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(54) **PYRAZOLO-HETEROARYL COMPOUNDS**

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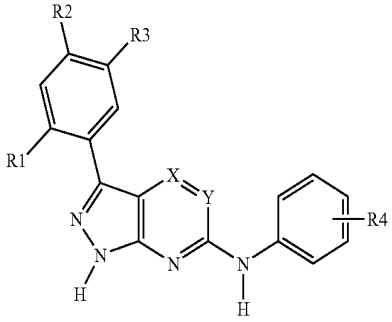
(57) **ABSTRACT**

A compound of formula I

I

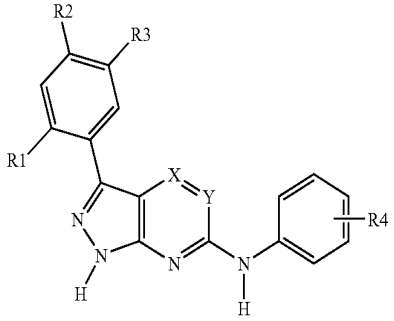


wherein the groups R1-R4, X and Y are as defined in the specification, useful to treat TNF-Alpha and IL-1 mediated diseases.

PYRAZOLO-HETEROARYL COMPOUNDS

[0001] This invention relates to pyrazolo-heteroaryl compounds, in particular to pyrazolo[3,4-.b.]pyridine, pyrazolo [3,4-.d.]pyrimidine and pyrazolo[3,4-.b.]pyrazine derivatives and to their use for treating TNFα and IL-1 mediated diseases such as rheumatoid arthritis and diseases of bone metabolism, e.g. osteoporosis.

[0002] Accordingly the present invention provides a compound of formula I



I

wherein

X and Y are independently carbon or nitrogen,

R1 is H, halogen, hydroxy, lower alkoxy, lower alkyl or halo-substituted lower alkyl;

R2 is H, or optionally substituted (heterocyclyl, lower alkyl, lower alkenyl, lower alkynyl or lower alkoxy);

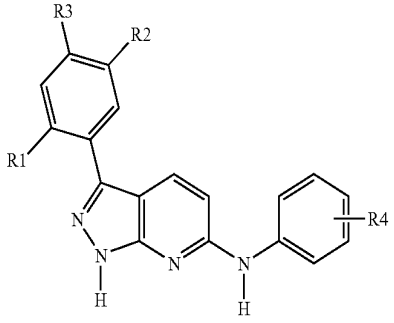
R3 is H, or optionally substituted (heterocyclyl, lower alkyl, lower alkenyl, lower alkynyl or lower alkoxy); or

R2 and R3 are linked together to form a 4- to 6-membered heterocyclic ring containing one or more hetero atoms selected from O, S, N or NR, where R is H or lower alkyl;

R4 represents one, two or three halogen substituents which may be the same or different,

or a pharmaceutically-acceptable and -cleavable ester or acid addition salt thereof.

[0003] Preferably —X═Y— in formula I is —CH═N— or —N═CH— and the compounds of formula I are pyrazolo [3,4-.b.]pyridine, pyrazolo[3,4-.d.]pyrimidine and pyrazolo [3,4-.b.]pyrazine derivatives of formulae I', I", I'"



I'

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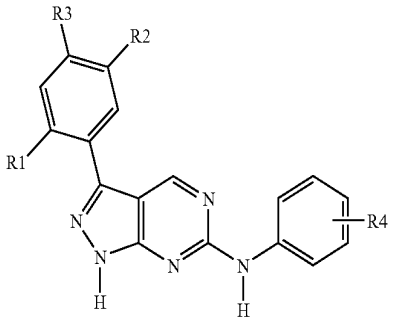
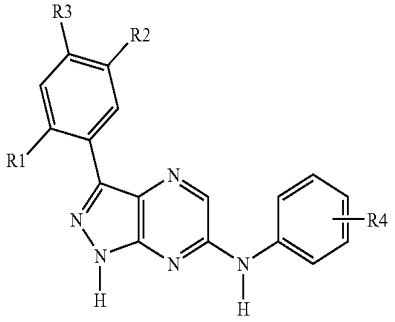


I"



I'"

wherein the substituents R1, R2, R3 and R4 are as defined above.

[0004] Above and elsewhere in the present description the following terms have the following meanings.

[0005] Halo or halogen denote I, Br, Cl or F, preferably Cl or F.

[0006] The term "lower" referred to above and hereinafter in connection with organic radicals or compounds respectively defines such as branched or unbranched with up to and including 7, preferably up to and including 4 and advantageously one or two carbon atoms.

[0007] A lower alkyl group is branched or unbranched and contains 1 to 7 carbon atoms, preferably 1-4 carbon atoms. Lower alkyl represents for example methyl, ethyl, propyl, butyl, isopropyl or isobutyl.

[0008] Halo-substituted lower alkyl is C_1-C_7lower alkyl substituted by up to 6 halo atoms.

[0009] A lower alkoxy group is branched or unbranched and contains 1 to 7 carbon atoms, preferably 1-4 carbon atoms. Lower alkoxy represents for example methoxy, ethoxy, propoxy, butoxy, isopropoxy, isobutoxy or tertiary butoxy.

