz, 1H); ESI (+) MS: m/z 308 (MH^+).

Example 35

2-Bromo-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (R1) and 2-(3-methoxy-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A11)



Step 1: Condensation to cyanoester (29)

To a suspension of sodium metal (81 mg, 3.5 mmol) in 10 mL anhydrous EtOH, ethylcyanoacetate (0.37 mL, 3.5 mmol) was added at 0°C. The solution was stirred until sodium was completely dissolved. The solvent was evaporated to obtain a white solid that was added portionwise to a stirred solution of bromoacetylpyridine **1** (1.0 g, 3.5 mmol) in anhydrous THF (20 mL) and DIEA (0.6 mL, 3.5 mmol). The reaction mixture was stirred overnight at rt. The solvent was removed, the residue was suspended in water and extracted with DCM. The organic extracts were dried over Na_2SO_4 and concentrated. The crude was purified by flash chromatography (DCM/MeOH 95:5) to give 710 mg (87%) of 2-cyano-4-oxo-4-pyridin-4-yl-butyric acid ethyl ester as a reddish oil.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.23 (t, *J*=7.07 Hz, 3H), 3.88 (d, *J*=5.25 Hz, 2H), 4.21 (q, *J*=7.07 Hz, 2H), 4.64 (t, *J*=5.25 Hz, 1H), 7.89 (d, *J*=6.00 Hz, 2H), 8.85 (d, *J*=6.00 Hz, 2H); ESI (+) MS: m/z 233 (MH^+).

Step 2: Formation of pyrrole ring (30)

To a solution of HBr (33% in AcOH, 13 mL, 43.1 mmol) at 0°C a solution of cyanoester **29** (1.0 g, 4.3 mmol), dissolved in Et_2O and DCM, was added dropwise. The reaction mixture was left for 20 min at 0°C and then at rt until disappearance of the starting material (2.5 h). The solid was filtered and washed with acetone and MeOH. The pyridinium salt was neutralized with 7N NH_3 in MeOH. The solid was purified by flash chromatography (DCM/MeOH 95:5) to give 800 mg (62%) of 2-bromo-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid ethyl ester as an orange solid.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.31 (t, *J*=7.12 Hz, 3H), 4.24 (q, *J*=7.12 Hz, 2H), 7.26 (s, 1H), 7.71 (d, *J*=6.22 Hz, 2H) 8.54 (d, *J*=6.22 Hz, 2H), 12.85 (s, 1H); ESI (+) MS: m/z 295 (MH^+).

Step 3: Saponification to carboxylic acid (31)

Ester **30** (1.0 g, 3.74 mmol), dissolved in 8 mL of 4M aq NaOH and 8 mL EtOH, was refluxed for 4 h. The solution was cooled and neutralized with AcOH. The precipitate was filtered and washed with water and acetone to afford 850 mg (85%) of 2-bromo-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid as a white solid.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 7.33 (s, 1H), 7.83 (d, *J*=6.00 Hz, 2H), 8.58 (d, *J*=6.00 Hz, 2H), 12.37 (bs, 1H), 12.91 (s, 1H); MS: m/z 266 [M-H].

Step 4: Condensation to amide (R1)

Acid **31** (450 mg, 1.68 mmol) was dissolved in anhydrous THF (20 mL) in the presence of DIEA (1.27 mL, 7.30 mmol). To the solution, cooled to 0 °C, EDCI (1.0 g, 5.5 mmol) and HOBT·NH_3 (812 mg, 5.34 mmol) were added. The reaction mixture was left overnight at rt. The solvent was evaporated, water was added and the slurry was extracted with DCM. The crude was purified by flash chromatography (DCM/MeOH 95:5) to yield 150 mg (33%) of 2-bromo-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide as a pale yellow solid.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 7.02 (s, 2H), 7.29 (s, 1H), 7.59 (d, *J*= 6.25 Hz, 2H), 8.52 (d, *J*=6.25 Hz, 2H), 12.54 (s, 1H); ESI (+) MS: m/z 267 (MH^+).

Step 5: Suzuki coupling to amides (A11)

To a solution of amide **R1** (110 mg, 0.41 mmol) in deoxygenated toluene/EtOH 1:1 (5 mL), deoxygenated 1M aq Na_2CO_3 (1.1 mL, 1.12 mmol), LiCl (57 mg, 1.35 mmol), the conveniently substituted phenyl boronic acid (0.67 mmol) and $(Ph_3P)_2PdCl_2$ (3 mg) were added and the mixture was stirred at 100°C until disappearance of the starting material. The solvent was evaporated and the crude was purified by flash chromatography (eluant: DCM/MeOH 95:5). When required the product was dissolved in EtOH, treated with 2N HCl in Et_2O until precipitation of the hydrochloride salt which was filtered affording 2-(3-methoxy-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (68% yield).

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 3.83 (s, 3H), 6.66 (bs, 2H), 7.28 (m, 3H), 7.40 (m, 2H), 8.24 (d, *J*=6.82 Hz, 2H), 9.11 (d, *J*=6.82 Hz); ESI (+) MS: m/z 294 (MH^+).

By using this procedure the following compounds were obtained.

Example 36

2-(4-Methoxy-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide hydrochloride (A12)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 3.84 (s, 3H), 7.07 (d, *J*=8.90 Hz, 2H), 7.33 (bs, 2H), 7.67 (d, *J*=8.90 Hz, 2H), 7.73 (s, 1H), 8.22 (d, *J*=6.50 Hz, 2H), 8.72 (d, *J*=6.50 Hz, 2H), 12.28 (s, 1H); ESI (+) MS: m/z 294 (MH^+).

Example 37

2-(2-Methoxy-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide hydrochloride (A10)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 3.76 (s, 3H), 6.95 (bs, 2H), 7.06 (t, *J*=8.05 Hz, 1H), 7.16 (d, *J*=8.05 Hz, 1H), 7.40 (dd, *J*=1.71 Hz, 7.44 Hz, 1H), 7.46 (m, 1H), 7.73 (s, 1H), 8.15 (d, *J*=7.00 Hz, 2H), 8.71 (d, *J*=7.00 Hz, 2H), 12.42 (s, 1H); ESI (+) MS: m/z 294 (MH^+).

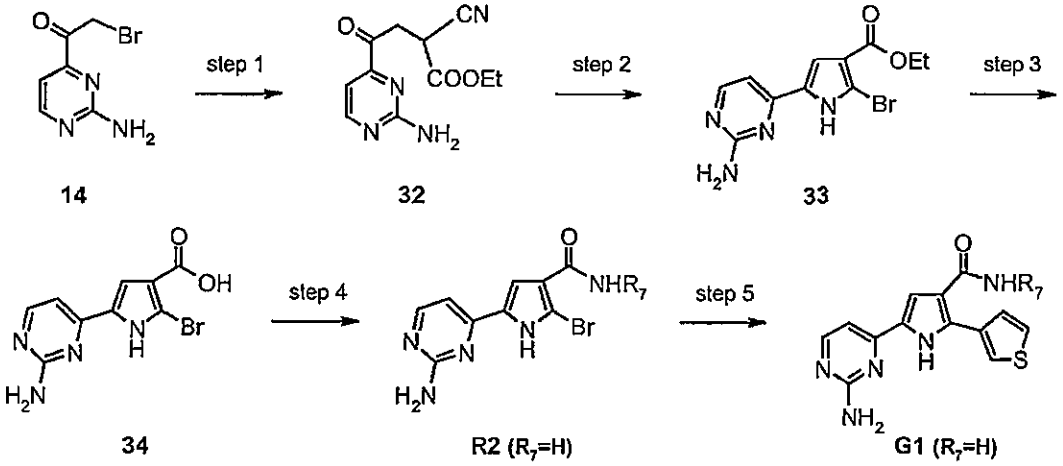
Example 38

2-(4-Nitro-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A15)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 7.40 (bs, 2H), 7.70 (s, 1H), 8.02 (d, *J*=8.78 Hz, 2H), 8.19 (d, *J*=6.20 Hz, 2H), 8.32 (d, *J*=8.78 Hz, 2H), 8.77 (d, *J*=6.20 Hz, 2H), 12.57 (bs, 1H); ESI (+) MS: m/z 309 (MH^+).

Example 39

5-(2-Amino-pyrimidin-4-yl)-2-bromo-1H-pyrrole-3-carboxylic acid amide (R2) and 5-(2-amino-pyrimidin-4-yl)-2-thiophen-3-yl-1H-pyrrole-3-carboxylic acid amide (G1)



Step 1: Condensation to cyanoester (32)

Ethylcyanoacetate (5.3 mL, 0.05 mol) was added to a suspension of sodium metal (1.15 g, 0.05 mol) in 150 mL of anhydrous EtOH at 0°C. After sodium dissolution the reaction mixture was concentrated and the resultant solid was added to a solution of bromoketone **14** (15 g, 0.05 mol) in 300 mL of anhydrous THF and DIEA (8.8 mL, 0.05 mol). The reaction mixture was stirred overnight at rt, concentrated and the residue was suspended in water and extracted with DCM. The organic extracts were dried (Na_2SO_4) and concentrated. The crude was purified by flash chromatography (DCM/MeOH 95:5) to give 4.5 g (37%) of 4-(2-amino-pyrimidin-4-yl)-2-cyano-4-oxo-butyric acid ethyl ester as an oil.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.21 (t, *J*=7.08 Hz, 3H), 3.73 (d, *J*=5.61 Hz, 2H), 4.18 (q, *J*=7.08 Hz, 2H), 4.58 (t, *J*=5.61 Hz, 1H), 6.97 (d, *J*=4.88 Hz, 1H), 7.04 (bs, 2H), 8.52 (d, *J*=4.88 Hz, 1H); ESI (+) MS: m/z 249(MH^+).

Step 2: Formation of pyrrole ring (33)

A solution of cyanoester **32** (364 mg, 1.47 mmol) in anhydrous Et_2O and DCM (1:1, 10 mL) was added dropwise to 4.5 mL of 33 % HBr in AcOH at 0°C. The mixture was left at 0°C for 30 min and then at rt until disappearance of the starting material. The solid was filtered, washed with acetone and MeOH, neutralized with 7N NH_3 in MeOH to afford 400 mg (88%) of 5-(2-amino-pyrimidin-4-yl)-2-bromo-1H-pyrrole-3-carboxylic acid ethyl ester.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.26 (t, *J*=7.10 Hz, 3H), 4.20 (q, *J*=7.10 Hz, 2H), 6.43 (bs, 2H), 6.99 (d, *J*=5.24 Hz, 1H), 7.23 (s, 1H), 8.23 (d, *J*=5.24 Hz, 1H); ESI (+) MS: m/z 312 (MH^+).

Step 3: Saponification to carboxylic acid (34)

A solution of ester **33** (2 g, 6 mmol), in 15 mL of EtOH and 15 mL of 4M aq NaOH, was refluxed at 100° C for 6 h. The acid was precipitated with AcOH, filtered and washed with acetone to give 80 mg (88%) of 5-(2-amino-pyrimidin-4-yl)-2-bromo-1H-pyrrole-3 carboxylic acid.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.06 (br, 2H), 6.87 (d, *J*=5.20 Hz, 1H), 7.08 (s, 1H), 8.00 (d, *J*=5.20 Hz, 1H); MS: m/z 282 [M-H].

Step 4: Condensation to amides (R2)

A solution of 500 mg (1.77 mmol) of acid **34** in 20 mL of dry THF and DIEA (0.6 mL, 3.54 mmol) was stirred at 0 °C. EDCI (508 mg, 2.65 mmol) and HOBT.NH_3 (404 mg,

2.65 mmol) were added and the reaction mixture was stirred overnight at rt. The solution was concentrated and the crude was purified by HPLC preparative. Obtained 5-(2-amino-pyrimidin-4-yl)-2-bromo-1H-pyrrole-3-carboxylic acid amide.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.97 (d, *J*=5.57 Hz, 1H) 7.00 (bs, 1H) 7.17 (bs, 1H) 8.24 (d, *J*=5.57 Hz, 1H) 12.66 (bs, 1H); ESI (+) MS: m/z 283 (MH^+).

Step 5: Suzuki coupling to amides (G1)

Bromoamide **R2** (224 mg, 0.79 mmol) was dissolved in EtOH (6 mL) and toluene (6 mL), LiCl (99 mg, 2.37 mmol), 1M aq Na_2CO_3 (1.97 mmol), 3-thiophenboronic acid (152 mg, 1.18 mmol) and $(Ph_3P)_2PdCl_2$ (6 mg, 0.008 mmol) were added and the reaction mixture was heated to reflux for 6 hr and then overnight at rt. The solvent was evaporated under reduced pressure and the crude material was purified by flash chromatography (DCM/MeOH 9:1) to afford 120 mg (53%) of 5-(2-amino-pyrimidin-4-yl)-2-thiophen-3-yl-1H-pyrrole-3-carboxylic acid amide.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.36 (bs, 2H), 6.87 (bs, 2H), 7.01 (d, *J*=5.24 Hz, 1H), 7.26 (d, *J*=2.44 Hz, 1H), 7.54 (d, *J*=2.93 Hz, 5.00, 1H), 7.65 (dd, *J*=1.22 Hz, 5.00, 1H), 8.11 (dd, *J*=1.22 Hz, 2.93, 1H), 8.20 (d, *J*=5.24 Hz, 1H), 11.52 (bs, 1H); ESI (+) MS: m/z 286 (MH^+).

The above procedure was employed to synthesize the following compounds.

Example 40

5-(2-Amino-pyrimidin-4-yl)-2-(4-fluoro-2-methyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (F13)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.15 (s, 3H), 6.31 (bs, 2H), 6.69 (bs, 1H), 6.92 (d, *J*=5.24 Hz, 1H), 7.05 (td, *J*=8.41, 2.56 Hz, 1H), 7.05 (dd, *J*=7.68, 2.56 Hz, 1H), 7.06 (bs, 1H), 7.28 (dd, *J*=8.41, 7.68 Hz, 1H), 7.32 (d, *J*=2.56 Hz, 1H), 8.18 (d, *J*=5.24 Hz, 1H), 11.75 (bs, 1H); ESI (+) MS: m/z 312 (MH^+).

Example 41

5-(2-Amino-pyrimidin-4-yl)-2-(5-fluoro-2-methyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (F14)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.11 (s, 3H), 6.32 (bs, 2H), 6.72 (bs, 1H), 6.93 (d, *J*=5.24 Hz, 1H), 7.04-7.19 (m, 3H), 7.25-7.31 (m, 1H), 7.33 (d, *J*=2.44 Hz, 1H), 8.18 (d, *J*=5.24 Hz, 1H), 11.82 (bs, 1H); ESI (+) MS: m/z 312 (MH^+).

Example 42

5-(2-Amino-pyrimidin-4-yl)-2-(2,3-dimethyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (F15)

See Ex.17.

Example 43

5-(2-Amino-pyrimidin-4-yl)-2-(2,3-difluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (F16)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.38 (bs, 2H), 6.82 (bs, 1H), 6.95 (d, *J*=5.24 Hz, 1H), 7.20-7.28 (m, 1H), 7.28-7.34 (m, 1H), 7.35 (d, *J*=2.56 Hz, 1H), 7.39-7.50 (m, 2H), 8.23 (d, *J*=5.24, 1H), 12.00 (bs, 1H); ESI (+) MS: m/z 316 (MH^+).

Example 44

5-(2-Amino-pyrimidin-4-yl)-2-(2,4-difluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (F17)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.41 (bs, 2H), 6.77 (bs, 1H), 6.94 (d, *J*=5.24 Hz, 1H), 7.13 (m, 1H), 7.28 (m, 1H), 7.35 (d, *J*=2.56 Hz, 1H), 7.38 (bs, 1H), 7.54 (m, 1H), 8.23 (d, *J*=5.24 Hz, 1H), 11.93 (bs, 1H); ESI (+) MS: m/z 316 (MH^+).

Example 45

5-(2-Amino-pyrimidin-4-yl)-2-(2,5-difluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (F18)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.40 (bs, 2H) 6.81 (bs, 1H) 6.94 (d, *J*=5.37 Hz, 1H) 7.33 (d, *J*=2.44 Hz, 1H) 7.42 (bs, 1H) 8.22 (d, *J*=5.24 Hz, 1H) 11.95 (bs, 1H); ESI (+) MS: m/z 316 (MH^+).

Example 46

5-(2-Amino-pyrimidin-4-yl)-2-(2-chloro-phenyl)-1H-pyrrole-3-carboxylic acid amide (F19)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.37 (bs, 2H), 6.69 (bs, 1H), 6.93 (d, *J*=5.24 Hz, 1H), 7.19 (bs, 1H), 7.33 (d, *J*=2.56 Hz, 1H), 7.35-7.45 (m, 3H), 7.48-7.53 (m, 1H), 8.19 (d, *J*=5.24, 1H), 11.90 (bs, 1H); ESI (+) MS: m/z 314 (MH^+).

Example 47

5-(2-Amino-pyrimidin-4-yl)-2-(3-chloro-phenyl)-1H-pyrrole-3-carboxylic acid amide (F20)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.38 (bs, 2H), 6.90 (bs, 1H), 7.01 (d, *J*=5.24 Hz, 1H), 7.27 (d, *J*=2.44 Hz, 1H), 7.35-7.44 (m, 2H), 7.47 (bs, 1H), 7.59-7.65 (m, 1H), 7.73 (t, *J*=1.22 Hz, 1H), 8.23 (d, *J*=5.24, 1H), 11.79 (bs, 1H); ESI (+) MS: m/z 314 (MH^+).

Example 48

5-(2-Amino-pyrimidin-4-yl)-2-(4-chloro-phenyl)-1H-pyrrole-3-carboxylic acid amide (F21)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.33 (bs, 2H), 6.86 (bs, 1H), 6.99 (d, *J*=5.24 Hz, 1H), 7.28 (d, *J*=2.07 Hz, 1H), 7.38-7.49 (m, 3H), 7.63-7.70 (m, 2H), 8.21 (d, *J*=5.24, 1H), 11.74 (bs, 1H); ESI (+) MS: m/z 314 (MH^+).

Example 49

5-(2-Amino-pyrimidin-4-yl)-2-(4-isobutyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (F22)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 0.90 (d, *J*=6.58 Hz, 6H), 1.80-1.95 (m, 1H), 2.48 (m, 2H), 6.35 (bs, 2H), 6.80 (bs, 1H), 7.01 (d, *J*=5.24 Hz, 1H), 7.19 (d, *J*=8.17 Hz, 2H), 7.25 (d, *J*=2.56 Hz, 1H), 7.28 (bs, 1H), 7.56 (d, *J*=8.17 Hz, 2H), 8.19 (d, *J*=5.24 Hz, 1H), 11.56 (bs, 1H); ESI (+) MS: m/z 336 (MH^+).

Example 50

5-(2-Amino-pyrimidin-4-yl)-2-(2-chloro-4-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (F23)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.38 (bs, 2H), 6.72 (bs, 1H), 6.92 (d, *J*=5.24 Hz, 1H), 7.22-7.33 (m, 2H), 7.35 (d, *J*=2.56 Hz, 1H), 7.45-7.54 (m, 2H), 8.22 (d, *J*=5.24 Hz, 1H), 11.95 (bs, 1H); ESI (+) MS: m/z 336 (MH^+).

Example 51

5-(2-Amino-pyrimidin-4-yl)-2-(2,5-dimethyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (F24)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.11(s, 3H) 2.31(s, 3H) 6.41 (bs, 2H) 6.70 (bs, 1H) 6.83(bs, 1H) 6.98 (d, *J*=5.37 Hz, 1H) 7.1-7.18 (m, 3H) 7.34 (d, *J*=2.68 Hz, 1H) 8.19(d, *J*=5.37 Hz, 1H) 11.74 (bs, 1H); ESI (+) MS: m/z 308 (MH^+).

Example 52

5-(2-Amino-pyrimidin-4-yl)-2-(5-chloro-2-methyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (F25)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.12 (s, 3H), 6.35 (bs, 2H), 6.73 (bs, 1H), 6.93 (d, *J*=5.24 Hz, 1H), 7.22 (bs, 1H), 7.25-7.30 (m, 2H), 7.32-7.36 (m, 2H), 8.20 (d, *J*=5.24 Hz, 1H), 11.85 (bs, 1H); ESI (+) MS: m/z 328 (MH^+).

Example 53

5-(2-Amino-pyrimidin-4-yl)-2-(2,4-dichloro-phenyl)-1H-pyrrole-3-carboxylic acid amide (F26)

See Ex.19.

Example 54

5-(2-Amino-pyrimidin-4-yl)-2-(5-chloro-2-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (F27)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.37 (bs, 2H) 6.80 (bs, 1H) 6.93 (d, *J*=5.24 Hz, 1H) 7.28 (t, *J*=9.21 Hz, 1H) 7.33 (d, *J*=2.44 Hz, 1H) 7.44 (bs, 1H) 7.47 (ddd, *J*=8.84, 4.33, 2.80 Hz, 1H) 7.55 (dd, *J*=6.22, 2.68 Hz, 1H) 8.22 (d, *J*=5.24 Hz, 1H) 11.98 (bs, 1H); ESI (+) MS: m/z 332 (MH^+).

Example 55

5-(2-Amino-pyrimidin-4-yl)-2-(2-fluoro-4-methyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (F28)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.37 (s, 3H), 6.37 (bs, 2H), 6.73 (bs, 1H), 6.95 (d, *J*=5.24 Hz, 1H), 7.02-7.09 (m, 2H), 7.26 (bs, 1H), 7.30 (d, *J*=2.56 Hz, 1H), 7.37 (t, *J*=7.90 Hz, 1H), 8.20 (d, *J*=5.24 Hz, 1H), 11.78 (bs, 1H); ESI (+) MS: m/z 312 (MH^+).

Example 56

5-(2-Amino-pyrimidin-4-yl)-2-(2-fluoro-5-methyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (F29)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.33 (s, 3H) 6.42 (bs, 2H) 6.75 (bs, 1H) 6.97 (d, *J*=5.37 Hz, 1H) 7.11 (dd, *J*=9.88, 8.41 Hz, 1H) 7.19-7.25 (m, 1H) 7.31 (bs, 1H) 7.30 (dd, *J*=6.77, 2.01 Hz, 1H) 7.32 (d, *J*=2.44 Hz, 1H) 8.21 (d, *J*=5.37 Hz, 1H) 11.85 (bs, 1H); ESI (+) MS: m/z 312 (MH^+).

Example 57

5-(2-Amino-pyrimidin-4-yl)-2-(2-fluoro-3-methyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (F30)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.27 (d, *J*=1.71 Hz, 3H) 6.39 (bs, 2H) 6.74 (bs, 1H) 6.95 (d, *J*=5.24 Hz, 1H) 7.12 (t, *J*=7.56 Hz, 1H) 7.28 (bs, 1H) 8.20 (d, *J*=5.37 Hz, 1H) 11.81 (bs, 1H); ESI (+) MS: m/z 312 (MH^+).

Example 58

5-(2-Amino-pyrimidin-4-yl)-2-(5-chloro-2-fluoro-3-methyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (F32)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.26 (s, 3H), 6.41 (bs, 2H), 6.80 (bs, 1H), 6.95 (d, *J*=5.24 Hz, 1H), 7.32 (d, *J*=2.32 Hz, 1H), 7.33-7.37 (m, 1H), 7.38-7.47 (m, 2H), 8.21 (d, *J*=5.24 Hz, 1H), 11.95 (bs, 1H); ESI (+) MS: m/z 346 (MH^+).

Example 59

5-(2-Amino-pyrimidin-4-yl)-2-(3-chloro-2-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (F33)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.41 (bs, 2H) 6.81 (bs, 1H) 6.94 (d, *J*=5.24 Hz, 1H) 7.23-7.27 (m, 1H) 7.35 (d, *J*=2.44 Hz, 1H) 7.42 (bs, 1H) 7.43-7.47 (m, 1H) 8.23 (d, *J*=5.24 Hz, 1H) 12.02 (bs, 1H); ESI (+) MS: m/z 332 (MH^+).

Example 60

5-(2-Amino-pyrimidin-4-yl)-2-(2,3-dichloro-phenyl)-1H-pyrrole-3-carboxylic acid amide (F34)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.35 (bs, 2H), 6.73 (bs, 1H), 6.90 (d, *J*=5.24 Hz, 1H), 7.34 (bs, 1H), 7.38-7.42 (m, 2H), 7.65-7.70 (m, 2H), 8.21 (d, *J*=5.24 Hz, 1H), 12.00 (bs, 1H); ESI (+) MS: m/z 349 (MH^+).

Example 61

5-(2-Amino-pyrimidin-4-yl)-2-(2-fluoro-3-methoxy-phenyl)-1H-pyrrole-3-carboxylic acid amide (F35)

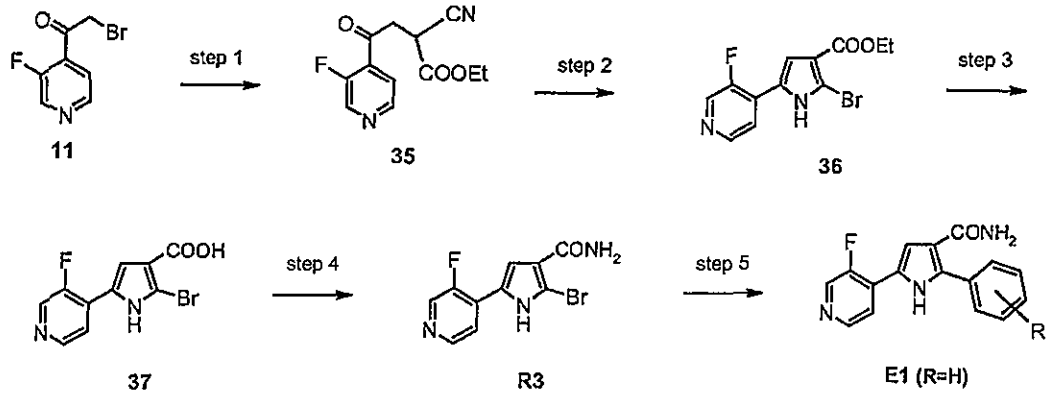
^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 3.86 (s, 3H) 6.39 (bs, 2H) 6.74 (bs, 1H) 6.95 (d, *J*=5.24 Hz, 1H) 6.99-7.03 (m, 1H) 7.12-7.16 (m, 1H) 7.18-7.20 (m, 1H) 7.29 (bs, 1H) 7.30 (d, *J*=2.44 Hz, 1H) 8.21 (d, *J*=5.24 Hz, 1H) 11.86 (bs, 1H); ESI (+) MS: m/z 328 (MH^+).

Example 62

5-(2-Amino-pyrimidin-4-yl)-2-benzo[b]thiophen-5-yl-1H-pyrrole-3-carboxylic acid amide (G15)

Example 63

2-Bromo-5-(3-fluoro-pyridin-4-yl)-1H-pyrrole-3-carboxylic acid amide (R3) and 5-(3-fluoro-pyridin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid amide (E1)



Step 1: Condensation to cyanoester (35)

Ethylcyanoacetate (715 µL, 6.7 mmol) was added to a suspension of sodium metal (154 mg, 6.7 mmol) in 20 mL of anhydrous EtOH at 0 °C. The solution was stirred until sodium dissolved completely. The solvent was evaporated and the solid was added to a solution of bromoketone **11** (2 g, 6.7 mmol) and DIEA (1.16 mL, 6.7 mmol) in 40 mL of anhydrous THF. The mixture was stirred overnight at rt. The solvent was evaporated, the residue was suspended in water and extracted with DCM. The organic extracts were dried (Na_2SO_4) and the crude material was purified by flash chromatography (DCM/MeOH 98:2) to afford 2-cyano-4-(3-fluoro-pyridin-4-yl)-4-oxo-butyric acid ethyl ester as an oil.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.22 (t, *J*=7.07 Hz, 3H), 3.78 (m, 2H), 4.20 (q, *J*=7.07 Hz, 2H), 4.61 (t, *J*=5.37 Hz, 1H), 7.81 (m, 1H), 8.64 (dd, *J*=1.22, 5.00 Hz, 1H), 8.82 (d, *J*=2.56 Hz, 1H); ESI (+) MS: m/z 251(MH^+).

Step 2: Formation of the pyrrole ring (36)

A solution of cyanoester **35** (1.0 g, 4 mmol) in anhydrous Et_2O (3 mL) and DCM (2 mL) was added to 33% HBr in AcOH (12 mL), cooled at 0°C. The reaction mixture was stirred for 3 h, the precipitate was filtered, washed with acetone and MeOH and

neutralized with 7N NH_3 in MeOH. The solvent was evaporated to give 1.0 g (80%) of 2-bromo-5-(3-fluoro-pyridin-4-yl)-1H-pyrrole-3-carboxylic acid ethyl ester as a solid.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.26 (t, *J*=7.07 Hz, 3H), 4.20 (q, *J*=7.07 Hz, 2H), 7.08 (d, *J*=3.53 Hz, 1H), 7.30 (bs, 1H), 7.83 (m, 1H), 8.39 (dd, *J*=0.85, 5.12 Hz, 1H), 8.55 (d, *J*=3.41 Hz, 1H); ESI (+) MS: m/z 314 (MH^+).

Step 3: Saponification to carboxylic acid (37)

Ester **36** was dissolved in 8 mL of EtOH and 8 mL of 1M aq NaOH and heated at 100°C for 6 h. The product was precipitated with AcOH, the solid was filtered and washed with acetone to afford 700 mg (77%) of 2-bromo-5-(3-fluoro-pyridin-4-yl)-1H-pyrrole-3-carboxylic acid.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.98 (d, *J*=5.12 Hz, 1H), 7.81 (q, *J*=5.12 Hz, 1H), 8.13 (d, *J*=5.60 Hz, 1H), 8.25 (d, *J*=4.02 Hz, 1H); MS: m/z 284 [M-H].

Step 4: Condensation to amide (R3)

Acid **37** (1.68 mmol) was dissolved in anhydrous THF (20 mL) in the presence of DIEA (1.27 mL, 7.30 mmol). To the solution, cooled to 0 °C, EDCI (1.0 g, 5.5 mmol) and HOBT·NH_3 (812 mg, 5.34 mmol) were added. The reaction mixture was left overnight at rt. The solvent was evaporated, water was added and the slurry was extracted with DCM. The crude was purified by flash chromatography (DCM/MeOH 98:2) to yield 2-bromo-5-(3-fluoro-pyridin-4-yl)-1H-pyrrole-3-carboxylic acid amide as a yellow solid (42% yield).

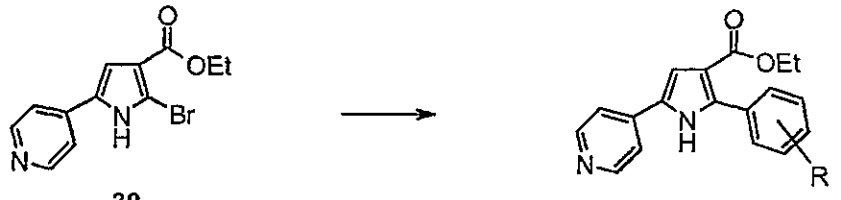
^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 7.09 (s, 2H) 7.35 (s, 1H) 7.98 (d, *J*=4.83 Hz, 1H) 8.47 (d, *J*=4.84 Hz, 1H) 8.61 (d, *J*=0.91 Hz, 1H) 12.05 (s, 1H); ESI (+) MS: m/z 285(MH^+).

Step 5: Suzuki coupling to amide (E1)

To a solution of amide **R3** (0.8 mmol) in deoxygenated toluene/EtOH 1:1 (10 mL), deoxygenated 1M aq Na_2CO_3 (2.2 mL, 2.2 mmol), LiCl (2.7 mmol), phenyl boronic acid (1.4 mmol) and $(Ph_3P)_2PdCl_2$ (6 mg) were added and the mixture was stirred at 100°C until disappearance of the starting material. The solvent was evaporated and the crude was purified by flash chromatography (eluant: DCM/MeOH 95:5). When required the product was dissolved in EtOH, treated with 2N HCl in Et_2O until precipitation of the hydrochloride salt which was filtered affording 5-(3-fluoro-pyridin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid amide (74% yield).

Example 64

2-(4-Methoxy-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A12)



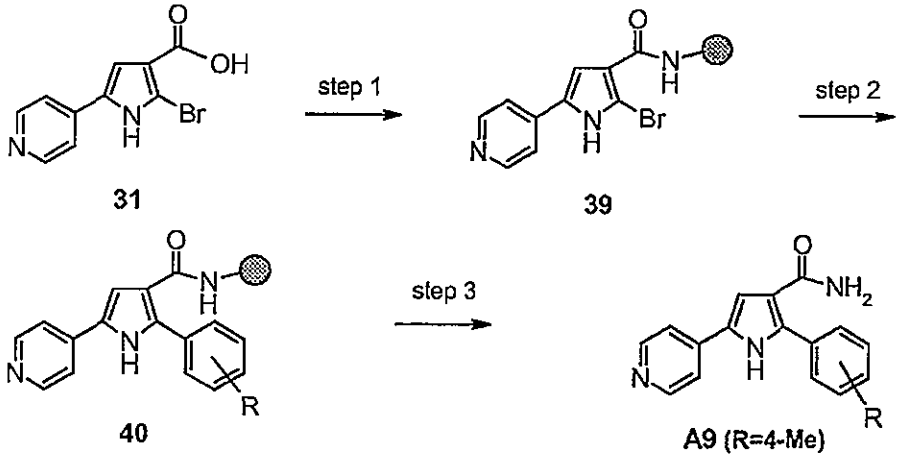
To ester **30** (40 mg, 0.135 mmol), dissolved in deoxygenated EtOH/toluene 1:1 (2 mL), 4-methoxy phenyl boronic acid (31 mg, 0.2 mmol), LiCl (17 mg, 0.4 mmol), deoxygenated 1M aq Na_2CO_3 (340 µL, 0.34 mmol) and $(Ph_3P)_2PdCl_2$ (1 mg) were added and the reaction mixture was stirred at reflux until disappearance of the starting material (2.5 h). The solvent was evaporated, water was added and the slurry was extracted with DCM and washed with water. The organic layers were dried (Na_2SO_4) and the crude was purified by flash chromatography (DCM/MeOH 95:5) to afford 28 mg (70%) of 2-(4-methoxy-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid ethyl ester **38** as a solid.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.20 (t, *J*=7.00 Hz, 3H), 3.82 (s, 3H), 4.10 (q, *J*=7.00 Hz, 2H), 7.10 (d, *J*=8.80 Hz, 2H), 7.70 (d, *J*=8.80 Hz, 2H), 7.68 (s, 1H), 8.25 (d, *J*=6.40 Hz, 2H), 8.70 (d, *J*=6.40 Hz, 2H), 12.30 (s, 1H); ESI (+) MS: m/z 323 (MH^+).

Ester **38** can be transformed in amide **A12** as already described in Example 1.

Example 65

5-pyridin-4-yl-2-p-tolyl-1H-pyrrole-3-carboxylic acid amide (A9)



Step 1: Condensation to amide (39)

Acid **31** (500 mg, 1.87 mmol) was loaded on Rink Amide MBHA resin (1.38 g, 0.935 mmol, theoretical loading 0.68mmol/g) by stirring with DIEA (0.65 mL, 3.74 mmol), EDCI (537 mg, 2.8 mmol) and HOBT (379 mg, 2.8 mmol) in 20 mL of DMF at rt overnight. The substitution rate was 78% and the resin had been previously cleaved with 20% piperidine in DMF.

Step 2: Suzuki coupling to amides (40)

The supported amide **39** (100 mg, 0.052 mmol) was heated at 100°C overnight with 4-methylphenylboronic acid (35 mg, 0.26 mmol), LiCl (9 mg, 0.208 mmol), Cs_2CO_3 (85 mg, 0.26 mmol) and $(PhP_3)_2PdCl_2$ (7.0 mg, 0.01 mmol) in 2 mL of deoxygenated DMF and 0.1 mL of deoxygenated water.

Step 3: Cleavage to amides (A9)

Amide **40** was cleaved with TFA/DCM 95:5. The solution was concentrated and the crude was purified by preparative HPLC to afford 5-pyridin-4-yl-2-p-tolyl-1H-pyrrole-3-carboxylic acid amide as a solid (yield: 54%).

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.37 (s, 3H), 7.00 (bs, 2H), 7.25 (d, *J*=8.00 Hz, 2H), 7.34 (d, *J*=2.56 Hz, 1H), 7.58 (d, *J*=8.00 Hz, 2H), 7.79 (d, *J*=6.22 Hz, 2H), 8.56 (d, *J*=6.22 Hz, 2H), 11.85 (s, 1H); ESI (+) MS: m/z 278 (MH^+).

The above procedure was employed to synthesize the following compounds.

Example 66

2-(3-Methoxy-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A11)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 3.83 (s, 3H), 6.66 (bs, 2H), 7.28 (m, 3H), 7.40 (m, 2H), 8.24 (d, *J*=6.82 Hz, 2H), 9.11 (d, *J*=6.82 Hz, 2H), 12.32 (s, 1H); ESI (+) MS: m/z 294 (MH^+).