[0010] A lower alkene or alkenyl group is branched or unbranched and contains 2 to 7 carbon atoms, preferably 1-4 carbon atoms and contains at least one carbon-carbon double bond. Lower alkene or lower alkenyl represents for example vinyl, propenyl, butenyl, isopropenyl or isobutenyl.

[0011] A lower alkyne or alkynyl group is branched or unbranched and contains 2 to 7 carbon atoms, preferably 1-4 carbon atoms and contains at least one carbon-carbon triple bond. Lower alkyne or alkynyl represents for example ethynyl, propynyl, butynyl, isopropynyl or isobutynyl.

[0012] Heterocyclyl may be aromatic, i.e. as C_{3-18}heteroaryl, partially unsaturated comprising from 3 to 18 ring members, or saturated, i.e. as C_{3-18}heterocycloalkyl, and

comprises at least 3 ring atoms, at least one of which is a hetero atom, e.g. O, S, N, or NR, where R is H or lower alkyl.

[0013] R1, R2 and R3 may be further substituted by one or more, e.g. up to six, substituents independently selected from halo, OH, CN, lower alkyl, lower alkoxy, heterocyclyl or NR5R6 where R5 and R6 are independently H or lower alkyl. The lower alkyl, lower alkoxy, heterocyclyl or NR5R6 substituents on R1, R2 and R3 may be further substituted by one or more, each by up to six, more usually up to three, e.g. 1 or 2, substituents independently selected from halo, OH, CN, lower alkyl, lower alkoxy, heterocyclyl or NR5R6, where R5 and R6 are as defined above.

[0014] R1 is preferably halo, C_1-C_4 lower alkyl, C_1-C_4lower alkoxy or halo-substituted C_1-C_4 lower alkyl. Most preferably R1 is Cl, F, methoxy or CF_3.

[0015] R2 and R3 are preferably, independently of one another, H or optionally substituted (C_1-C_4 lower alkyl, C_1-C_4 lower alkoxy, C_1-C_7alkenyl, C_1-C_7alkynyl, C_5-C_7N-heterocyclyl, C_5-C_7heterocyclylC_1-C_4lower alkoxy, C_5-C_7heterocyclylC_1-C_4lower alkyl, C_5-C_7heterocyclylC_1-C_4lower alkenyl, C_5-C_7heterocyclylC_1-C_4lower alkynyl) wherein the C_5-C_7heterocyclyl optionally contains a second hetero atom, e.g. O, S, N, NR (where R is H or lower alkyl), and the optional substitution comprises 1 or 2 substituents, separately selected from C_1-C_4 alkyl, halogen, hydroxy, C_1-C_4 alkoxy, or optionally mono- or di-N—C_{1-4}alkyl substituted amino.

[0016] In particular R2 is H, C_1-C_4 lower alkoxy, or C_5-C_7heterocyclylC_1-C_4lower alkoxy. For example, in particular embodiments R2 is H, methoxy and N-morpholinylethoxy.

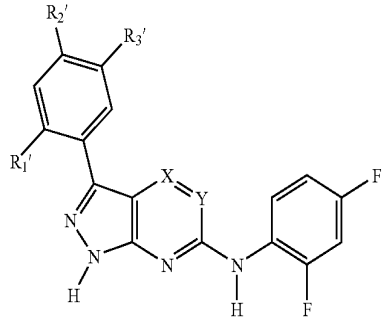
[0017] More preferably R3 is H or optionally substituted (C_1-C_4 lower alkyl, C_1-C_4 lower alkenyl, C_1-C_4 lower alkynyl, C_1-C_4 lower alkoxy, morpholino, pyridyl, morpholino-C_1-C_4 lower alkoxy, imidazolyl, piperidyl, C_1-C_4 lower alkylamino-C_1-C_4 lower alkyl, piperazyl C_1-C_4 lower alkyl, morpholino C_1-C_4 lower alkyl, tetrahydropyranylamino C_1-C_4 lower alkyl, pyridylaminocarbonyl, morpholino C_1-C_4 lower alkenyl, piperidyl C_1-C_4 lower alkenyl, piperazyl C_1-C_4 lower alkenyl, morpholino C_1-C_4 lower alkyl, piperidyl C_1-C_4 lower alkynyl, piperazyl C_1-C_4 lower alkynyl).

[0018] Particular examples of substituents as R3 include: H, methoxy, N-morpholino, pyrid-4-yl, pyrid-2-ylaminocarbonyl2-(N-morpholino)ethoxy, 1,5-dimethylimidazol-3-yl, 1-methyl-4-hydroxypiperid-4-yl, methylaminomethyl, 1-methylpiperaz-4-ylmethyl, piperaz-1-ylmethyl, propylaminomethyl, tetrahydropyran-4-ylaminomethyl, N-morpholinylmethyl, methylaminomethyl, methoxy, 3-amino-3-methyl-but-1-ynyl, 3-amino-3-methyl-butyl, 3-hydroxy-3-methyl-but-1-ynyl, 3-hydroxy-3-methyl-butyl, 3-dimethylaminoprop-1-ynyl, 3-morpholin-4-yl-prop-1-ynyl, 3-(4-methyl-piperazin-1-yl)-prop-1-ynyl, 1-methyl-4-hydroxy-piperid-4-ylethynyl, (E)-3-dimethylamino-propenyl, (E)-3-morpholin-4-ylpropenyl, (E)-3-(4-methyl-piperazi-1-yl)-propenyl, wherein the optional substituents are as defined above.