Example 67

2-(2-Nitro-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A13)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.96 (bs, 2H), 7.37 (s, 1H), 7.58-7.65 (m, 4H), 7.79 (m, 1H), 8.07 (dd, *J*=1.22, 8.17 Hz, 1H), 8.55 (d, *J*=6.22 Hz, 2H), 12.19 (s, 1H); ESI (+) MS: m/z 309 (MH^+).

Example 68

2-(3-Nitro-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A14)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 7.30 (bs, 2H), 7.35 (d, *J*=2.69 Hz, 1H), 7.76 (m, 3H), 8.15 (m, 1H), 8.22 (m, 1H), 8.58 (dd, *J*=1.58, 4.63 Hz, 2H), 8.61 (t, *J*=1.81 Hz, 1H), 12.07 (s, 1H); ESI (+) MS: m/z 309 (MH^+).

Example 69

5-Pyridin-4-yl-2-o-tolyl-1H-pyrrole-3-carboxylic acid amide (A7)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.19 (s, 3H), 6.78 (bs, 2H), 7.25-7.38 (m, 5H), 7.64 (d, *J*=5.90 Hz, 2H), 8.50 (d, *J*=5.90 Hz, 2H), 11.90 (s, 1H); ESI (+) MS: m/z 278 (MH^+).

Example 70

5-Pyridin-4-yl-2-m-tolyl-1H-pyrrole-3-carboxylic acid amide (A8)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.20 (s, 3H), 6.90 (bs, 2H), 7.20-7.40 (m, 5H), 7.70 (d, *J*=6.00 Hz, 2H), 8.55 (d, *J*=6.00 Hz, 2H), 11.88 (s, 1H); ESI (+) MS: m/z 278 (MH^+).

Example 71

2-Furan-3-yl-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (C2)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 7.17 (s, 1H), 7.30 (bs, 2H), 7.64 (s, 1H), 7.77 (s, 1H), 8.03 (d, *J*=6.30 Hz, 2H), 8.52 (s, 1H), 8.69 (d, *J*=6.30 Hz, 2H), 11.88 (s, 1H); ESI (+) MS: m/z 254 (MH^+).

Example 72

5-Pyridin-4-yl-2-thiophen-3-yl-1H-pyrrole-3-carboxylic acid amide (C1)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 7.30 (bs, 2H), 7.57 (d, *J*=2.56 Hz, 1H), 7.62 (m, 2H), 8.03 (d, *J*=6.50 Hz, 2H), 8.14 (m, 1H), 8.66 (d, *J*=6.50 Hz, 2H), 12.01 (s, 1H); ESI (+) MS: m/z 270 (MH^+).

Example 73

2-(2,5-Dimethyl-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A19)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.12 (s, 3H), 2.31 (s, 3H), 6.72 (bs, 2H), 7.13 (m, 2H), 7.29 (d, *J*=2.81 Hz, 1H), 7.62 (dd, *J*=1.58, 4.63 Hz, 2H), 8.48 (dd, *J*=1.58, 4.63 Hz, 2H), 11.86 (s, 1H); ESI (+) MS: m/z 292 (MH^+).

Example 74

2-(2,3-Dimethyl-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A20)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.06 (s, 3H), 2.31 (s, 3H), 6.65 (bs, 2H), 7.16-7.32 (m, 4H), 7.63 (d, *J*=5.40 Hz, 2H), 8.49 (d, *J*=5.40 Hz, 2H), 11.88 (s, 1H); ESI (+) MS: m/z 292 (MH^+).

Example 75

2-(3,4-Dimethyl-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A21)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.28 (s, 3H), 2.55 (s, 3H), 7.20 (m, 1H), 7.22 (d, *J*=2.81 Hz, 1H), 7.38 (m, 1H), 7.43 (s, 1H), 7.69 (d, *J*=5.85 Hz, 2H), 8.51 (m, 2H), 11.72 (s, 1H); ESI (+) MS: m/z 292 (MH^+).

Example 76

2-(3-Acetylamino-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A18)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.06 (s, 3H), 6.99 (bs, 2H), 7.28 (m, 1H), 7.36 (m, 1H), 7.57 (d, *J*=2.44 Hz, 1H), 7.65 (d, *J*=8.17 Hz, 1H), 7.79 (s, 1H), 8.03 (d, *J*=6.20 Hz, 2H), 8.66 (d, *J*=6.20 Hz, 2H), 10.05 (s, 1H), 12.21 (s, 1H); ESI (+) MS: m/z 321 (MH^+).

Example 77

2-(2-Cyano-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A22)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.88 (bs, 2H), 7.39 (s, 1H), 7.59 (m, 1H), 7.64 (m, 3H), 7.75 (t, *J*=7.19 Hz, 1H), 7.88 (d, *J*=7.08 Hz, 1H), 8.56 (d, *J*=4.75 Hz, 2H), 12.21 (s, 1H); ESI (+) MS: m/z 289 (MH^+).

Example 78

2-(3-Cyano-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A23)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.99 (bs, 2H), 7.32 (d, *J*=2.56 Hz, 1H), 7.64 (t, *J*=7.56 Hz, 1H), 7.69 (d, *J*=6.10 Hz, 2H), 7.82 (m, 2H), 8.03 (m, 2H), 8.14 (m, 1H), 8.56 (d, *J*=6.10 Hz, 2H), 11.95 (s, 1H); ESI (+) MS: m/z 289 (MH^+).

Example 79

2-(3-Acetyl-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A16)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.64 (s, 3H), 6.94 (bs, 2H), 7.31 (d, *J*=2.68 Hz, 1H), 7.57 (t, *J*=7.80 Hz, 1H), 7.70 (dd, *J*=1.59, 4.64 Hz, 2H), 7.93 (m, 2H), 8.28 (t, *J*=1.71 Hz, 1H), 8.54 (m, 2H), 11.94 (s, 1H); ESI (+) MS: m/z 306 (MH^+).

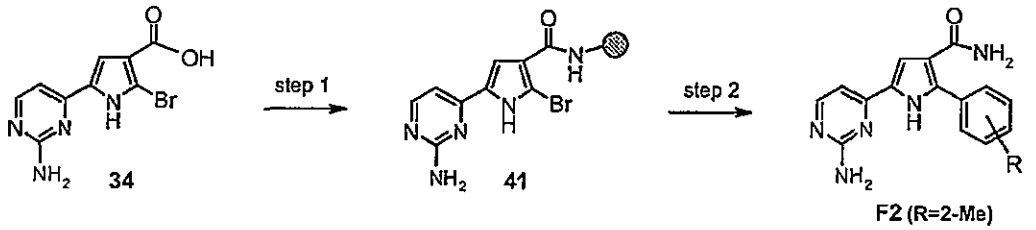
Example 80

2-(3-Hydroxymethyl-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A17)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 4.57 (s, 2H), 5.25 (s, 1H), 6.90 (bs, 2H), 7.29 (d, *J*=2.68 Hz, 1H), 7.36 (m, 2H), 7.52 (m, 1H), 7.58 (s, 1H), 7.74 (d, *J*=5.90 Hz, 2H), 8.53 (d, *J*=5.90 Hz, 2H), 11.86 (s, 1H); ESI (+) MS: m/z 294 (MH^+).

Example 81

5-(2-Amino-pyrimidin-4-yl)-2-o-tolyl-1H-pyrrole-3-carboxylic acid amide (F2)



F2 (R=2-Me)

Step 1: Condensation to amide (41)

Acid **34** (20 mg, 0.07 mmol) was loaded on Rink Amide MBHA resin (52 mg, 0.035 mmol, theoretical loading 0.68 mmol/g) by stirring with DIEA (24 μL, 0.14 mmol), EDCI (20 mg, 0.105 mmol) and HOBT (14 mg, 0.105 mmol) in 1.5 mL of DMF overnight at rt. The resin had been previously cleaved with 20% piperidine in DMF.

Step 2: Suzuki coupling and cleavage to amides (F2)

Supported amide **41** (0.035 mmol), 2-methylphenylboronic acid (24 mg, 0.175 mmol), LiCl (6 mg, 0.14 mmol), Cs_2CO_3 (57 mg, 0.175 mmol) and $(PhP_3)_2PdCl_2$ (5.0 mg, 0.07 mmol) in 1 mL of DMF and 50 μL H_2O were heated at 100°C overnight. The product supported on the resin was cleaved with TFA/DCM 95:5. The solution was concentrated and the crude was purified by preparative HPLC to afford 5-(2-amino-pyrimidin-4-yl)-2-o-tolyl-1H-pyrrole-3-carboxylic acid amide as a solid.

The above procedure was employed to synthesize the following compounds.

Example 82

5-(2-Amino-pyrimidin-4-yl)-2-(2-ethyl-phenyl)-1H-pyrrole-3-carboxylic acid amide (F3)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 0.99 (t, *J*=7.56 Hz, 3H), 2.50 (m, 2H), 6.30 (bs, 2H), 6.67 (bs, 2H), 6.93 (d, *J*=5.24 Hz, 1H), 7.23 (m, 2H), 7.30-7.40 (m, 3H), 8.15 (d, *J*=5.24 Hz, 1H), 11.77 (bs, 1H); ESI (+) MS: m/z 308 (MH^+).

Example 83

5-(2-Amino-pyrimidin-4-yl)-2-(2-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (F4)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.92 (bs, 2H), 7.27 (m, 3H), 7.45-7.54 (m, 2H), 7.62 (bs, 1H), 7.84 (bs, 2H), 8.28 (d, *J*=6.58 Hz, 1H), 12.41 (bs, 1H); ESI (+) MS: m/z 298 (MH^+).

Example 84

5-(2-Amino-pyrimidin-4-yl)-2-naphthalen-1-yl-1H-pyrrole-3-carboxylic acid amide (F5)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.33 (bs, 2H), 6.65 (bs, 2H), 6.96 (d, *J*=5.27 Hz, 1H), 7.40-7.60 (m, 5H), 7.98 (m, 2H), 8.17 (d, *J*=5.27 Hz, 1H), 11.95 (bs, 1H); ESI (+) MS: m/z 330 (MH^+).

Example 85

5-(2-Amino-pyrimidin-4-yl)-2-naphthalen-2-yl-1H-pyrrole-3-carboxylic acid amide (F6)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.37 (bs, 2H), 6.87 (bs, 1H), 7.05 (d, *J*=5.24 Hz, 1H), 7.32 (d, *J*=2.32 Hz, 1H), 7.39 (bs, 1H), 7.51-7.59 (m, 2H), 7.78 (dd, *J*=8.41, 1.71 Hz, 1H), 7.88-7.97 (m, 3H), 8.16 (d, *J*=1.22 Hz, 1H), 8.23 (d, *J*=5.24 Hz, 1H), 11.80 (bs, 1H); ESI (+) MS: m/z 330 (MH^+).

Example 86

5-(2-Amino-pyrimidin-4-yl)-2-(4-phenoxy-phenyl)-1H-pyrrole-3-carboxylic acid amide (F7)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.35 (bs, 2H), 6.81 (bs, 1H), 6.98-7.11 (m, 5H), 7.15-7.21 (m, 1H), 7.27 (d, *J*=2.19 Hz, 1H), 7.34 (bs, 1H), 7.40-7.46 (m, 2H), 7.67 (d, *J*=8.90 Hz, 2H), 8.20 (d, *J*=5.24 Hz, 1H), 11.62 (bs, 1H); ESI (+) MS: m/z 372 (MH^+).

Example 87

5-(2-Amino-pyrimidin-4-yl)-2-biphenyl-4-yl-1H-pyrrole-3-carboxylic acid amide (F8)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.35 (bs, 2H), 6.85 (bs, 1H), 6.90-7.15 (m, 5H), 7.15-7.25 (m, 2H), 7.34 (bs, 1H), 7.40-7.45 (m, 2H), 7.70 (d, *J*=8.90 Hz, 2H), 8.18 (d, *J*=5.24 Hz, 1H), 11.73 (bs, 1H); ESI (+) MS: m/z 356 (MH^+).

Example 88

5-(2-Amino-pyrimidin-4-yl)-2-biphenyl-3-yl-1H-pyrrole-3-carboxylic acid amide (F9)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.89 (bs, 2H), 7.02 (d, *J*=5.24 Hz, 1H), 7.30 (d, *J*=2.44 Hz, 1H), 7.34-7.43 (m, 2H), 7.46-7.53 (m, 4H), 7.61-7.68 (m, 2H), 7.74 (d, *J*=8.41 Hz, 2H), 7.96 (t, *J*=1.70 Hz, 1H), 8.21 (d, *J*=5.24 Hz, 1H), 11.78 (bs, 1H); ESI (+) MS: m/z 356 (MH^+).

Example 89

5-(2-Amino-pyrimidin-4-yl)-2-biphenyl-2-yl-1H-pyrrole-3-carboxylic acid amide (F10)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.33 (bs, 2H), 6.90 (bs, 1H), 7.03 (d, *J*=5.24 Hz, 1H), 7.28 (d, *J*=2.44 Hz, 1H), 7.34-7.56 (m, 6H), 7.56-7.79 (m, 4H), 8.20 (d, *J*=5.24 Hz, 1H), 11.78 (bs, 1H); ESI (+) MS: m/z 356 (MH^+).

Example 90

5-(2-Amino-pyrimidin-4-yl)-2-(2-methoxy-phenyl)-1H-pyrrole-3-carboxylic acid amide (F11)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 3.75 (s, 3H), 6.34 (bs, 2H), 6.69 (bs, 1H), 6.88-7.04 (m, 3H), 7.08 (d, *J*=6.10 Hz, 1H), 7.23 (d, *J*=2.56 Hz, 1H), 7.32-7-41 (m, 2H), 8.16 (d, *J*=5.37 Hz, 1H), 11.50 (bs, 1H); ESI (+) MS: m/z 310 (MH^+).

Example 91

5-(2-Amino-pyrimidin-4-yl)-2-benzo[1,3]dioxol-5-yl-1H-pyrrole-3-carboxylic acid amide (F12)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.06 (s, 2H), 6.35 (bs, 2H), 6.82 (bs, 1H), 6.97 (d, *J*=8.05 Hz, 1H), 7.01 (d, *J*=5.24 Hz, 1H), 7.16 (dd, *J*=8.05, 1.34 Hz, 1H), 7.23-7.25 (m, 3H), 8.20 (d, *J*=5.24 Hz, 1H), 11.52 (bs, 1H); ESI (+) MS: m/z 324 (MH^+).

Example 92

5-(2-Amino-pyrimidin-4-yl)-2-(5-chloro-thiophen-2-yl)-1H-pyrrole-3-carboxylic acid amide (G4)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.40 (bs, 2H), 6.98 (bs, 1H), 7.03 (d, *J*=5.24 Hz, 1H), 7.11 (d, *J*=3.20 Hz, 1H), 7.32 (s, 1H), 7.59 (bs, 1H), 7.63 (d, *J*=3.20 Hz, 1H), 8.23 (d, *J*=5.24 Hz, 1H), 11.70 (bs, 1H); ESI (+) MS: m/z 320 (MH^+).

Example 93

5-(2-Amino-pyrimidin-4-yl)-2-benzo[b]thiophen-2-yl-1H-pyrrole-3-carboxylic acid amide (G5)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.42 (bs, 2H), 6.99 (bs, 1H), 7.08 (d, *J*=5.12 Hz, 1H), 7.32 (s, 1H), 7.33-7.41 (m, 2H), 7.56 (bs, 1H), 7.84 (bs, 1H), 7.91-8.03 (m, 2H), 8.25 (d, *J*=5.12 Hz, 1H), 11.82 (bs, 1H); ESI (+) MS: m/z 336 (MH^+).

Example 94

5-(2-Amino-pyrimidin-4-yl)-2-benzo[b]thiophen-3-yl-1H-pyrrole-3-carboxylic acid amide (G6)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.35 (bs, 2H), 6.76 (bs, 1H), 6.99 (d, *J*=5.24 Hz, 1H), 7.20 (s, 1H), 7.35-7.42 (m, 3H), 7.51-7.57 (m, 1H), 7.90 (s, 1H), 8.00-8.06 (m, 1H), 8.20 (d, *J*=5.24 Hz, 1H), 11.91 (bs, 1H); ESI (+) MS: m/z 336 (MH^+).

Example 95

5-(2-Amino-pyrimidin-4-yl)-2-benzofuran-2-yl-1H-pyrrole-3-carboxylic acid amide (G9)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.53 (bs, 2H), 7.07 (bs, 1H), 7.11 (d, *J*=5.12 Hz, 1H), 7.27 (td, *J*= 7.56, 0.98 Hz, 1H), 7.34 (td, *J*= 7.56, 0.98 Hz, 1H), 7.42 (s, 1H), 7.61 (dd, *J*=7.56, 0.98 Hz, 1H), 7.65 (bs, 1H), 7.70 (dd, *J*=7.56, 0.98 Hz, 1H), 7.87 (d, *J*=0.98 Hz, 1H), 8.26 (d, *J*=5.12 Hz, 1H), 11.61 (bs, 1H); ESI (+) MS: m/z 320 (MH^+).

Example 96

5-(2-Amino-pyrimidin-4-yl)-2-dibenzofuran-1-yl-1H-pyrrole-3-carboxylic acid amide (G10)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.52 (bs, 2H), 6.82 (bs, 1H), 7.03 (d, *J*=5.38 Hz, 1H), 7.36 (bs, 1H), 7.38-7.56 (m, 3H), 7.64-7.73 (m, 2H), 8.16 (dd, *J*=7.68, 1.22 Hz, 1H), 8.19 (d, *J*=7.68 Hz, 1H), 8.24 (d, *J*=5.38 Hz, 1H), 12.00 (bs, 1H); ESI (+) MS: m/z 370 (MH^+).

Example 97

5-(2-Amino-pyrimidin-4-yl)-2-pyridin-3-yl-1H-pyrrole-3-carboxylic acid amide (G11)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.63 (bs, 2H), 7.23 (d, *J*=5.24 Hz, 1H), 7.15 (bs, 1H), 7.32-7.38 (m, 1H), 7.66 (s, 1H), 7.85-7.91 (m, 1H), 8.20 (d, *J*=5.24 Hz, 1H), 8.28 (bs, 1H), 8.60-8.66 (m, 1H), 8.77-8.86 (m, 1H), 11.37 (s, 1H); ESI (+) MS: m/z 281 (MH^+).

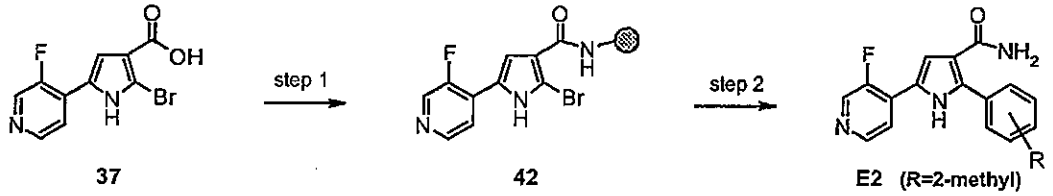
Example 98

5-(2-Amino-pyrimidin-4-yl)-2-pyridin-2-yl-1H-pyrrole-3-carboxylic acid amide (G12)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.62 (bs, 2H), 7.03 (d, *J*=5.12 Hz, 1H), 7.16 (bs, 1H), 7.33-7.40 (m, 2H) 7.86-7.93 (m, 1H), 8.25 (d, *J*=5.12 Hz, 1H), 8.28 (bs, 1H), 8.43 (d, *J*=8.17 Hz, 1H), 8.62-8.67 (m, 1H), 11.29 (s, 1H); ESI (+) MS: m/z 281 (MH^+).

Example 99

5-(3-Fluoro-pyridin-4-yl)-2-o-tolyl-1H-pyrrole-3-carboxylic acid amide (E2)



37 42 E2 (R=2-methyl)

Step 1: Condensation to amide (42)

Acid **37** (50 mg, 0.175 mmol) was loaded on Rink Amide MBHA resin (128 mg, 0.087 mmol, theoretical loading 0.68 mmol/g) using DIEA (61 µL, 0.35 mmol), EDCI (50 mg, 0.26 mmol), HOBT (35 mg, 0.26 mmol) in 2.5 mL of DMF. The reaction mixture was stirred overnight at rt. The resin had been first cleaved with 20% piperidine in DMF.

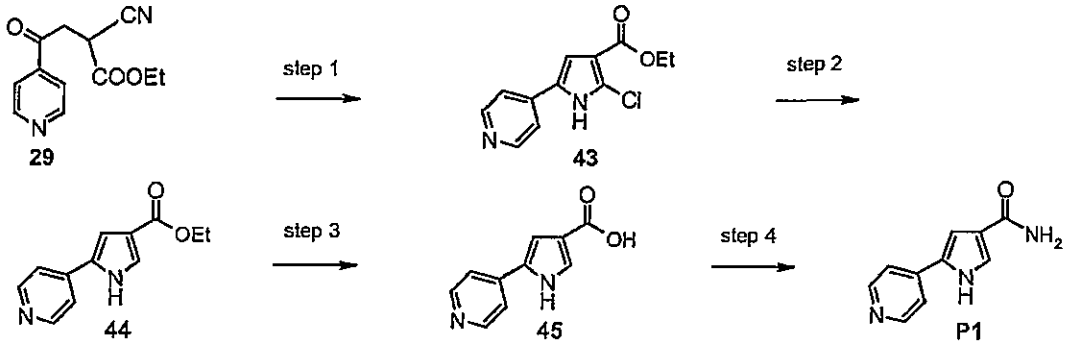
Step 2: Suzuki coupling and cleavage to amides (E2)

Supported amide **42** (0.087 mmol), 2-methylphenylboronic acid (60 mg, 0.44 mmol), LiCl (15 mg, 0.35 mmol), Cs_2CO_3 (142 mg, 0.435 mmol) and $(PhP_3)_2PdCl_2$ (12 mg, 0.0175 mmol) in 1.5 mL of DMF and 75 µL of H_2O were heated at 100°C overnight. The product supported on the resin was cleaved with TFA/DCM 95:5. The solution was concentrated and the crude material was purified by preparative HPLC to afford 5-(3-fluoro-pyridin-4-yl)-2-o-tolyl-1H-pyrrole-3-carboxylic acid amide as a white solid.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.16 (s, 3H), 6.86 (bs, 2H), 7.23 (bs, 1H), 7.18-7.38 (m, 4H), 7.91-7.98 (m, 1H), 8.39 (d, *J*=5.12 Hz, 1H), 8.56 (d, *J*=3.41 Hz, 1H), 11.95 (bs, 1H); ESI (+) MS: m/z 296 (MH^+).

Example 100

5-Pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (P1)



Step 1: Formation of pyrrole ring (43)

To a solution of cianoester **29** (550 mg, 2.37 mmol) in Et_2O (1 mL) at 0°C, 4N HCl in dioxane (6 mL, 23.7 mmol) was added dropwise. The reaction mixture was left for 10 min at 0 °C and then stirring was continued at rt for 6 h. The solid was filtered and washed with Et_2O to yield 500 mg (84%) of 2-chloro-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid ethyl ester as a yellow solid. The product was used without further purification.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.34 (t, *J*=7.07 Hz, 3H), 4.27 (q, *J*=7.07 Hz, 2H), 7.73 (s, 1H), 8.25 (d, *J*=5.61 Hz, 2H), 8.78 (m, 2H); ESI (+) MS: m/z 251 (MH^+).

Step 2: Dehalogenation to ester (44)

A mixture of ester **43** (630 mg, 2.2 mmol) in 30 mL of MeOH, $HCOONH_4$ (1.26 g, 19.8 mmol) and 10% Pd/C (630 mg) was stirred at rt under argon until disappearance of the starting material. The catalyst was removed by filtration through celite and the filtrate concentrated. Saturated aq $NaHCO_3$ was added and the slurry was extracted with EtOAc affording 300 mg (63%) of 5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid ethyl ester as a solid.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.30 (t, *J*=7.07 Hz, 3H), 4.24 (q, *J*=7.07 Hz, 2H), 7.20 (m, 1H), 7.63 (m, 1H), 7.68 (dd, *J*=1.50, 4.60 Hz, 2H), 7.20 (m, 1H), 7.63 (m,

1H), 7.68 (dd, *J*=1.50, 4.60 Hz, 2H), 8.52 (dd, *J*=1.50, 4.60 Hz, 2H), 12.27 (s, 1H); ESI (+) MS: m/z 217 (MH^+).

Step 3: Saponification to acid (45)

Ester **44** (200 mg, 0.92 mol) in 4M aq NaOH (4.6 mL) and EtOH (4 mL) was heated at 100 °C for 1 h. The reaction mixture was cooled to 0°C and the product was precipitated by adding conc HCl. The solid was filtered to obtain 160 mg (78%) of 5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid as a white solid.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 7.60 (s, 1H), 7.81 (m, 1H), 8.14 (d, *J*=5.49 Hz, 2H), 8.72 (m, 2H), 12.70 (s, 1H); MS: m/z 187 [M-H].

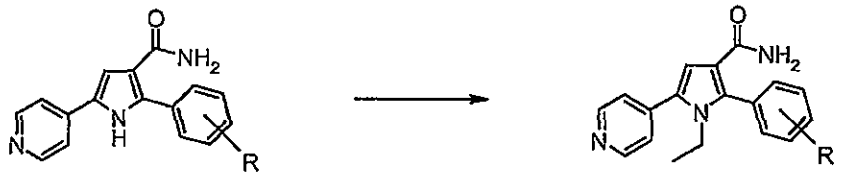
Step 4: Condensation to amide (P1)

To a solution of acid **45** (137 mg, 0.61 mmol) in DIEA (213 µL, 1.22 mmol) and anhydrous THF (8 mL), cooled at 0°C, EDCI (175 mg, 0.09 mmol) and HOBT·NH_3 (137 mg, 0.9 mmol) were added and the solution was stirred overnight at rt. The solution was concentrated, water was added and the product was extracted with DCM. The organic layer was washed with water, dried and concentrated to give a solid that was triturated with Et_2O to afford 50 mg (44%) of 5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.98 (bs, 2H) 7.61 (bs, 1H) 7.79-7.82 (m, 1H) 8.06 (d, *J*=6.58 Hz, 2H) 8.71 (d, *J*=6.83 Hz, 2H) 12.57 (s, 1H); ESI (+) MS: m/z 188 (MH^+).

Example 101

1-Ethyl-2-phenyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (D1)



A1 **D1 (R=H)**

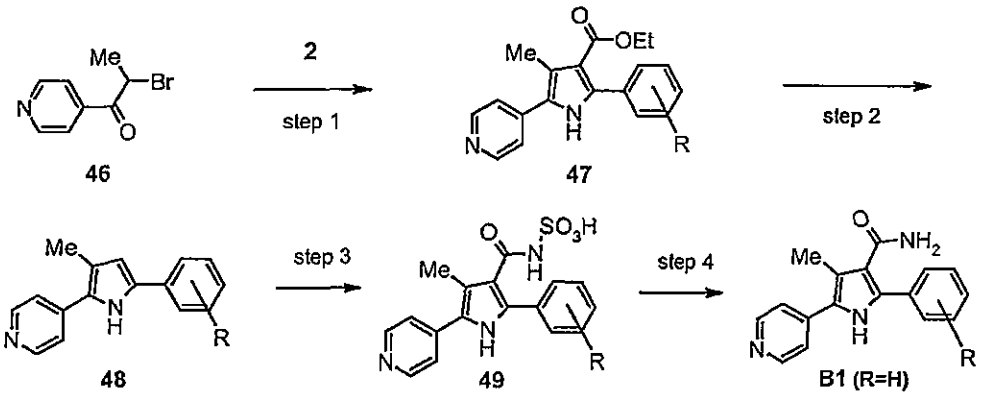
To a solution of amide **A1** (R=H, 31 mg, 0.118 mmol) in DMF (0.5 mL), Cs_2CO_3 (100 mg, 0.235 mmol) and EtI (19 µL, 0.235 mmol) were added. The mixture was treated with microwaves at 60°C for 15 min ("cooling while heating" technique) then the solvent was removed. To the residue EtOAc and water were added, the layers were separated, the aqueous layer was extracted with EtOAc and the combined organic layers

were washed with water, dried (Na_2SO_4), filtered and concentrated. The crude material was purified by flash chromatography (DCM/MeOH 95:5), affording the title compound. This was suspended in MeOH and acidified to pH 1 with 1.25M HCl in MeOH. After solvent removal the residue was treated with Et_2O, the resulting solid was filtered, washed with Et_2O and dried, affording the hydrochloric salt of 1-ethyl-2-phenyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (9 mg, 26% yield).

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 0.88 (t, *J*=7.13 Hz, 3H) 4.02 (q, *J*=7.11 Hz, 2H) 6.86 (s, 2H) 7.29 (s, 1H) 7.39-7.58 (m, 5H) 7.95 (d, *J*=6.58 Hz, 2H) 8.80 (d, *J*=6.71 Hz, 2H); ESI (+) MS: m/z 292 (MH^+).

Example 102

4-Methyl-2-phenyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (B1)



Step 1: Formation of pyrrole ring (47)

2-Bromo-1-pyridin-4-yl-propan-1-one hydrobromide **46** (0.6 g, 2 mmol) was added to a mixture of 3-oxo-3-phenyl-propionic acid ethyl ester **2** (R=H, 0.3 g, 1.56 mmol) in 300 mL of dry THF and NaH (0.18 g) at 0 °C. The solution was left at 0°C for 1 h and then stirred at 50°C for 4 h. The solvent was removed and the residue was dissolved in 20 mL of EtOH, ammonium acetate (0.7 g, 9.3 mmol) was added and the reaction mixture was left overnight at rt. The reaction mixture was concentrated, water was added and the slurry extracted with EtOAc. The combined organic layers were washed with water, dried (Na_2SO_4), filtered and concentrated. The crude was purified by flash chromatography (DCM/MeOH 95:5) affording 170 mg (36%) of 4-methyl-2-phenyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid ethyl ester as a solid.

^{1}H NMR (DMSO-d_6 / 300 MHz) δ ppm 1.08 (t, *J*=7.03 Hz, 3H) 2.41 (s, 3H) 4.08 (q, *J*=7.03 Hz, 2H) 7.21-7.71 (m, 7H) 8.58 (dd, *J*=4.69, 1.76 Hz, 2H) 11.77 (s, 1H); ESI (+) MS: m/z 307 (MH^+).

Step 2: Decarboxylation to pyrrole (48)

Ester **47** (0.17 g, 0.56 mmol), dissolved in 1.5 mL of EtOH and 2.2 mL of 4M aq NaOH, was heated at 100 °C until decarboxylation was complete (5 h). The reaction mixture was concentrated, water was added and the slurry extracted with EtOAc. The combined organic layers were washed with water, dried (Na_2SO_4), filtered and concentrated to yield 4-(3-methyl-5-phenyl-1H-pyrrol-2-yl)-pyridine as a white solid (92 mg, 70%).

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 2.30 (s, 3H) 6.52-6.54 (m, 1H) 7.18-7.26 (m, 1H) 7.35-7.43 (m, 2H) 7.58 (dd, *J*=4.69, 1.76 Hz, 2H) 7.73-7.79 (m, 2H) 8.53 (dd, *J*=4.69, 1.47 Hz , 2H) 11.21 (s, 1H); ESI (+) MS: m/z 235 (MH^+).

Step 3: Formation of sulfamic acid (49)

To pyrrole **48** (90 mg, 0.39 mmol), dissolved in CH_3CN (3 mL), $ClSO_2NCO$ was added and the reaction mixture was stirred at rt until disappearance of starting material. Water was added and pH was adjusted to 8 with 10% aq KOH. After extraction with EtOAc (x 2) and concentration under reduced pressure of the aqueous solution, the precipitate was filtered, washed with little water and dried. Obtained (4-methyl-2-phenyl-5-pyridin-4-yl-1H-pyrrole-3-carbonyl)-sulfamic acid as a white solid (90% yield).

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.27 (s, 3H) 7.22-7.34 (m, 1H) 7.34-7.45 (m, 2H) 7.55 (dd, *J*=4.76, 1.59 Hz, 2H) 7.62-7.66 (m, 2H) 8.54 (dd, *J*=4.63, 1.46 Hz, 2H) 9.28 (s, 1H) 11.29 (s, 1H); MS: m/z 356 [M-H].

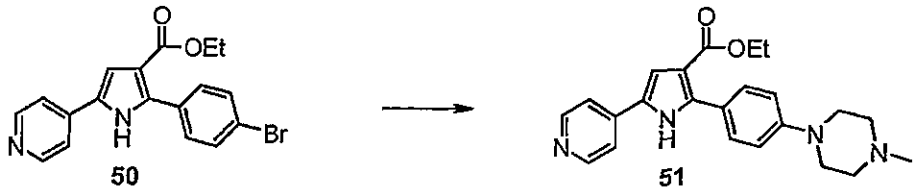
Step 4: Formation of amides (B1)

Acid **49** was hydrolized by dissolution in conc. HCl at rt. The acidic aqueous solution was basified with 2N NaOH and extracted with EtOAc (x 3). The crude product was purified by flash chromatography (DCM/MeOH 95:5, then 93:7) affording 4-methyl-2-phenyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide in 85% yield.

^{1}H NMR (DMSO-d_6 / 500 MHz) δ ppm 2.41 (s, 3H) 7.39 (t, *J*=7.48 Hz, 1H) 7.47 (t, *J*=7.48 Hz, 2H) 7.71 (d, *J*=7.32 Hz, 2H) 8.16 (d, *J*=7.02 Hz, 2H) 8.73 (d, *J*=7.02 Hz, 2H); ESI (+) MS: m/z 278 (MH^+).

Example 103

2-[4-(4-Methyl-piperazin-1-yl)-phenyl]-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid ethyl ester (51)



A mixture of ester **50** (30 mg, 0.08 mmol, obtained as described in Example 1), $Pd(OAc)_2$ (1 mg, 0.0045 mmol), (2-biphenylyl)dicyclohexylphosphine (3 mg, 0.008 mmol), ^tBuONa (16 mg, 0.17 mmol), 1-methylpiperazine (60 µL, 0.54 mmol), in toluene (1 mL) and anhydrous DMF (0.2 mL) was subdued to the action of microwaves at 130°C for 20 min. After filtration on celite and aqueous work-up (EtOAc/water) the crude 2-[4-(4-methyl-piperazin-1-yl)-phenyl]-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid ethyl ester was obtained.

^1H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.25 (t, *J*=7.07 Hz, 3H), 2.86 (bs, 3H), 3.11-3.54 (m, 8H), 4.20 (q, *J*=7.07 Hz, 2H), 7.12 (d, *J*=8.80 Hz, 2H), 7.64 (d, *J*=8.80 Hz, 2H), 7.78-7.82 (m, 1H), 8.34-8.41 (m, 2H), 8.75 (d, *J*=6.46 Hz, 2H), 12.49 (bs, 1H); ESI (+) MS: m/z 391 (MH^+).

Employing the above procedure and starting from the corresponding bromophenyl ester derivatives, obtained described in Example 1, the following compounds have been prepared:

2-(3-Morpholin-4-yl-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid ethyl ester (52)

^1H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.19 (t, *J*=7.07 Hz, 3H) 3.14-3.20 (m, 4H) 3.73-3.79 (m, 4H) 4.13 (q, *J*=7.07 Hz, 2H) 7.01 (dd, *J*=8.17, 2.19 Hz, 1H) 7.08 (d, *J*=7.68 Hz, 1H) 7.18 (t, *J*=1.70 Hz, 1H) 7.26 (d, *J*=2.80 Hz, 1H) 7.31 (t, *J*=7.93 Hz, 1H) 7.77 (dd, *J*=4.69, 1.52 Hz, 2H) 8.51 (d, *J*=5.85 Hz, 2H) 12.03 (bs, 1H); ESI (+) MS: m/z 306 (MH^+).

2-(4-Morpholin-4-yl-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid ethyl ester (53)

ESI (+) MS: m/z 306 (MH^+).

Using the procedure already described in Example 1 the above esters were respectively hydrolyzed to the following acids:

2-[4-(4-Methyl-piperazin-1-yl)-phenyl]-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid (54)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.83 (bs, 3H), 3.09-3.53 (m, 8H), 7.10 (d, *J*=8.80 Hz, 2H), 7.63 (d, *J*=8.80 Hz, 2H), 7.92 (s, 1H), 8.05-8.21 (m, 2H), 8.58-8.69 (m, 2H), 12.23 (bs, 1H); ESI (+) MS: m/z 361 [M-H].

2-(3-Morpholin-4-yl-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid (55)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 3.13-3.17 (m, 4H) 3.73-3.78 (m, 4H) 6.90 (dt, *J*=7.19, 2.13 Hz, 1H) 7.10 (s, 1H) 7.22 (s, 1H) 7.24 (s, 1H) 7.43 (s, 1H) 7.71 (dd, *J*=4.76, 1.59 Hz, 2H) 8.46 (d, *J*=6.22 Hz, 2H) 11.52 (bs, 1H); MS: m/z 348 [M-H].

2-(4-Morpholin-4-yl-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid (56)

MS: m/z 348 [M-H].

By the standard amidation method already described in Example 1, the above acids were respectively transformed into the following amides:

Example 104

2-[4-(4-Methyl-piperazin-1-yl)-phenyl]-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A24)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.82 (bs, 3H), 3.15-3.52 (m, 8H), 7.08 (d, *J*=8.80 Hz, 2H), 7.67 (d, *J*=8.80 Hz, 2H), 7.94 (s, 1H), 7.97-8.11 (m, 2H), 8.56-8.72 (m, 2H), 12.04 (bs, 1H); ESI (+) MS: m/z 362 (MH^+).