[0019] When R2 and R3 are linked to form a heterocylic ring they are preferably linked by a methylenedioxy linker or the heterocyclic ring is preferably an imidazole ring optionally substituted by 1 or 2 substituents, separately selected from C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, or optionally mono- or di-N—C_{1-4}alkyl substituted amino. Most preferably when R2 and R3 are linked to form a heterocylic ring they are preferably linked by a methylenedioxy linker.

[0020] A preferred significance for R4 is a dihalo, more preferably difluoro, especially 2,4-difluoro.

[0021] Thus in preferred embodiments the invention provides compounds of Formulae II



II

Wherein

[0022] X and Y are independently carbon or nitrogen,

R1' is halo, C_1-C_4 lower alkyl, C_1-C_4lower alkoxy or halo-substituted C_1-C_4 lower alkyl;

R2' and R3' are, independently of one another, H or optionally substituted (C_1-C_4 lower alkyl, C_1-C_4 lower alkoxy, C_1-C_7alkenyl, C_1-C_7alkyl, C_5-C_7N-heterocyclyl, C_5-C_7heterocyclylC_1-C_4lower alkoxy, C_5-C_7heterocyclylC_1-C_4lower alkyl, C_5-C_7heterocyclylC_1-C_4lower alkenyl, C_5-C_7heterocyclylC_1-C_4lower alkynyl) wherein the C_5-C_7heterocyclyl optionally contains a second hetero atom and the optional substitution comprises 1 or 2 substituents, separately selected from C_1-C_4 alkyl, halogen, hydroxy, C_1-C_4 alkoxy, or optionally mono- or di-N—C_{1-4}alkyl substituted amino or

R2' and R3' are linked by a methylenedioxy linker or are linked in an imidazole ring optionally substituted by 1 or 2 substituents, separately selected from C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, or optionally mono- or di-N—C_{1-4}alkyl substituted amino;

or a pharmaceutically-acceptable and -cleavable ester or acid addition salt thereof.

[0023] In particular the invention includes the following compounds:

EXAMPLE 1

[0024] (2,4-Difluoro-phenyl)-[3-(2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

EXAMPLE 2

[0025] [3-(6-Chloro-benzo[1,3]dioxol-5-yl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-(2,4-difluoro-phenyl)-amine

EXAMPLE 3

[0026] [3-(2-Chloro-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-(2,4-difluoro-phenyl)-amine

EXAMPLE 4

[0027] (2,4-Difluoro-phenyl)-[3-(2-trifluoromethyl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

EXAMPLE 5

[0028] (2,4-Difluoro-phenyl)-[3-(2,4-dimethoxy-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

EXAMPLE 6

[0029] [3-(2-Chloro-4,5-dimethoxy-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-(2,4-difluoro-phenyl)-amine

EXAMPLE 7

[0030] (2,4-Difluoro-phenyl)-[3-(2-methoxy-5-morpholin-4-yl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

EXAMPLE 22

[0031] (2,4-Difluoro-phenyl)-{3-[2-methoxy-5-(4-methyl-piperazin-1-yl)-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-amine

EXAMPLE 8

[0032] (2,4-Difluoro-phenyl)-[3-(2-methoxy-5-pyridin-4-yl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

EXAMPLE 13

[0033] (2,4-Difluoro-phenyl)-[3-(2-methoxy-5-methylaminomethyl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

EXAMPLE 14

[0034] (2,4-Difluoro-phenyl)-{3-[2-methoxy-5-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-amine

EXAMPLE 12

[0035] 4-{3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl]-4-methoxy-phenyl}-1-methyl-piperidin-4-ol

EXAMPLE 15

[0036] (2,4-Difluoro-phenyl)-[3-(2-methoxy-5-morpholin-4-ylmethyl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

EXAMPLE 16

[0037] (2,4-Difluoro-phenyl)-[3-(2-methoxy-5-piperazin-1-ylmethyl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

EXAMPLE 20

[0038] {3-[5-(3-Amino-3-methyl-but-1-ynyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-(2,4-difluoro-phenyl)-amine

EXAMPLE 21

[0039] {3-[5-(3-Amino-3-methyl-butyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-(2,4-difluoro-phenyl)-amine

EXAMPLE 9

[0040] {3-[2-Chloro-5-methoxy-4-(2-morpholin-4-yl-ethoxy)-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-(2,4-difluoro-phenyl)-amine

EXAMPLE 10

[0041] {3-[2-Chloro-4-methoxy-5-(2-morpholin-4-yl-ethoxy)-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-(2,4-difluoro-phenyl)-amine