Example 105

2-(3-Morpholin-4-yl-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide hydrochloride (A25)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 3.14-3.21 (m, 4H) 3.74-3.79 (m, 4H) 7.04 (dd, *J*=8.23, 2.13 Hz, 1H) 7.15 (d, *J*=7.68 Hz, 1H) 7.31 (s, 1H) 7.33 (t, *J*=7.93 Hz, 1H) 7.71 (d, *J*=2.56 Hz, 1H) 8.23 (d, *J*=6.71 Hz, 2H) 8.73 (d, *J*=6.95 Hz, 2H) 12.34 (bs, 1H) 15.08 (bs, 1H); ESI (+) MS: m/z 349 (MH^+).

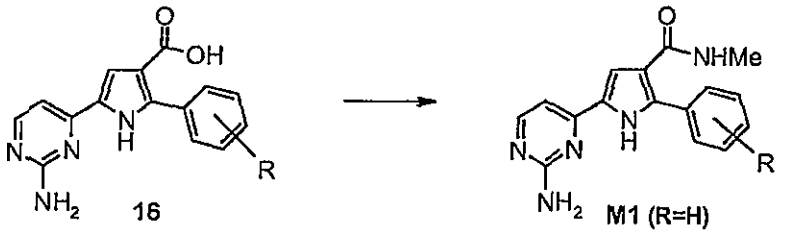
Example 106

2-(4-Morpholin-4-yl-phenyl)-5-pyridin-4-yl-1H-pyrrole-3-carboxylic acid amide (A26)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 3.15-3.20 (m, 4H), 3.73-3.79 (m, 4H), 6.82 (bs, 1H), 6.99 (d, *J*=8.80 Hz, 2H), 7.08 (bs, 1H), 7.23 (d, *J*=2.68 Hz, 1H), 7.56 (d, *J*=8.80 Hz, 2H), 7.68 (d, *J*=6.35 Hz, 2H), 8.49 (d, *J*=6.35 Hz, 2H), 11.63 (bs, 1H); ESI (+) MS: m/z 349 (MH^+).

Example 107

5-(2-Amino-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid methylamide (M1)



To a solution of acid **16** (R=H, 20 mg, 0.07 mmol) in anhydrous DMF, CDI (25 mg, 2 eq.) was added and the mixture stirred at 45°C for 1 h. After cooling to rt the solution was treated with 0.5 mL of 33% $MeNH_2$ in EtOH. The mixture was stirred overnight, filtered and the filtrate was poured into water. After extraction with EtOAc (x 2) the organic layer was concentrated, dissolved in EtOH and treated with excess 1.25M HCl in MeOH. Et_2O was added and the yellow crystalline solid was filtered, washed with Et_2O and recovered. Obtained 8 mg (37% yield) of 5-(2-amino-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid methylamide.

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.70 (d, *J*=4.63 Hz, 3H) 7.36 (d, *J*=6.58 Hz, 1H) 7.39-7.49 (m, 3H) 7.53 (d, *J*=2.44 Hz, 1H) 7.64-7.70 (m, 2H) 7.84 (bs, 3H) 8.02 (bq, *J*=4.51 Hz, 1H) 8.29 (d, *J*=6.46 Hz, 1H) 12.20 (bs, 1H); ESI (+) MS: m/z 294 (MH^+).

The above procedure was employed to synthesize the following compounds.

Example 108

5-(2-Amino-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid isopropylamide (M2)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 1.09 (t, *J*=6.58 Hz, 6H), 3.93-4.06 (m, 1H), 6.36 (bs, 2H), 7.04 (d, *J*=5.24 Hz, 1H), 7.23 (d, *J*=2.44 Hz, 1H), 7.30-7.43 (m, 3H), 7.59-7.67 (m, 3H), 8.21 (d, *J*=5.24 Hz, 1H), 11.61 (bs, 1H); ESI (+) MS: m/z 322 (MH^+).

Example 109

5-(2-Amino-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid benzylamide (M3)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 4.37 (d, *J*=6.10 Hz, 2H), 6.37 (bs, 2H), 7.05 (d, *J*=5.24 Hz, 1H), 7.18-7.44 (m, 9H), 7.64 (d, *J*=8.30 Hz, 2H), 8.21 (d, *J*=5.24 Hz, 1H), 8.48 (t, *J*=6.10 Hz, 1H), 11.70 (bs, 1H); ESI (+) MS: m/z 370 (MH^+).

Example 110

5-(2-Amino-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid cyclohexylmethyl-amide (M4)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 0.79-0.94 (m, 2H), 1.06-1.27(m, 4H), 1.40-4.52 (m, 1H), 1.57-1.74 (m, 4H), 2.99 (t, *J*=6.46 Hz, 2H), 6.36 (bs, 2H), 7.04 (d, *J*=5.24 Hz, 1H), 7.23 (d, *J*=2.44 Hz, 1H), 7.29-7.46 (m, 3H), 7.63 (d, *J*=8.15 Hz, 2H), 7.82 (t, *J*=5.85 Hz, 1H), 8.21 (d, *J*=5.24 Hz, 1H), 11.63 (bs, 1H); ESI (+) MS: m/z 376 (MH^+).

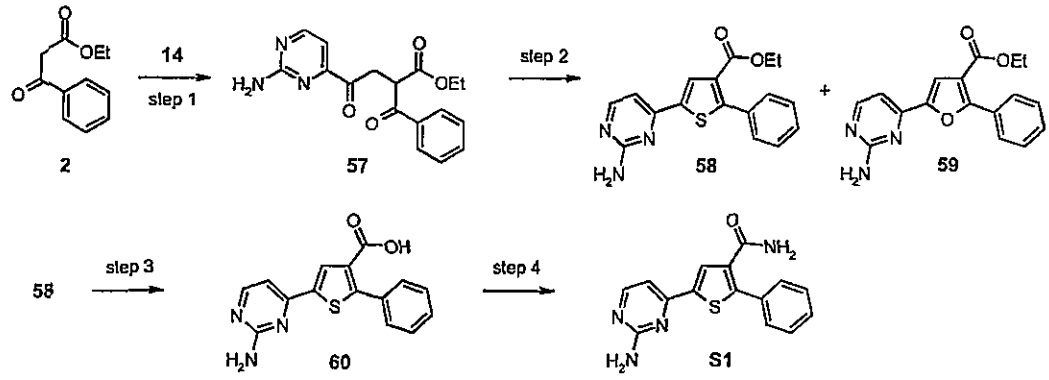
Example 111

5-(2-Amino-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid phenethyl-amide (M5)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 2.80 (t, *J*=7.35 Hz, 2H), 3.42 (q, *J*=7.35 Hz, 2H), 6.37 (bs, 2H), 7.03 (d, *J*=5.24 Hz, 1H), 7.18-7.42 (m, 9H), 7.60 (d, *J*=8.30 Hz, 2H), 7.98 (t, *J*=7.35 Hz, 1H), 8.21 (d, *J*=5.24 Hz, 1H), 11.65 (bs, 1H); ESI (+) MS: m/z 384 (MH^+).

Example 112

Synthesis of 5-(2-amino-pyrimidin-4-yl)-2-phenyl-thiophene-3-carboxylic acid amide (S1)



Step 1: ketoester alkylation (57)

To a stirred solution of 3-oxo-3-phenyl-propionic acid ethylester **2** (2 g, 10 mmol) and NaH (1 g, 2.5 eq, 25 mmol) in dry THF (200 mL) at 0°C, 1-(2-amino-pyrimidin-4-yl)-2-bromo-ethanone **14** (3.56 g, 1.2 eq, 12 mmol) was added. The reaction mixture was stirred at 0°C for 30 min, then more **14** (0.5 eq, 1.48 g) was added and the reaction mixture was stirred at rt overnight. After solvent removal, the residue was diluted in DCM and washed with brine, dried (Na_2SO_4) and the solvent removed under reduced pressure to give 4-(2-amino-pyrimidin-4-yl)-2-benzoyl-4-oxo-butyric acid ethyl ester (3.27 g, 97%). ESI (+) MS: m/z 328 (MH^+).

Step 2: ring formation (58 + 59)

A mixture of ester **57** (3.27 g, 10 mmol) and Lawesson's reagent (2.43 g, 0.66 eq, 6 mmol) in toluene (100 mL) were refluxed under N_2 for 4 h. After solvent removal, the residue was taken up in DCM, filtered and eluted through the Horizon system (hexane/EtOAc 9:1, then DCM/MeOH 98:2). The mixture of thiophene and furan derivatives was then passed through the Horizon system again (DCM/MeOH 99:1) to give a first fraction of the thiophene derivative **58** (250 mg) and a second fraction of the furan derivative **59** (236 mg) as yellow solids.

5-(2-Amino-pyrimidin-4-yl)-2-phenyl-thiophene-3-carboxylic acid ethyl ester (58)

^1H NMR (DMSO-d_6 / 400 MHz) δ ppm: 1.14 (t, 3H), 4.16 (q, 2H), 6.73 (m, 2H), 7.20(d, 1H), 7.53 (m, 5H), 8.18 (s, 1H), 8.30 (d, 1H); ESI (+) MS: m/z 326 (MH^+).

5-(2-Amino-pyrimidin-4-yl)-2-phenyl-furan-3-carboxylic acid ethyl ester (59)

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm: 1.29 (t, 3H), 4.27 (q, 2H), 6.76 (m, 2H), 7.07 (d, 1H), 7.52 (m, 3H), 8.03 (m, 2H), 8.34 (d, 1H); ESI (+) MS: m/z 310 (MH^+).

Step 3: Saponification to carboxylic acid (60)

To a solution of ester **58** (220 mg, 0.68 mmol) in 1:1 H_2O/EtOH (9 mL), 4M aq NaOH (10 eq) was added and the mixture stirred at 100°C for 1 h. After cooling to rt, the solution was acidified with 2M HCl yielding 5-(2-amino-pyrimidin-4-yl)-2-phenyl-thiophene-3-carboxylic acid as a solid which was filtered, washed with water and dried under reduced pressure (185 mg, 90%).

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 7.28 (d, 1H), 7.43-7.58 (m, 5H), 8.25 (s, 1H), 8.31 (d, 1H); ESI (+) MS: m/z 296 [M-H].

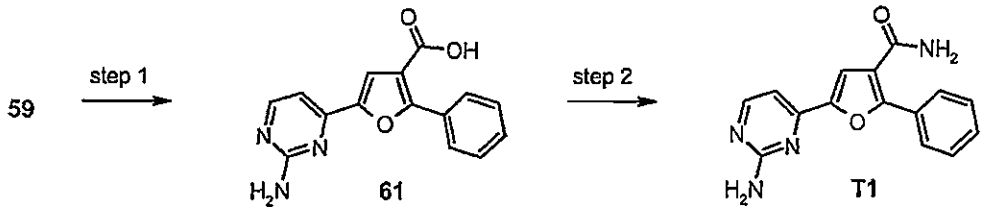
Step 4: Condensation to amide (S1)

To a mixture of acid **60** (185 mg, 0.62 mmol) and DIEA (218 µL, 1.26 mmol, 2 eq) in dry THF (4 mL), EDCI (141.7 mg, 0.93 mmol) and HOBT.NH_3 (141.5 mg, 0.93 mmol) were added at 0°C. The reaction mixture was stirred at rt overnight. After solvent evaporation the residue was taken up with DCM and washed with water. The organic layers were dried (Na_2SO_4), concentrated and the obtained solid was purified by re-precipitation with DCM/hexane to give 5-(2-amino-pyrimidin-4-yl)-2-phenyl-thiophene-3-carboxylic acid amide as a yellow solid (87 mg, 48%).

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm: 6.69 (bs, 2H), 7.10 (d, 1H), 7.38-7.44 (m, 5H), 7.56 (d, 2H), 7.71 (bs, 1H), 8.29 (d, 1H); ESI (+) MS: m/z 297 (MH^+).

Example 113

Synthesis of 5-(2-amino-pyrimidin-4-yl)-2-phenyl-furan-3-carboxylic acid amide (T1)



Step 1: Saponification to carboxylic acid (61)

To a solution of ester **59** (221 mg, 0.71 mmol) in 1:1 H_2O/EtOH (9 mL), 4M aq NaOH (10 eq) was added and the reaction mixture was stirred at 100°C for 1 h. After cooling to rt, the solution was acidified with 2M HCl yielding 5-(2-amino-pyrimidin-4-yl)-2-

phenyl-furan-3-carboxylic acid as a white solid which was filtered, washed with water and dried under reduced pressure (quant.).

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 6.75 (d, 2H), 7.06 (d, 1H), 7.51 (m, 3H), 8.0 (d, 2H), 8.33 (d, 1H); ESI (+) MS: m/z 280 [M-H].

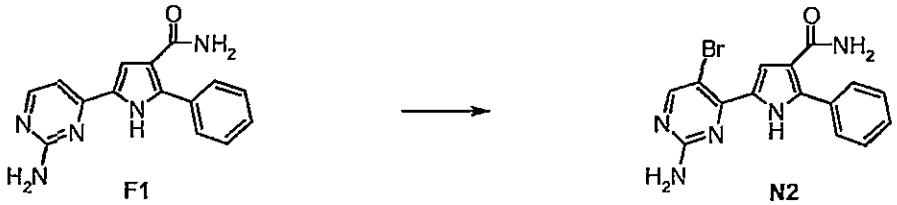
Step 2: Condensation to amide (T1)

To a mixture of acid **61** (172 mg, 0.61 mmol) and DIEA (213 µL, 1.22 mmol) in dry THF (4 mL), EDCI (139.6 mg, 0.92 mmol) and HOBT.NH_3 (140 mg, 0.92 mmol) were added at 0°C. The reaction mixture was stirred at rt overnight. After solvent evaporation the residue was taken up with DCM and washed with water. The aqueous phase was extracted with EtOAc, the organic layer was dried (Na_2SO_4) and concentrated to give 5-(2-amino-pyrimidin-4-yl)-2-phenyl-furan-3-carboxylic acid amide as a yellow solid (80 mg, 48%).

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm: 6.69 (bs, 2H), 7.01 (d, 1H), 7.41-7.48 (m, 4H), 7.53 (s, 1H), 7.92 (bs, 1H), 8.05 (d, 2H), 8.33 (d, 1H); ESI (+) MS: m/z 281 (MH^+).

Example 114

5-(2-Amino-5-bromo-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid amide (N2)



To amide **F1** (280 mg, 1 mmol) in DMF (2 mL), NBS (180 mg, 1 mmol) was added and the mixture was stirred at rt for 15 h. The reaction mixture was poured into stirred water, the precipitate was filtered, washed thoroughly and dried. Obtained the title compound as a yellow solid (270 mg, 75%).

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 6.65 (s, 2H) 6.89 (s, 1H) 7.23-7.46 (m, 4H) 7.64-7.68 (m, 2H) 7.64 (d, *J*=2.68 Hz, 1H) 7.64 (d, *J*=2.68 Hz, 1H) 8.35 (s, 1H) 11.27 (s, 1H); ESI (+) MS: m/z 358 (MH^+).

The above procedure was employed to synthesize, from **F4**, the following compound:

Example 115

5-(2-Amino-5-bromo-pyrimidin-4-yl)-2-(2-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (N8)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.60 (bs, 2H), 6.80 (bs, 1H), 7.18-7.30 (m, 2H), 7.31-7.56 (m, 3H), 7.71 (s, 1H), 8.36 (s, 1H), 11.55 (bs, 1H); ESI (+) MS: m/z 377 (MH^+).

The above procedure was employed to synthesize from **F1** the following compound, using N-chloro succinimide as the halogenating agent, in DMF at 100°C for 20 h (72% yield).

Example 116

5-(2-Amino-5-chloro-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid amide (N1)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.62 (s, 2H) 6.88 (s, 1H) 7.31-7.46 (m, 4H) 7.58 (d, *J*=2.68 Hz, 1H) 7.58 (d, *J*=2.68 Hz, 1H) 7.64-7.69 (m, 2H) 8.27 (s, 1H) 11.27 (s, 1H); ESI (+) MS: m/z 314 (MH^+).

The above procedure was employed to synthesize, from F4, the following compound:

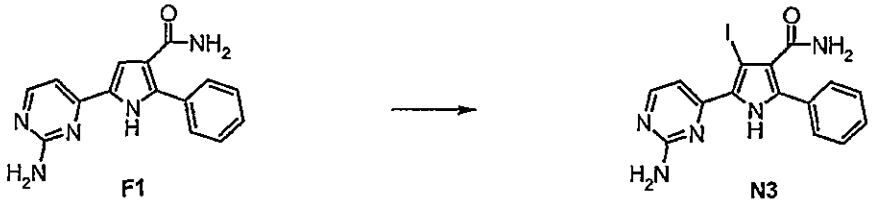
Example 117

5-(2-Amino-5-chloro-pyrimidin-4-yl)-2-(2-fluoro-phenyl)-1H-pyrrole-3-carboxylic acid amide (N7)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.58 (bs, 2H), 6.81 (bs, 1H), 7.19-7.31 (m, 2H), 7.36-7.59 (m, 3H), 7.67 (s, 1H), 8.29 (s, 1H), 11.60 (bs, 1H); ESI (+) MS: m/z 332 (MH^+).

Example 118

5-(2-Amino-pyrimidin-4-yl)-4-iodo-2-phenyl-1H-pyrrole-3-carboxylic acid amide (N3)



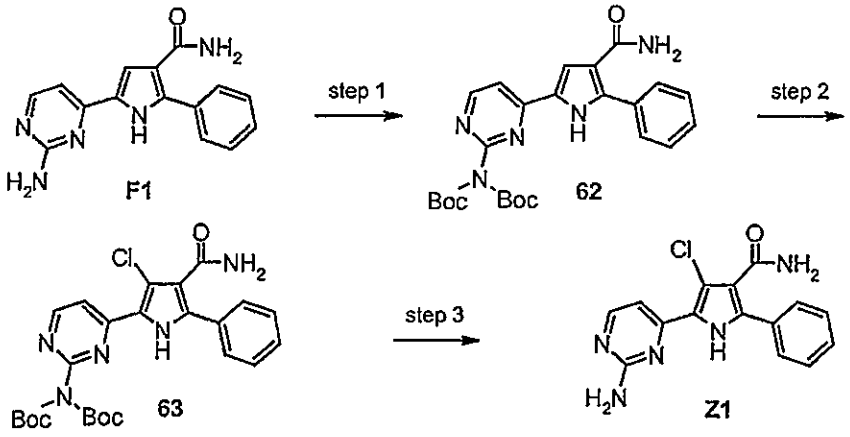
To amide **F1** (140 mg, 0.5 mmol) in DMF (1 mL), NIS (110 mg, 0.5 mmol) was added and the mixture was stirred at rt for 4 h. The reaction mixture was poured into stirred

water, the precipitate was filtered, washed thoroughly and dried. Obtained the title compound as a greenish solid (145 mg, 72%).

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm: 6.57 (s, 2H) 7.31-7.37 (m, 2H) 7.39 (s, 1H) 7.40-7.47 (m, 2H) 7.56 (s, 1H) 7.62-7.68 (m, 2H) 8.31 (d, *J*=5.37 Hz, 1H) 11.74 (s, 1H); ESI (+) MS: m/z 406 (MH^+).

Example 119

5-(2-Amino-pyrimidin-4-yl)-4-chloro-2-phenyl-1H-pyrrole-3-carboxylic acid amide (Z1)



Step 1: Protection of aminopyrimidine (62)

A solution of amide **F1** (850 mg, 3 mmol), $(Boc)_2O$ (1.7 g, 8 mmol) and DMAP (50 mg) in THF (20 mL) and DMF (1 mL) was stirred at room temperature for 48 hours. The mixture as poured into water and the precipitate was filtered. It was dissolved in ethyl acetate, washed with water, dried (Na_2SO_4) and concentrated. The residue, composed by a mixture of mono-, di- and tri-Boc derivatives, was purified by flash chromatography (EtOAc/n-hexane 9:1) affording the di-Boc derivative **62** (14%). ESI (+) MS: m/z 480 (MH^+).

Step 2: Chlorination of pyrrole ring (63)

A solution of amide **62** (165 mg, 0.34 mmol) and N-chlorosuccinimide (46 mg, 0.34 mmol) in DMF (1 mL) was stirred at 100°C for 2 hours. After cooling the mixture was poured into stirred water, extracted with ethyl acetate, washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (EtOAc/n-hexane 5:1) affording **63** (80 mg, 45%). ESI (+) MS: m/z 514 (MH^+).

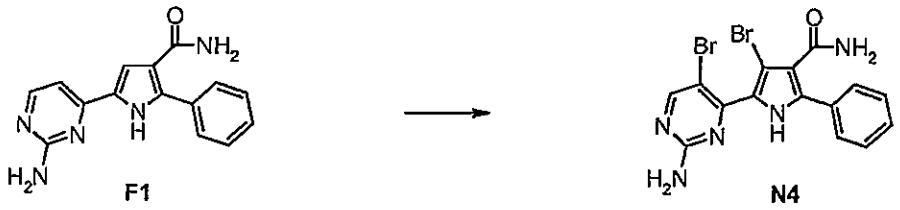
Step 3: Deprotection of aminopyrimidine (Z1)

To a solution of **63** (80 mg, 0.156 mmol) in MeOH (1 mL), 4N HCl in dioxane (3 mL) was added and the mixture was stirred at room temperature for 20 hours and then at 50°C for 1 hour. After concentration diethyl ether was added under stirring and the mixture stirred for 30 minutes. The precipitate was filtered, washed with diethyl ether and dried. Obtained the title compound (45 mg, 82%).

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.47 (bs, 2H), 7 .15 (d, *J*=5.24 Hz, 1H), 7.35 (t, *J*=8.50 Hz, 1H), 7.39-7.45 (m, 3H), 7.60 (bs, 1H), 7.64 (d, *J*=8.54 Hz, 2H), 8.29 (d, *J*=5.24 Hz, 1H), 11.64 (bs, 1H); ESI (+) MS: m/z 314 (MH^+).

Example 120

5-(2-Amino-5-bromo-pyrimidin-4-yl)-4-bromo-2-phenyl-1H-pyrrole-3-carboxylic acid amide (N4)



To amide **F1** (140 mg, 0.5 mmol) in DMF (1.5 mL), NBS (180 mg, 1 mmol) was added and the mixture was stirred at rt for 15 h. The reaction mixture was poured into stirred water, the precipitate was filtered, washed thoroughly and dried. Obtained the title compound as orange solid (195 mg, 90%).

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm 6.96 (s, 2H) 7.28-7.34 (m, 1H) 7.35 (s, 1H) 7.38-7.45 (m, 2H) 7.48 (s, 1H) 7.56-7.63 (m, 2H) 8.46 (s, 1H) 12.01 (s, 1H); ESI (+) MS: m/z 438 (MH^+).

The above procedure was employed to synthesize, from **F1**, the following compound, using N-iodo succinimide as the halogenating agent.

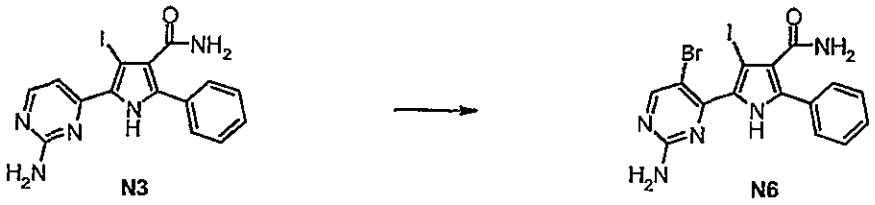
Example 121

5-(2-Amino-5-iodo-pyrimidin-4-yl)-4-iodo-2-phenyl-1H-pyrrole-3-carboxylic acid amide (N5)

^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 6.91 (bs, 2H), 7.25-7.33 (m, 1H), 7.35 (bs, 2H), 7.38-7.46 (m, 2H), 7.59 (d, *J*=8.30 Hz, 2H), 8.57 (s, 1H), 11.96 (s, 1H); ESI (+) MS: m/z 532 (MH^+).

Example 122

5-(2-Amino-5-bromo-pyrimidin-4-yl)-4-iodo-2-phenyl-1H-pyrrole-3-carboxylic acid amide (N6)

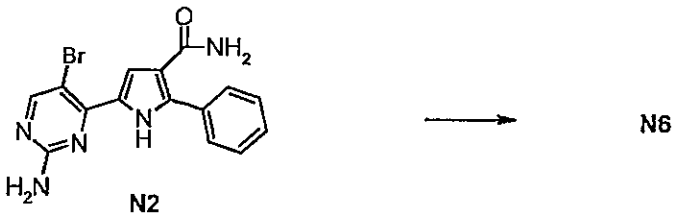


To amide **N3** (120 mg, 0.3 mmol) in DMF (1.5 mL), NBS (60 mg, 0.34 mmol) was added and the mixture was stirred at rt for 15 h. The reaction mixture was poured into stirred water, the precipitate was filtered, washed thoroughly and dried. Obtained the title compound as orange solid (83%).

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm: 6.95 (s, 2H) 7.24-7.34 (m, 2H) 7.36-7.46 (m, 3H) 7.55-7.61 (m, 2H) 8.45 (s, 1H) 12.01 (s, 1H); ESI (+) MS: m/z 485 (MH^+).

Example 123

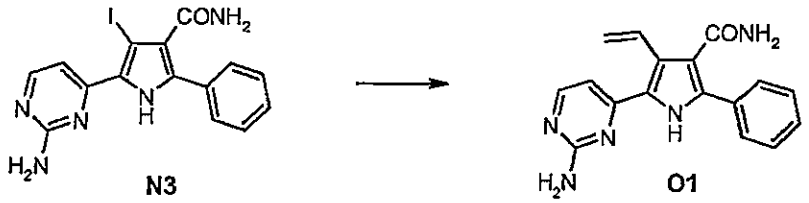
5-(2-Amino-5-bromo-pyrimidin-4-yl)-4-iodo-2-phenyl-1H-pyrrole-3-carboxylic acid amide (N6)



To amide **N2** (243 mg, 0.68 mmol) in DMF (1.5 mL), NIS (160 mg, 0.71 mmol) was added and the mixture was stirred at 50°C for 4 h, then overnight at rt. The reaction mixture was poured into stirred water, the precipitate was filtered, washed thoroughly and dried. The title compound was obtained as orange solid (270 mg, 82%).

Example 124

5-(2-Amino-pyrimidin-4-yl)-2-phenyl-4-vinyl-1H-pyrrole-3-carboxylic acid amide (O1)

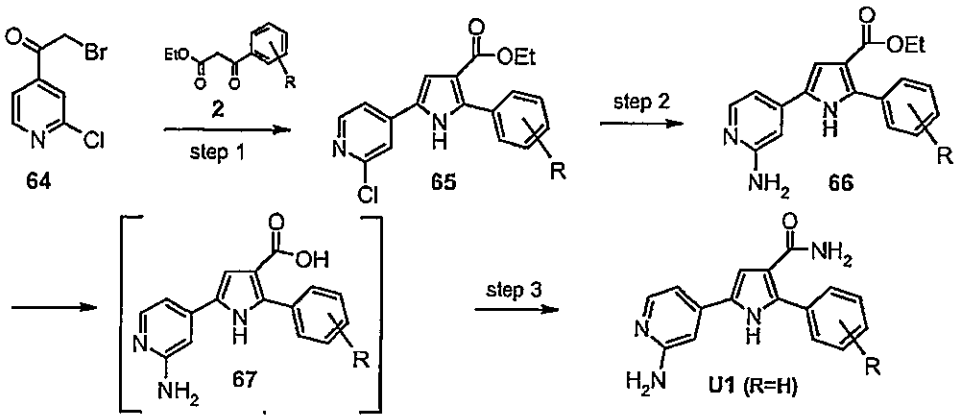


To a stirred solution of **N3** (50 mg, 0.125 mmol) in dioxane (5 mL) and DMF (0.5 mL), 2,6-dimethyl-4-ter-butyl phenol (5 mg), palladium tetrakis (5 mg) and tributylvinyl stannane (145 µL) were added. The mixture was warmed at 110°C for 8 hours, cooled and concentrated. The crude product was purified by flash chromatography (DCM/MeOH 20:1) affording the title compound as a pale yellow solid (24% yield).

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm: 5.15 (dd, *J*=11.58, 2.07 Hz, 1H), 5.64 (dd, *J*=11.58, 1.95 Hz, 1H), 6.49 (bs, 2H), 6.97 (d, *J*=5.24 Hz, 1H), 7.28-7.37 (m, 2H), 7.40-7.57 (m, 3H), 7.61-7.71 (m, 3H), 8.23 (d, *J*=5.24 Hz, 1H), 11.40 (bs, 1H); ESI (+) MS: m/z 306 (MH^+).

Example 125

5-(2-Amino-pyridin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid amide (U1)



Step 1: Pyrrole ring formation (65)

To a solution of ketoester **2** (350 mg, 2 mmol) in THF (45 mL) at 0°C, NaH (180 mg, 4.5 mmol) was added and the mixture was stirred for 20 min at 0°C. Bromoketone hydrochloride **64** (635 mg, 2 mmol) was added and the reaction mixture was stirred at 0°C for 2 hours, then at room temperature for 2 hours. After solvent removal, absolute

ethanol (25 mL) and ammonium acetate (500 mg, 6.5 mmol) were added and the mixture was stirred at room temperature for 20 hours. The solvent was removed and the residue was taken up with ethyl acetate and water. The organic phase was dried and charged for flash chromatography (eluant: DCM/MeOH 95:5). Obtained 5-(2-chloro-pyridin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid ethyl ester (340 mg, 50%).

^{1}H NMR (DMSO-d_6 / 400 MHz) δ ppm: 1.19 (t, *J*=7.07 Hz, 3H), 4.14 (q, *J*=7.07 Hz, 2H), 7.38-7.52 (m, 4H), 7.62-7.68 (m, 2H), 7.80 (d, *J*=5.37, 1H), 7.97 (s, 1H), 8.33 (d, *J*=5.37 Hz, 1H), 12.37 (bs, 1H); ESI (+) MS: m/z 327 (MH^+).

Step 2: Amination of pyridine ring (66)

A mixture of ester **65** (120 mg, 0.37 mmol), t-butyl-carbamate (215 mg, 1.84 mmol), Xantphos (16 mg, 0.028 mmol), palladium diacetate (4.1 mg, 0.0183 mmol) and cesium carbonate (240 mg, 0.73 mmol) in dioxane (3 mL) was stirred at 140°C in a microwave cavity for 20 minutes. The crude material was taken up with methanol, filtered through celite, treated with ethylacetate and water, dried and concentrated. The residue was purified by flash chromatography (eluant: DCM/EtOAc 95:5). Obtained 5-(2-amino-pyridin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylic acid ethyl ester (45 mg, 40%). ESI (+) MS: m/z 308 (MH^+).

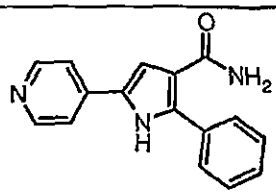
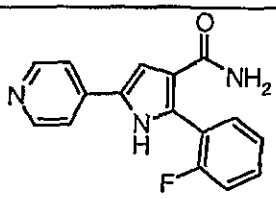
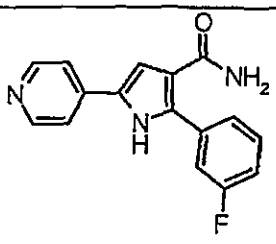
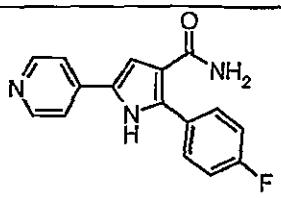
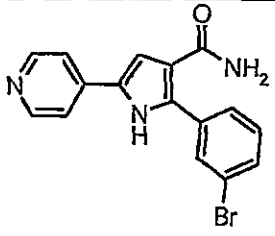
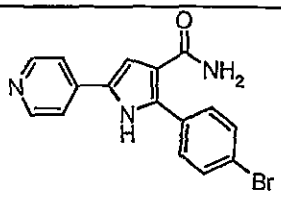
Step 3: Condensation to amides (U1)

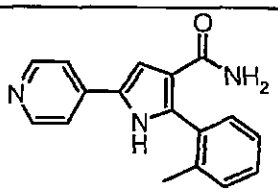
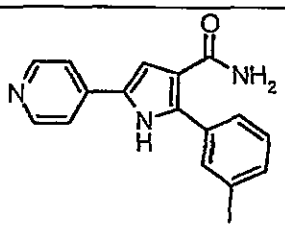
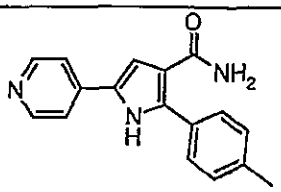
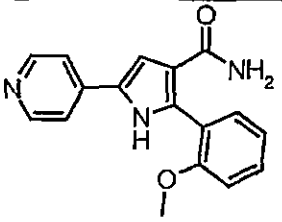
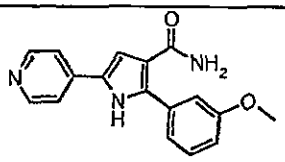
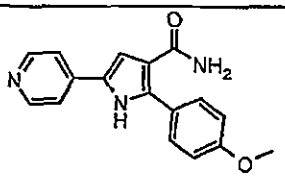
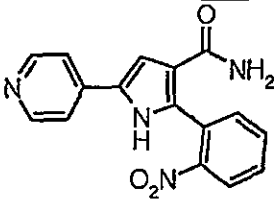
A solution of ester **66** (42 mg, 0.15 mmol) in ethanol (0.5 mL) and 4N NaOH (0.5 mL) was warmed at reflux for 2 hours. The mixture was acidified with acetic acid and stripped under reduced pressure. The residue, the crude acid **67**, was dissolved in DMF (2 mL) and treated with HOBT.NH_3 (42 mg, 0.27 mmol), EDCI (52 mg, 0.27 mmol) and DIPEA (0.12 mL) for 3 days at room temperature (two more additions of the same amount of reagents after one and two days). After concentration and aqueous work-up with ethyl acetate, the residue was purified by reverse phase flash chromatography on a Waters FractionLynx System (see General Methods). Obtained the title compound (33 mg, 80%).

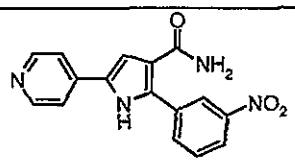
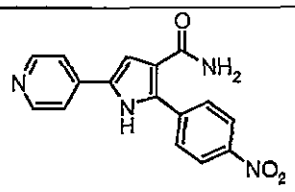
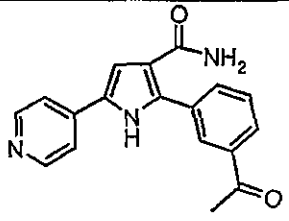
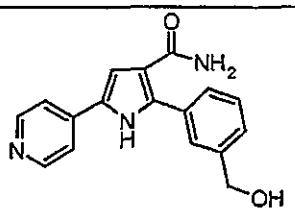
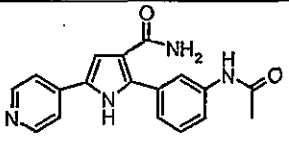
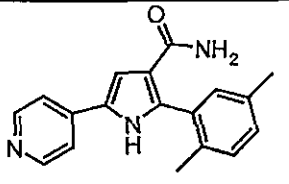
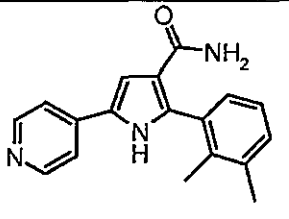
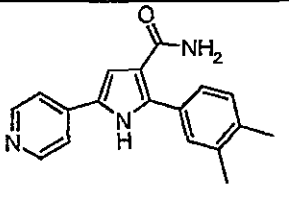
^{1}H NMR (DMSO-d_6/ 400 MHz) δ ppm 5.81 (bs, 2H) 6.74 (s, 1H), 6.81 (bs, 1H), 6.88 (d, *J*=5.78 Hz, 1H), 7.02 (d, *J*=2.68 Hz, 1H), 7.25 (bs, 1H), 7.31-7.46 (m, 3H), 7.65 (d, *J*=8.17 Hz, 2H), 7.90 (d, *J*=5.78 Hz, 1H), 11.64 (bs, 1H); ESI (+) MS: m/z 308 (MH^+).