EXAMPLE 17

[0042] (2,4-Difluoro-phenyl)-[3-(2-methoxy-5-propylaminomethyl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

EXAMPLE 18

[0043] (2,4-Difluoro-phenyl)-(3-{2-methoxy-5-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl)-amine

EXAMPLES 11 AND 19

[0044] (2,4-Difluoro-phenyl)-{3-[5-(1,2-dimethyl-1.H.-imidazol-4-yl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-amine

EXAMPLE 23

[0045] 3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl]-4-methoxy-.N.-pyridin-2-yl-benzamide

EXAMPLE 24

[0046] {3-[5-(3-Amino-3-methyl-but-1-ynyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl}-(2,4-difluoro-phenyl)-amine

EXAMPLE 25

[0047] 4-{3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo[3,4-.d.]pyrimidin-3-yl]-4-methoxy-phenyl}-2-methyl-but-3-yn-2-ol

EXAMPLE 26

[0048] 4-{3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo[3,4-.d.]pyrimidin-3-yl]-4-methoxy-phenyl}-2-methyl-butan-2-ol

EXAMPLE 27

[0049] (2,4-Difluoro-phenyl)-{3-[5-(3-dimethylamino-prop-1-ynyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl}-amine

EXAMPLE 28

[0050] (2,4-Difluoro-phenyl)-{3-[2-methoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-phenyl]-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl}-amine

EXAMPLE 29

[0051] (2,4-Difluoro-phenyl)-(3-{2-methoxy-5-[3-(4-methyl-piperazin-1-yl)-prop-1-ynyl]-phenyl}-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl)-amine

EXAMPLE 30

[0052] 4-{3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo[3,4-.d.]pyrimidin-3-yl]-4-methoxy-phenylethynyl}-1-methyl-piperidin-4-ol

EXAMPLE 31

[0053] (2,4-Difluoro-phenyl)-{3-[5-((E)-3-dimethylamino-propenyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl}-amine

EXAMPLE 32

[0054] (2,4-Difluoro-phenyl)-{3-[2-methoxy-5-((E)-3-morpholin-4-yl-propenyl)-phenyl]-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl}-amine

EXAMPLE 33

[0055] (2,4-Difluoro-phenyl)-(3-{2-methoxy-5-[(E)-3-(4-methyl-piperazin-1-yl)-propenyl]-phenyl}-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl)-amine

EXAMPLE 34

[0056] 4-{3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo[3,4-.b.]pyrazin-3-yl]-4-methoxy-phenyl}-2-methyl-but-3-yn-2-ol

EXAMPLE 35

[0057] (2,4-Difluoro-phenyl)-{3-[5-(3-dimethylamino-prop-1-ynyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.b.]pyrazin-6-yl}-amine

or a pharmaceutically-acceptable and -cleavable ester or acid addition salt thereof.

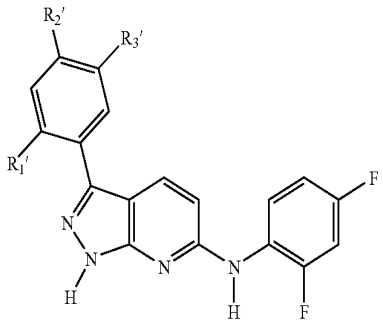
[0058] The novel pyrazolopyridine, pyrazolopyrimidine and pyrazolopyrazine compounds of the invention, in particular the compounds of formulae I and II and the specific compounds listed above are hereinafter referred to "Agents of the Invention".

[0059] The Agents of the Invention which comprise free hydroxyl groups may also exist in the form of pharmaceutically acceptable, physiologically cleavable esters, and as such are included within the scope of the invention. Such pharmaceutically acceptable esters are preferably prodrug ester derivatives, such being convertible by solvolysis or cleavage under physiological conditions to the corresponding Agents of the Invention which comprise free hydroxyl groups. Suitable pharmaceutically acceptable prodrug esters are those derived from a carboxylic acid, a carbonic acid monoester or a carbamic acid, advantageously esters derived from an optionally substituted lower alkanoic acid or an arylcarboxylic acid.

[0060] Agents of the Invention may also exist in the form of pharmaceutically acceptable salts, and as such are included within the scope of the invention. Pharmaceutically acceptable salts include acid addition salts with conventional acids, for example, mineral acids, e.g., hydrochloric acid, sulfuric or phosphoric acid, or organic acids, for example, aliphatic or aromatic carboxylic or sulfonic acids, e.g., acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, fumaric, hydroxymaleic, pyruvic, pamoic, methanesulfonic, toluenesulfonic, naphthalenesulfonic, sulfanilic or cyclohexylsulfamic acid; also amino acids, such as arginine and lysine. For compounds of the invention having acidic groups, for example, a free carboxy group, pharmaceutically acceptable salts also represent metal or ammonium salts, such as alkali metal or alkaline earth metal salts, e.g., sodium, potassium, magnesium or calcium salts, as well as ammonium salts, which are formed with ammonia or suitable organic amines.