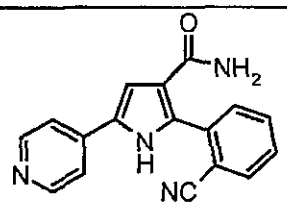
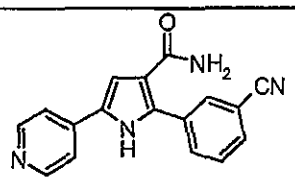
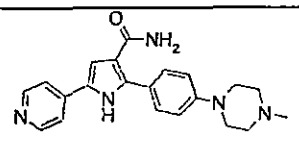
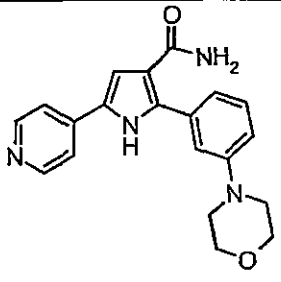
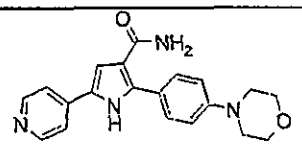
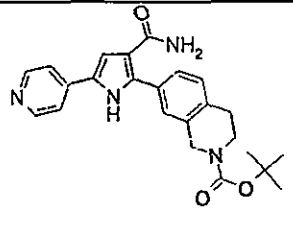
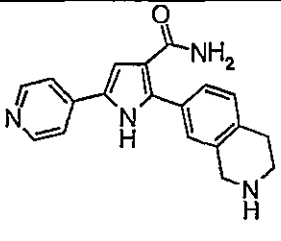
Selected compounds of formula (I), prepared by the methods described in the examples, are listed in Table X. The table shows the characterization data (HRMS calculated and found) and the structures, where the hydrogen atoms on carbons are not shown.

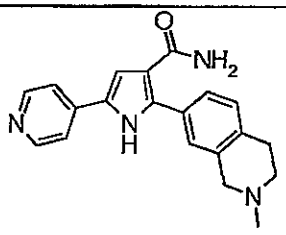
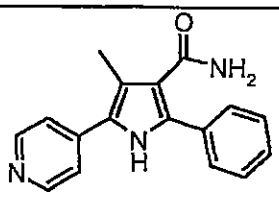
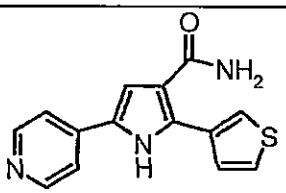
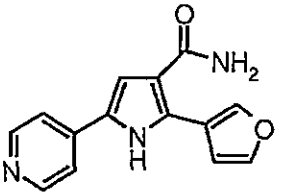
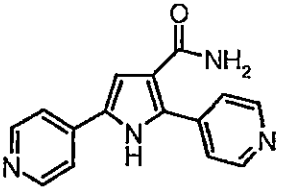
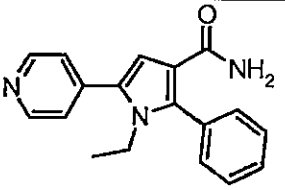
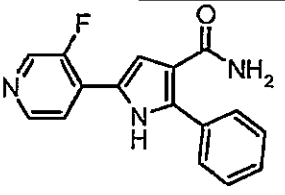
Table X. Structures and data for Selected Compounds of Formula I

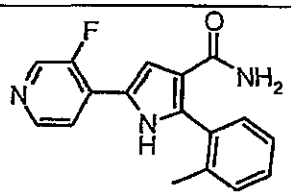
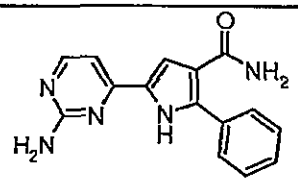
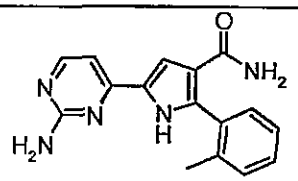
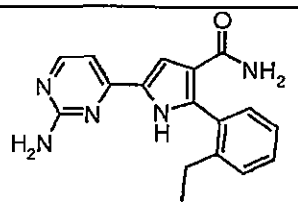
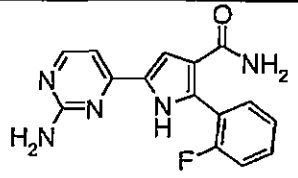
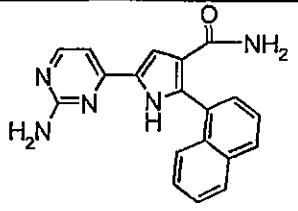
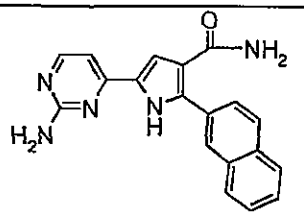
Cpd no.	Structure	M+H (calcul.)	M+H (found)
A1		264.1131	264.1127
A2		282.1037	282.1045
A3		282.1037	282.1046
A4		282.1037	282.1049
A5		342.0236	342.0233
A6		342.0236	342.0240

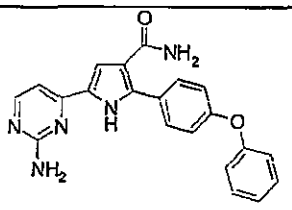
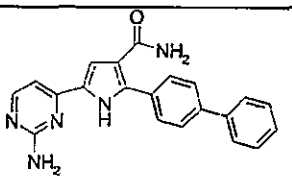
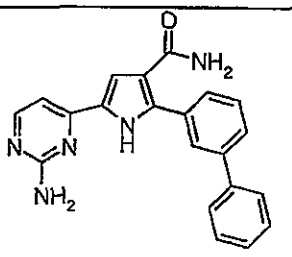
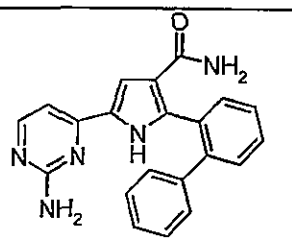
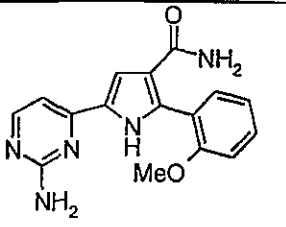
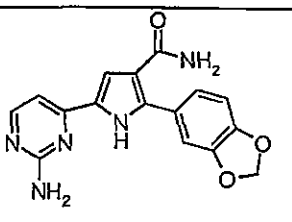
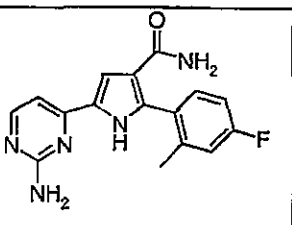
A7		278.1288	278.1276
A8		278.1288	278.1300
A9		278.1288	278.1279
A10		294.1237	294.1223
A11		294.1237	294.1237
A12		294.1237	294.1244
A13		309.0982	309.0980

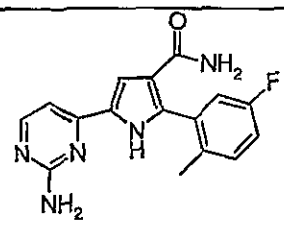
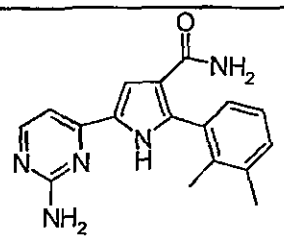
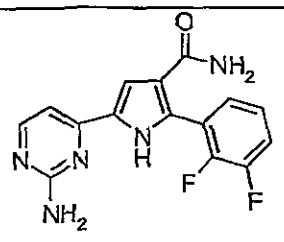
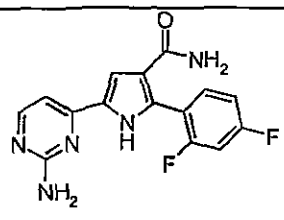
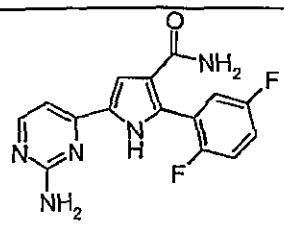
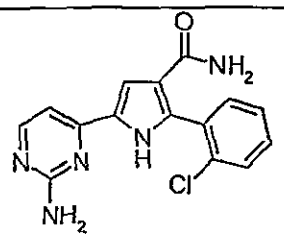
A14		309.0982	309.0980
A15		309.0982	309.0981
A16		306.1237	306.1223
A17		294.1237	294.1227
A18		321.1346	321.1341
A19		292.1444	292.1433
A20		292.1444	292.1430
A21		292.1444	292.1433

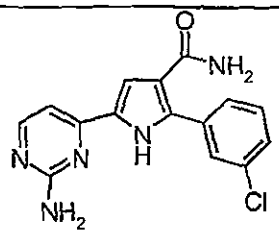
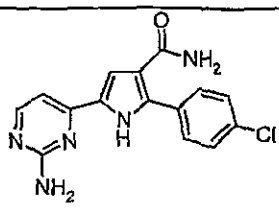
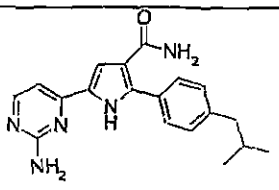
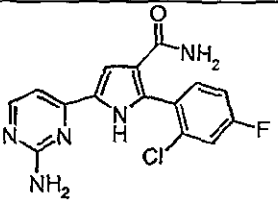
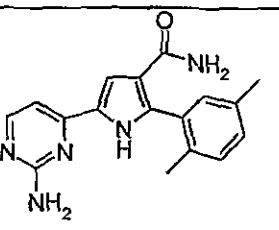
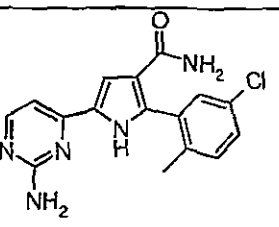
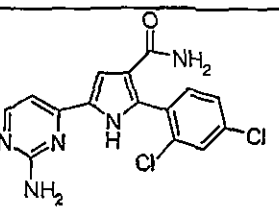
A22		289.1084	289.1075
A23		289.1084	289.1072
A24		362.1975	362.1977
A25		349.1659	349.1672
A26		349.1659	349.1667
A27		419.2078	419.2072
A28		319.1553	319.1552

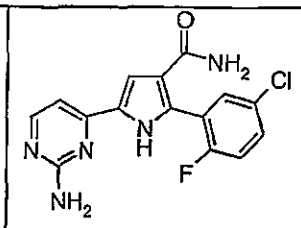
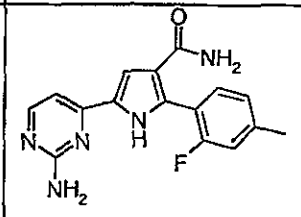
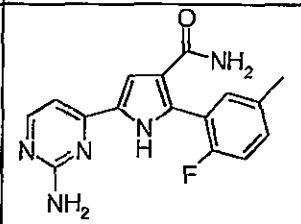
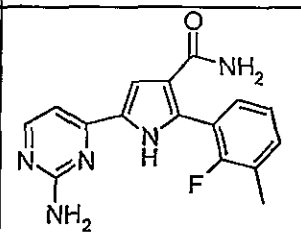
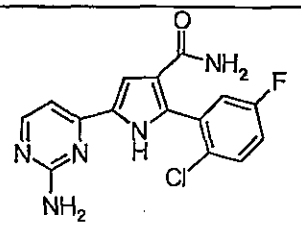
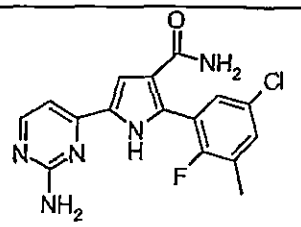
A29		333.1710	333.1698
B1		278.1288	278.1280
C1		270.0696	270.0698
C2		254.0924	254.0912
C3		265.1084	65.1078
D1		292.1444	292.1444
E1		282.1037	282.1039

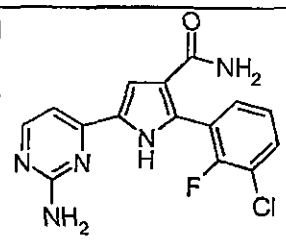
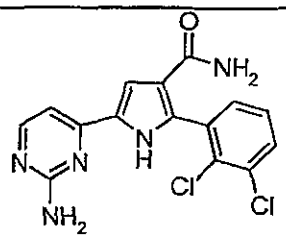
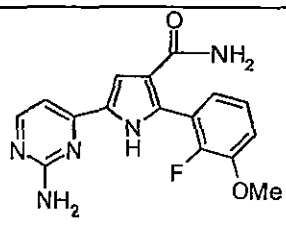
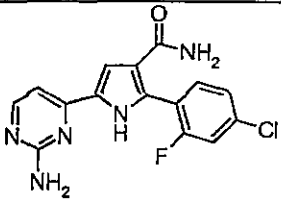
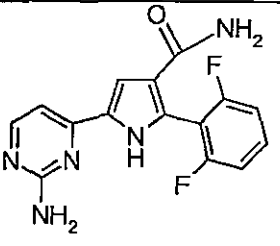
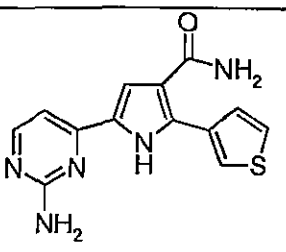
E2		296.1194	296.1191
F1		280.1193	280.1194
F2		294.1349	294.1341
F3		308.1506	308.1511
F4		298.1099	298.1092
F5		330.1349	330.1359
F6		330.1349	330.1350

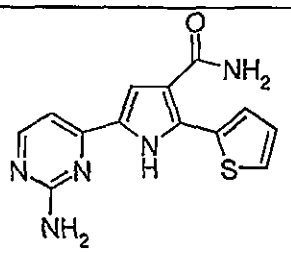
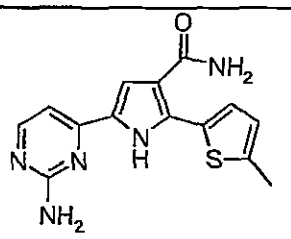
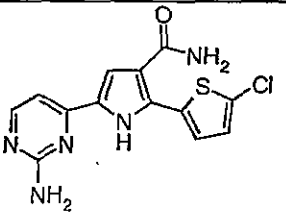
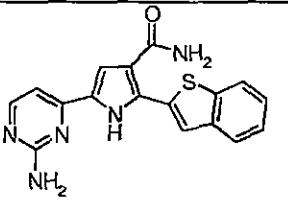
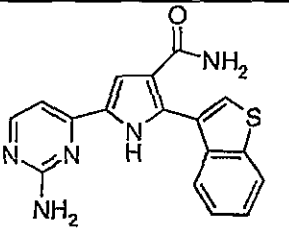
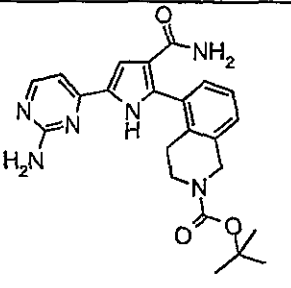
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F9		356.1506	356.1521
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F11		310.1298	310.1299
F12		324.1091	324.1094
F13		312.1255	312.1258

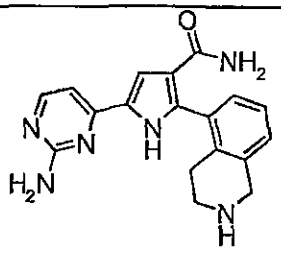
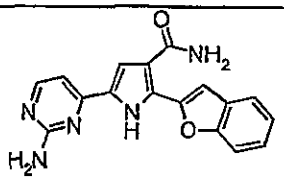
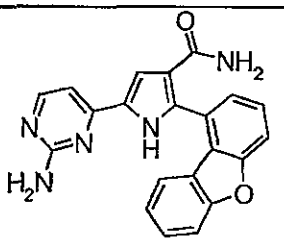
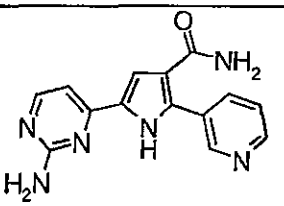
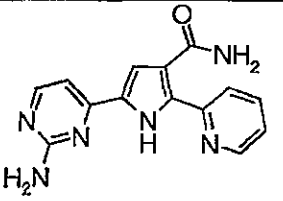
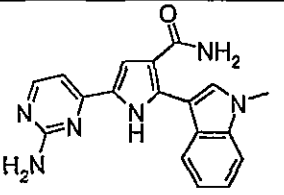
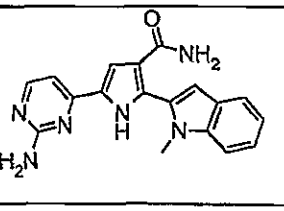
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F19		314.0803	314.0804

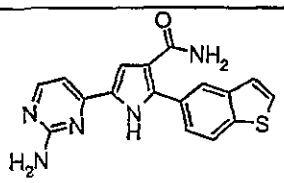
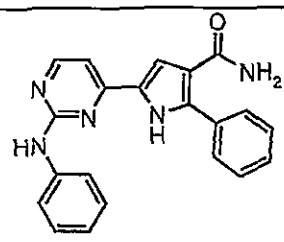
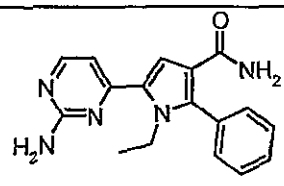
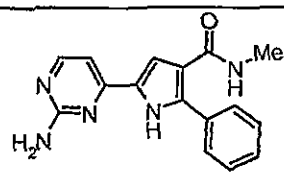
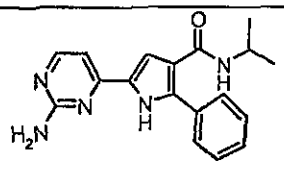
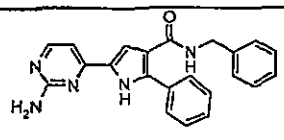
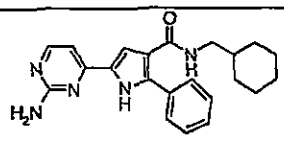
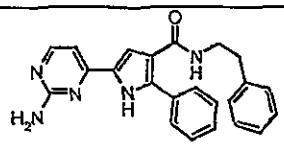
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F26		348.0414	348.0431

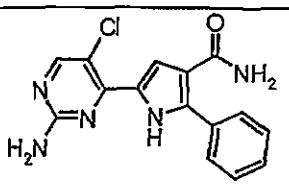
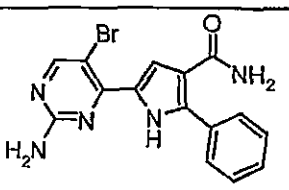
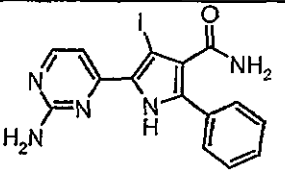
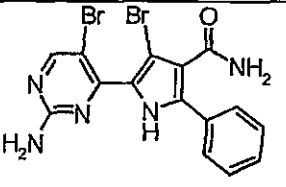
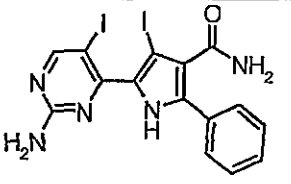
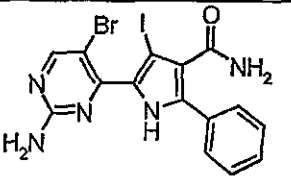
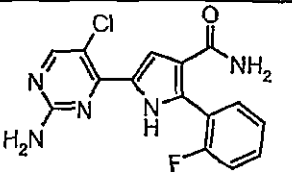
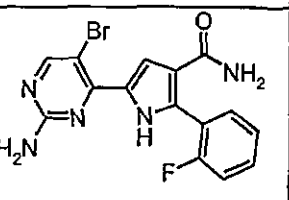
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F30		312.1255	312.1249
F31		332.0709	332.0696
F32		346.0866	346.0859