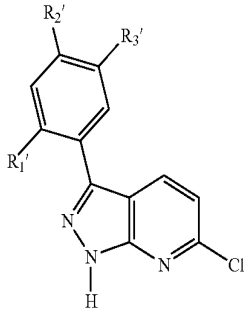
[0061] Agents of the Invention of formula II'

II'



[0062] wherein R1', R2', and R3' are as defined above may be prepared by coupling a 6-chloro-3-phenyl-1.H.-pyrazolo[3,4-.b.]pyridine of formula III

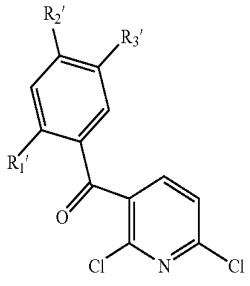
III



wherein R1', R2' and R3' are as defined above, with 2,4-difluoroaniline. Preferably the coupling reaction is carried out as a Buchwald condensation; for instance, in solution, e.g. in hot dioxane, in the presence of e.g. R-(+)-BINAP, $Pd(OAc)_2$, and NaOtBu with refluxing e.g. for about 3 hours.

[0063] The compound of formula III may be obtained by cyclisation of the corresponding (2,6-dichloro-pyridin-3-yl)-phenyl-methanone of formula IV

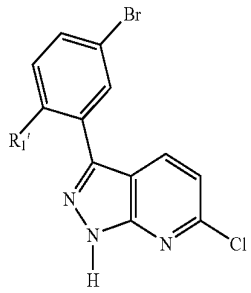
IV



wherein R1', R2' and R3' are as defined above, with hydrazine (H_2NNH_2); for instance, in organic solvent, e.g. EtOH/1-BuOH, under reflux.

[0064] Alternatively the compound of formula III in which R2' is H may be obtained by coupling a bromo derivative of formula V

V

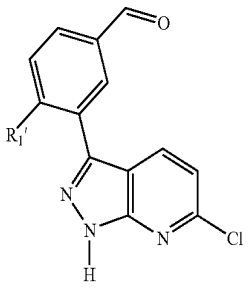


wherein R1' is as defined above, with a corresponding R3' precursor, e.g. N-methyl-4-piperidone when R3' is 1-hydroxy-4-N-methylpiperidine-1-yl, N-methylpiperazine when R3' is 4-N-methylpiperazin-1-yl, or 3-amino-3-methylbutyn-1-yl when R3' is 3-amino-3-methylbutyn-1-yl. Conditions used for these coupling reactions are described hereinafter in the Examples.

[0065] Compounds of formula II in which R3' is an alkyl substituent, e.g. amino substituted alkyl, such as a 3-amino-3-methylbutyn-1-yl substituent, may be prepared by reduction of the corresponding alkyne substituted, e.g. 3-amino-3-methylbutyn-1-yl, compound of formula II; for instance as hereinafter described in the Examples.

[0066] Compounds of formula III in which R2' is H and R3' is —CH_2—NR5R6, wherein R5 is H and R6 is lower alkyl or R5 and R6 are linked together in an N-heterocyclyl comprising at least 3 ring atoms and optionally a further heteroatom selected from O, S, N or NR where R is H or lower alkyl, may be prepared by reaction of a 3-(6-chloro-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl)-4-methoxy-benzaldehyde compound of formula VI

VI

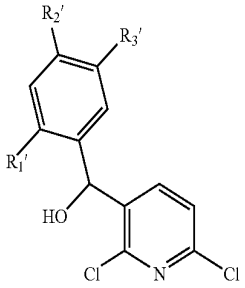


wherein R1' is as defined above, with a lower alkyl amine or N-heterocyclic precursor; for instance as hereinafter described in the Examples. Compounds of formula III in which R2' is H and R3' is CH_2—NR5R6, wherein R5 is H and R6 is lower alkyl or R5 and R6 are linked together in an N-heterocyclyl comprising at least 3 ring atoms and optionally a further heteroatom selected from O, S, N or NR where R is H or lower alkyl, may be converted to compounds of formula II as described above.

[0067] Compounds of formula VI may be prepared by reacting a bromo derivative of formula V with DMF; for instance after treatment with an alkyl lithium agent such as nBuLi, preferably with cooling.

[0068] Compounds of formula IV as defined above may be obtained by oxidation of the corresponding alcohol of formula VII

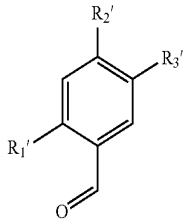
VII



wherein R1', R2' and R3' are as defined above. Oxidation may be carried out using Jones reagent; for instance as hereinafter described in the Examples.

[0069] The alcohol of formula VII may be obtained by coupling of 2,6 dichloropyridine with the appropriate benzaldehyde precursor of formula VIII

VIII

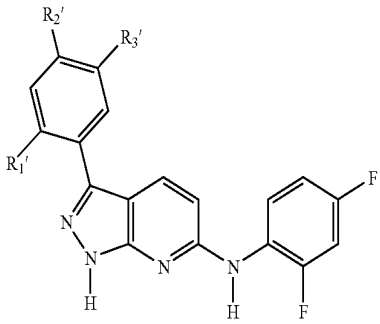


wherein R1', R2' and R3' are as defined above. For example, the coupling reaction may be carried out in solution, e.g. in THF, preferably containing diisopropylamine which has been pre-treated with nBuLi, preferably with cooling.

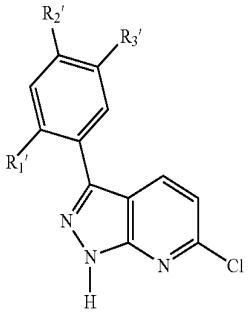
[0070] Novel synthetic steps as described above, in particular the coupling of compounds of formula III with 2,6-difluoroaniline, are included within the scope of the present invention.

[0071] Accordingly the invention further provides a process for the preparation of Agents of the Invention of formula II

II



[0072] wherein R1', R2', and R3' are as defined above, comprising coupling a 6-chloro-3-phenyl-1.H.-pyrazolo[3,4-.b.]pyridine of formula III



III

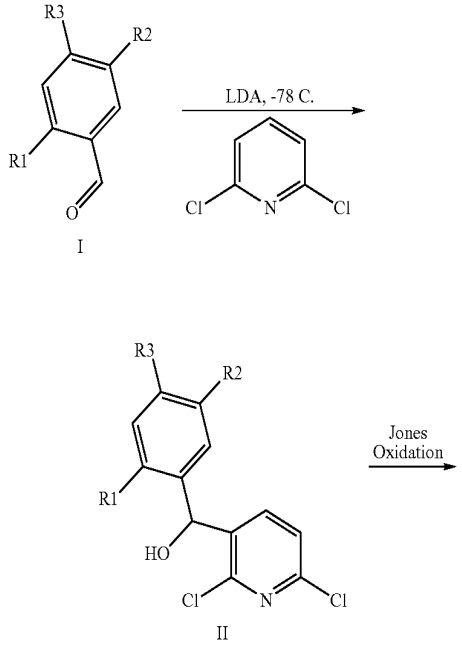
wherein R1', R2' and R3' are as defined above, with 2,4-difluoroaniline.

[0073] The invention is further described by way of illustration only in the following examples which relate to the preparation of Agents of the Invention of formula II.

EXAMPLES

[0074] Methods are specifically described for preparation of Agents of the Invention. Agents of the Invention may be prepared according to scheme 1 from aldehydes I:

Scheme 1 (Examples 1-11)



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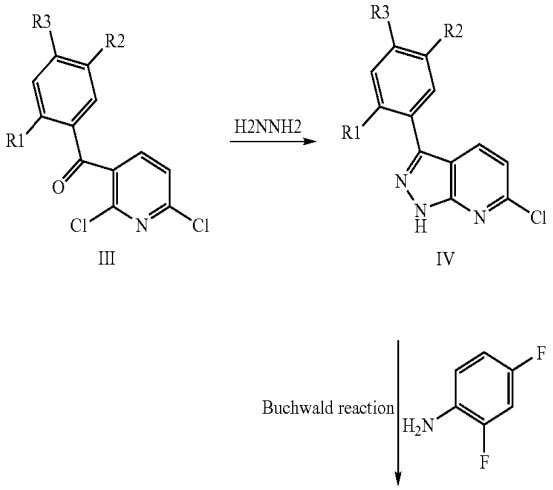
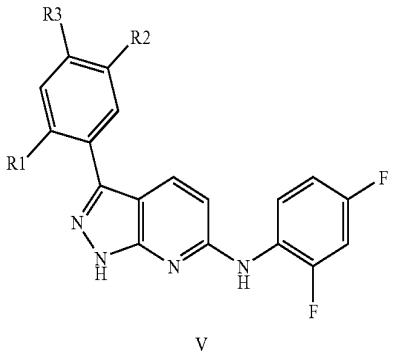




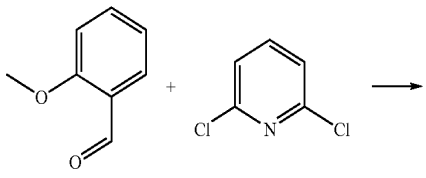
[0075] The preparation of (2,4-difluoro-phenyl)-[3-(2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine (Example 1) exemplifies the 4-step synthetic method of scheme 1 from commercially available 2-methoxybenzaldehyde:

Example 1

(2,4-Difluoro-phenyl)-[3-(2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

1a) (2,6-Dichloro-pyridin-3-yl)-(2-methoxy-phenyl)-methanol

[0076]



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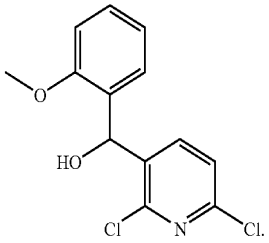