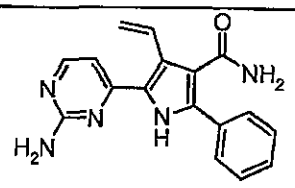
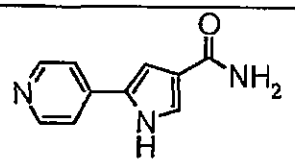
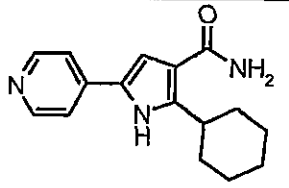
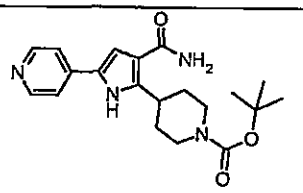
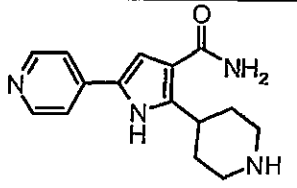
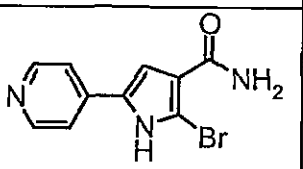
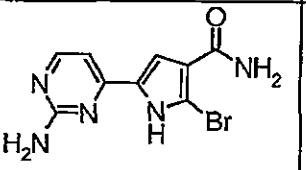
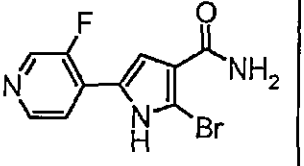
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F35		328.1205	328.1203
F36		332.0709	332.0709
F37		316.1005	316.1000
G1		286.0757	286.0756

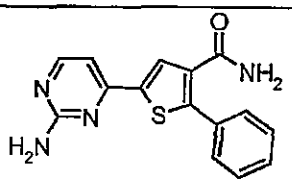
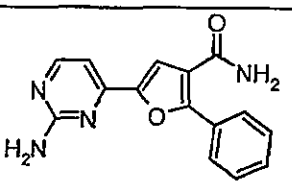
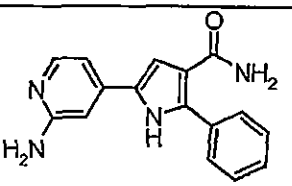
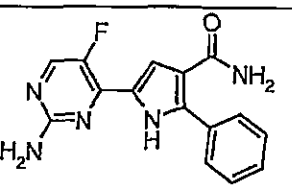
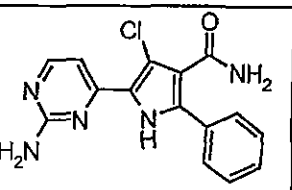
G2		286.0757	286.0765
G3		300.0914	300.0911
G4		320.0367	320.0355
G5		336.0914	336.0908
G6		336.0914	336.0919
G7		435.2139	435.2141

G8		335.1615	335.1621
G9		320.1142	320.1142
G10		370.1298	370.1304
G11		281.1145	281.1143
G12		281.1145	281.1141
G13		333.1458	333.1463
G14		333.1458	333.1473

G15		336.0914	336.0922
H1		356.1506	356.1518
L1		308.1506	308.1504
M1		294.1349	294.1335
M2		322.1662	322.1667
M3		370.1662	370.1668
M4		376.2132	376.2142
M5		384.1819	384.1806

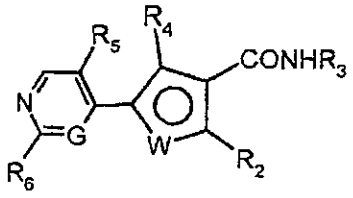
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N2		358.0298	358.0302
N3		406.0159	406.0143
N4		435.9403	435.9396
N5		531.9126	531.9113
N6		483.9264	483.9260
N7		332.0709	332.0710
N8		376.0204	376.0206

O1		306.1349	306.1363
P1		188.0818	188.0822
Q1		270.1601	270.1602
Q2		371.2078	371.2083
Q3		271.1553	271.1548
R1		265.9923	265.9935
R2		281.9985	281.9981
R3		283.9829	283.9832

S1		297.0805	297.0804
T1		281.1033	281.1023
U1		279.1240	279.1248
V1		298.1099	298.1100
Z1		314.0803	314.0796

Claims

1. A compound of the formula (I) :



(I)

wherein
G is CH or nitrogen atom;
W is an oxygen atom, NR_1 or S $(O)_n$; n is 0, 1 or 2;
R_1 and R_3 independently represent hydrogen atom or an optionally substituted group selected from alkyl, cycloalkyl, alkenyl, alkynyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heterocyclyloxy- alkyl and alkoxycarbonyl group, wherein cycloalkyl is a cyclic alkyl group of from 3 to 10 carbon atoms having single or multiple cyclic rings and aryl is a monovalent aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring or multiple condensed rings which condensed rings may or may not be aromatic provided that the point of attachment is at an aromatic carbon atom;
R_2 is hydrogen or halogen atom, or an optionally substituted group selected from aryl, cycloalkyl and heterocyclyl group,
wherein cycloalkyl and aryl are as defined above and heterocyclyl is a saturated group having a single ring or multiple condensed rings, from 1 to 10 carbon atoms and from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen within the ring wherein, in fused ring systems, one or more of the rings can be cycloalkyl, aryl or heteroaryl provided that the point of attachment is through the heterocyclic ring or
is an unsatutered group having a single ring or multiple condensed rings, from 1 to 10 carbon atoms and from I to 4 hetero atoms selected from the group consisting of sulfur and oxygen within the ring wherein, in fused ring systems, one or more of the rings can be cycloalkyl, aryl or heteroaryl provided that the point of attachment is through the heterocyclic ring ;
R_4 is hydrogen or halogen atom, or an optionally substituted alkyl or alkynyl group;
R_5 is hydrogen or halogen atom;
R_6 is hydrogen atom or NHR_7;
R_7 is hydrogen atom, an optionally substituted group selected from alkyl, aryl, cycloalkyl and heterocyclyl group or- CO- R_1 wherein R_1 is as defined above, wherein cycloalkyl and aryl are as defined above; and
wherein any substituted alkyl refers to an alkyl group having from 1 to 3 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogens, hydroxyl, nitro, carboxyl, carboxyl esters, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl;
any substituted cycloalkyl refers to a cycloalkyl, having from 1 to 5 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogen, hydroxyl, nitro, carboxyl, carboxyl esters, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl;
any substituted alkenyl refers to alkenyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogen, hydroxyl, nitro, carboxyl, carboxyl esters, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl with the proviso that any hydroxyl substitution is not attached to a vinyl (unsaturated) carbon atom;
any substituted alkynyl refers to alkynyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogen, hydroxyl, nitro, carboxyl, carboxyl esters, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl with the proviso that any hydroxyl substitution is not attached to an acetylene (unsaturated) carbon atom;
any substituted heterocyclyl refers to heterocyclyl groups that are substituted with from 1 to 3 of the same substituents as defined for substituted cycloalkyl;

any substituted aryl refers to aryl groups which are substituted with from 1 to 3 substituents, selected from the group consisting of hydroxy, acyl, acylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, carboxyl, carboxyl esters, cyano, cycloalkyl, substituted cycloalkyl, halo, nitro, heterocyclyl, substituted heterocyclyl, heterocyclyloxy, substituted heterocyclyloxy, amino sulfonyl (NH_2- SO_2-), and substituted aminosulfonyl; and
any substituted alkoxy refers to the group substituted alkyl- O- ";
or a pharmaceutically acceptable salt thereof, with the proviso that the following compounds are excluded:
2, 5- di (pyridin- 4- yl)- thiophene- 3- carboxylic acid amide,
2, 5- di (pyridin- 4- yl)- thiophene- 3- carboxylic acid methylamide,
5- pyridin- 4- yl- furan- 3- carboxylic acid [4- methoxy- 3- (4- methyl- piperazin- 1- yl)- phenyl]- amide,
5- pyridin- 4- yl- furan- 3- carboxylic acid (1- methyl- 1, 2, 3, 4- tetrahydro- quinolin- 7- yl)- amide and N- [2- amino- 1- (2, 4- dichlorobenzyl) ethyl]- 5- [2- (methylamino) pyrimidin- 4- yl]
thiophene- 3- carboxamide.

2. A compound of formula (I) as defined in claim 1 **characterized in that W** is NR_1, R_1 and R_3 independently represent hydrogen atom or an optionally substituted alkyl group, and R_6 is NHR_7 wherein R_7 is hydrogen atom or an optionally substituted aryl group.

3. A compound of formula (I) as defined in claim 1 or 2, **characterized in that W** is NR_1; R_1 represent hydrogen atom or an optionally substituted alkyl group; R_3 and R_4 represent hydrogen atoms, R_2 is an optionally substituted aryl or heterocyclyl group, wherein the heterocyclyl is as defined in Claim 1 for R_2; and R_6 is NH_2.

4. A compound of formula (I) as defined in any of the preceding claims, wherein **W** is **NH** or R_3 represents hydrogen atom.

5. A compound of formula (I) as defined in any of the preceding claims, or a pharmaceutically acceptable salt thereof, which is selected from the group consisting of:

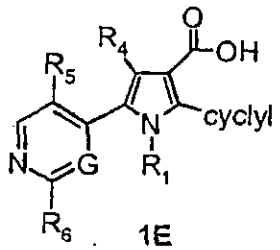
2- phenyl- 5- pyridin- 4- yl- 1H- pyrrole- 3- carboxylic acid amide,
2- (2- fluoro- phenyl)- 5- pyridin- 4- yl- 1H- pyrrole- 3- carboxylic acid amide,
2- (3- fluoro- phenyl)- 5- pyridin- 4- yl- 1H- pyrrole- 3- carboxylic acid amide,
2- (4- fluoro- phenyl)- 5- pyridin- 4- yl- 1H- pyrrole- 3- carboxylic acid amide,
5- pyridin- 4- yl- 2- o- tolyl- 1H- pyrrole- 3- carboxylic acid amide,
5- pyridin- 4- yl- 2- m- tolyl- 1H- pyrrole- 3- carboxylic acid amide,
5- pyridin- 4- yl- 2- p- tolyl- 1H- pyrrole- 3- carboxylic acid amide,
2- (3- methoxy- phenyl)- 5- pyridin- 4- yl- 1H- pyrrole- 3- carboxylic acid amide,
2- (4- methoxy- phenyl)- 5- pyridin- 4- yl- 1H- pyrrole- 3- carboxylic acid amide,
2- (2- nitro- phenyl)- 5- pyridin- 4- yl- 1H- pyrrole- 3- carboxylic acid amide,
2- (3- nitro- phenyl)- 5- pyridin- 4- yl- 1H- pyrrole- 3- carboxylic acid amide,
2- (2, 3- dimethyl- phenyl)- 5- pyridin- 4- yl- 1H- pyrrole- 3- carboxylic acid amide,
5- pyridin- 4- yl- 2- thiophen- 3- yl- 1H- pyrrole- 3- carboxylic acid amide,
2- furan- 3- yl- 5- pyridin- 4- yl- 1H- pyrrole- 3- carboxylic acid amide,
5- (3- fluoro- pyridin- 4- yl)- 2- phenyl- 1H- pyrrole- 3- carboxylic acid amide,
5- (3- fluoro- pyridin- 4- yl)- 2- o- tolyl- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- phenyl- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- o- tolyl- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2- fluoro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (4- fluoro- 2- methyl- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (5- fluoro- 2- methyl- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2, 3- dimethyl- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2, 3- difluoro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2, 4- difluoro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2, 5- difluoro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin4- yl)- 2- (2- chloro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2- chloro- 4- fluoro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2, 4- dichloro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2- fluoro- 4- methyl- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2- fluoro- 3- methyl- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2- chloro- 5- fluoro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (3- chloro- 2- fluoro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2, 3- dichloro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,

5- (2- amino- pyrimidin- 4- yl)- 2- (2- fluoro- 3- methoxy- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (4- chloro- 2- fluoro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2- bromo- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2- chloro- 3- methoxy- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (3- methoxy- 2- methyl- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2- chloro- 3- fluoro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (3- bromo- 2- chloro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2- bromo- 3- chloro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2, 3- dibromo- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (3- bromo- 2- fluoro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (3- bromo- 2- methyl- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2- bromo- 3- methyl- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (4- methoxy- 3- methyl- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (3, 4- dimethoxy- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2- fluoro- 4- methoxy- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2- chloro- 4- methoxy- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (2- bromo- 4- fluoro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (4- methoxy- 2- methyl- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- thiophen- 3- yl- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- thiophen- 2- yl- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (5- methyl- thiophen- 2- yl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- (5- chloro- thiophen- 2- yl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- 5- chloro- pyrimidin- 4- yl)- 2- phenyl- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- 5- bromo- pyrimidin- 4- yl)- 2- phenyl- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 4- iodo- 2- phenyl- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- 5- chloro- pyrimidin- 4- yl)- 2- (2- fluoro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- 5- bromo- pyrimidin- 4- yl)- 2- (2- fluoro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide,
5- (2- amino- pyrimidin- 4- yl)- 2- phenyl- thiophene- 3- carboxylic acid amide,
5- (2- amino- 5- fluoro- pyrimidin- 4- yl)- 2- phenyl- 1H- pyrrole- 3- carboxylic acid amide and
5- (2- amino- pyrimidin- 4- yl)- 4- chloro- 2- phenyl- 1H- pyrrole- 3- carboxylic acid amide.

6. A compound of formula (I) as defined in any of the preceding claims, or a pharmaceutically acceptable salt thereof, which is 5- (2- amino- pyrimidin- 4- yl)- 2- (2, 4- dichloro- phenyl)- 1H- pyrrole- 3- carboxylic acid amide.

7. A process for preparing a compound of formula (I) as defined in claim 1, which process comprises:

a) coupling a compound of formula **1E**

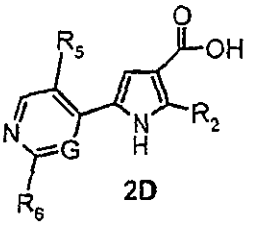


1E

wherein R_1, R_4, R_5, R_6 and G are as defined in claim 1 and cyclyl is an optionally substituted group selected form aryl, cycloalkyl and heterocyclyl group, wherein cycloalkyl and aryl are as defined in claim 1 and heterocyclyl is as defined in claim 1 for R_2,
either with an activated form of ammonia, optionally in the presence of a condensing agent, or with an amine of formula R_3-NH_2, wherein R_3 is as defined in claim 1, thus obtaining a compound of formula (I) as defined in claim 1 wherein W is NR_1, wherein R_1 is as defined in claim 1, and R_2 is an optionally substituted group selected form aryl, cycloalkyl and heterocyclyl group, wherein cycloalkyl and aryl are as defined in claim 1 and heterocyclyl is as defined in claim 1 for R_2;
b) optionally converting a compound of formula (I) into another different compound of formula (I), and, if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt thereof or converting a salt into the free compound (I), wherein any substituted cycloalkyl, any substituted heterocyclyl and any substituted aryl are as defined in claim 1.

8. A process for preparing a compound of formula (I) as defined in claim 1, which process comprises:

a') coupling a compound of formula **2D**



2D

wherein R_2 is hydrogen or halogen atom, and R_5, R_6, and G are as defined in claim 1, either with an activated form of ammonia, optionally in the presence of a condensing agent, or with an amine of formula R_3-NH_2, wherein R_3 is as defined in claim 1, thus obtaining a compound of formula (I) wherein W is N, R_1 is hydrogen atom and R_2 is hydrogen atom or halogen atom;

a'$_1$) optionally converting the resultant compound of formula (I) wherein R_2 is halogen atom into another compound of formula (I) wherein R_2 is hydrogen atom or an optionally substituted group selected form aryl, cycloalkyl and heterocyclyl group wherein cycloalkyl and aryl are as defined in claim 1 and heterocyclyl is as defined in claim 1 for R_2, and/or

a'$_2$) converting the resultant compound of formula (I) wherein R_1 is hydrogen atom into another compound of formula (I) wherein R_1 is an optionally substituted group selected from alkyl, cycloalkyl, alkenyl, alkenyl, heterocyclyl, aryl, heterocyclyloxy- alkyl and alkoxycarbonyl, wherein cycloalkyl and aryl are as defined in claim 1; and, if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt thereof or converting a salt into the free compound (I),

wherein any substituted alkyl, any substituted cycloalkyl, any substituted alkenyl, any substituted alkynyl, any substituted heterocyclyl, any substituted aryl, and any substituted alkoxy are as defined in claim 1.

9. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1, for use as a medicament.

10. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1, for use as a medicament for treating cell proliferative disorders caused by and/or associated with an altered protein kinase activity such as Cdc7 kinase activity.

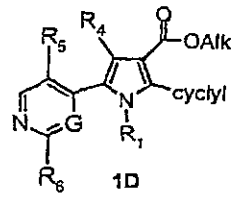
11. A compound of formula (I) or a pharmaceutically acceptable salt thereof, according to claim 9, **characterized in that** it is for use as a medicament for treating cell proliferative disorder that is a cancer selected from carcinoma, hematopoietic tumors of lymphoid lineage, hematopoietic tumors of myeloid lineage; tumors of mesenchymal origin; tumors of the central and peripheral nervous system; melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer and Kaposi's sarcoma.

12. A compound of formula (I) or a pharmaceutically acceptable salt thereof, according to claim 9, **characterized in that** it is for use as a medicament for treating a cell proliferative disorder that is is selected from benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

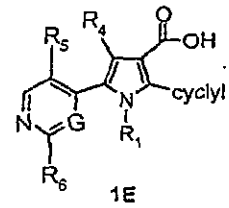
13. A compound of formula (I) or a pharmaceutically acceptable salt thereof, according to claim 9, **characterized in that** it is for use as a medicament together a radiation therapy or in a chemotherapy regimen in combination with at least one cytostatic or cytotoxic agent.

14. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1, and at least one pharmaceutically acceptable excipient, carrier and/or diluent.

15. An intermediate of the formula 1D or 1E:



1D



1E

wherein G, R_1, R_5 and R_6 are as defined in claim 1; R_4 is hydrogen, halogen atom or an alkenyl group optionally substituted with from 1 to 3 substituents, and preferably I to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogen, hydroxyl, nitro, carboxyl, carboxyl esters, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl with the proviso that any hydroxyl substitution is not attached to a vinyl (unsaturated) carbon atom; cyclyl is as defined in claim 7 and Alk is a C_1-C_5 alkyl goup.