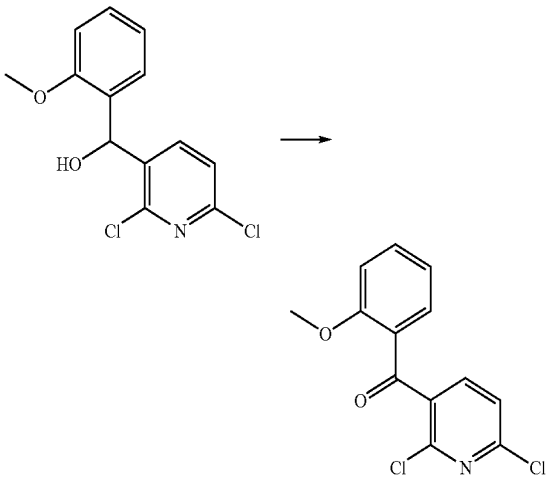
[0077] Diisopropylamine (10.3 ml; 74 mmol) in THF (200 ml) is cooled to −78° C. and treated with nBuLi (42 ml; 67.6 mmol of a 1.6M solution in hexane). After 5 min at −78° C., 2,6-dichloropyridine (10 g; 67.6 mmol) in THF (20 ml) is added dropwise and stirred for 50 min at −78° C. 2-Methoxy-benzaldehyde (8.75 g; 64.3 mmol) in THF (15 ml) is added dropwise. After 10 min of stirring at −75 C, the reaction mixture is warmed to −30 C and poured on aqueous 20% NaCl-solution (500 ml) and extracted with TBME three times. The combined organic phases are dried over Na_2SO_4, evaporated to dryness and the residue purified by chromatography (SiO_2; acetone/hexanes 5/95>3/7) to yield the title compound (16.0 g; 87%) as a slightly colored viscous oil.

[0078] 1H-NMR (400 MHz; DMSO): 3.73 (s, 3H): 6.07 (d, 1H); 6.15 (d, 1H); 6.97 (m, 2H); 7.29 (m, 2H); 7.55 (d, 1H); 7.83 (d, 1H).

[0079] MS (m/z) ES−: 284 (MH−; 30); 282 (35); 146 (100).

1b) (2,6-Dichloro-pyridin-3-yl)-(2-methoxy-phenyl)-methanone

[0080]



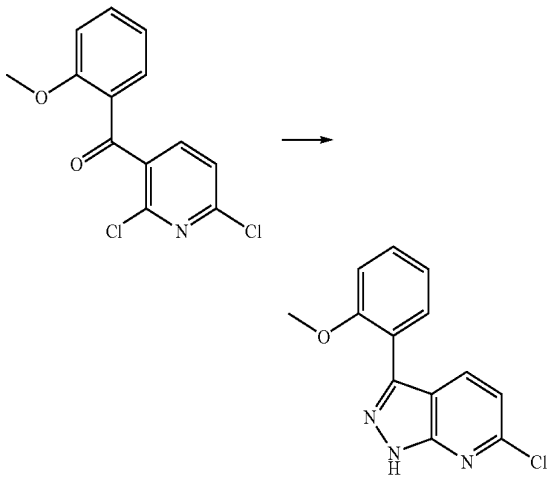
[0081] (2,6-Dichloro-pyridin-3-yl)-(2-methoxy-phenyl)-methanol (16 g; 56.3 mol) is dissolved in acetone (250 ml) and treated with Jones reagent (24 ml; 56 mmol) for 5 min. The reaction mixture is diluted with hexanes (1000 ml), filtered through a short bed of SiO_2, yielding the title compound (14.3 g; 90%) after evaporation of the solvent as brownish crystals.

[0082] 1H-NMR (400 MHz; DMSO): 3.60 (s, 3H); 7.13 (t, 1H); 7.18 (d, 1H); 7.62-7.75 (m, 3H); 7.98 (d, 1H);

[0083] MS (m/z) EI: 283 (M+1, 50); 281 (M−1, 70); 246 (100); 135 (70); 77 (50).

1c) 6-Chloro-3-(2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridine

[0084]



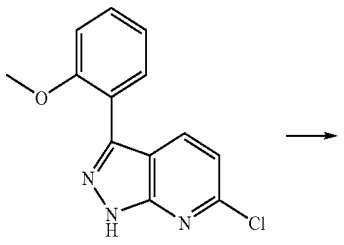
[0085] (2,6-Dichloro-pyridin-3-yl)-(2-methoxy-phenyl)-methanone (4 g; 14.2 mmol) dissolved in EtOH/1-BuOH (66 ml 10/1) is treated with H_2NNH_2 120 (24% in water) (5 ml; 37.5 mmol) under reflux for 30 min. A second portion of $H_2NNH_2.H_2O$ (24% in water)(4 ml; 30 mmol) is added and refluxed for another 30 min. 1-BuOH is evaporated and the residual aqueous phase extracted with TBME three times. The combined organic phases are dried over Na_2SO_4, evaporated to dryness and the residue purified by chromatography (SiO_2; acetone/hexanes 2/8) to yield the title compound in pure form after triturating with a small volume of acetone (800 mg; 22%) as yellow crystals.

[0086] 1H-NMR (400 MHz; DMSO): 3.82 (s, 3H); 7.09 (t, 1H); 7.22 (d, 1H); 7.27 (d, 1H); 7.47 (t, 1H); 7.64 (dd, 1H); 8.21 (d, 1H).

[0087] MS (m/z) EI: 259 (M+, 100); 230 (40); 194 (30); 152 (25); 77 (25).

1d): (2,4-Difluoro-phenyl-[3-(2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

[0088]



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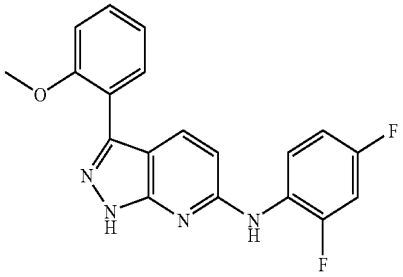


[0089] 6-Chloro-3-(2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridine (710 mg; 2.74 mmol) is dissolved in hot dioxane (10 ml), R-(+)-BINAP (40 mg; 0.06 mmol), $Pd(OAc)_2$ (40 mg; 0.17 mmol), 2,4-difluoroaniline (1.1 ml; 10.9 mmol) and NaOtBu (1.05 g; 10.9 mmol) are sequentially added and the reaction mixture refluxed for 3 hours. It is then poured directly on a silica gel column and purified by chromatography (TBME/hexanes 4/6>8/2, then acetone/hexanes 1/1) to yield the title compound as off-white crystals after recrystallisation from acetone/hexanes (675 mg; 69%).

[0090] 1H-NMR (400 MHz; DMSO): 3.85 (s, 3H); 6.81 (d, 1H); 7.07 (t, 1H); 7.12 (t, 1H); 7.20 (1H); 7.35 (t, 1H); 7.43 (t, 1H); 7.60 (d, 1H); 7.88 (d, 1H); 8.20 (m, 1H); 8.98 (s, 1H); 13.1 (s, 1H).

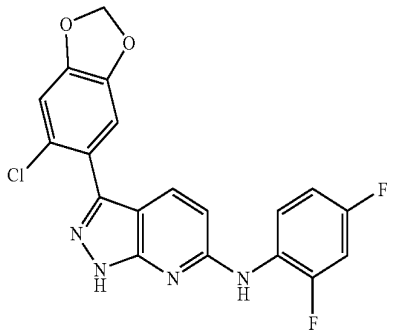
[0091] MS (m/z) ES: 351 (MH–, 100); 331 (20).

[0092] The compounds of example 2, 3, 4 and 5 are prepared by analogy to example 1 from commercially available aldehydes:

Example 2

[3-(6-Chloro-benzo[1,3]dioxol-5-yl)-1.H.-pyrazolo [3,4-.b.]pyridin-6-yl]-(2,4-difluoro-phenyl-amine

[0093]



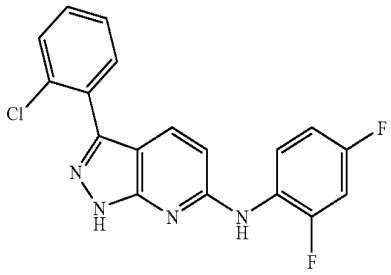
[0094] 1H-NMR (400 MHz; DMSO): 6.15 (s, 2H); 6.82 (d, 1H); 7.08 (s, 1H); 7.12 (dt, 1H); 7.23 (s, 1H); 7.32 (dt, 1H); 7.78 (d, 1H); 8.13 (m, 1H); 9.04 (s, 1H), 13.2 (s, 1H).

[0095] MS (m/z) Cm: 401 (MH+, 100); 259 (35); 213 (40); 179 (60); 169 (70); 141 (80); 131 (100).

Example 3

[3-(2-Chloro-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-(2,4-difluoro-phenyl)-amine

[0096]



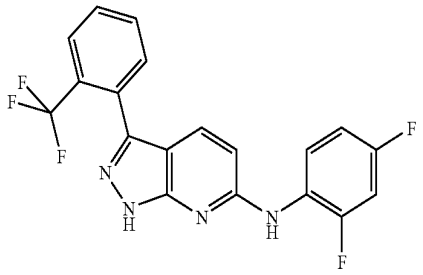
[0097] 1H-NMR (400 MHz; DMSO): 6.84 (d, 1H); 7.13 (bt, 1H); 7.33 (bt, 1H); 7.48 (m, 2H); 7.62 (m, 2H); 7.81 (d, 1H); 8.14 (m, 1H); 9.05 (s, 1H), 13.2 (s, 1H).

[0098] MS (m/z) ES: 355 (MH–, 100); 335 (15).

Example 4

(2,4-Difluoro-phenyl)-[3-(2-trifluoromethyl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

[0099]



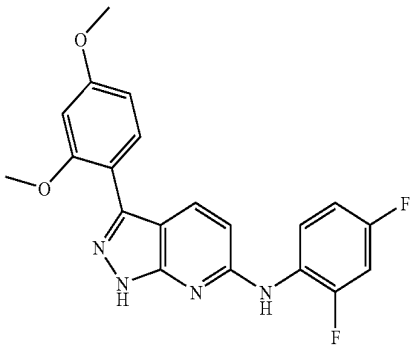
[0100] 1H-NMR (400 MHz; DMSO): 6.82 (d, 1H); 7.11 (bt, 1H); 7.33 (bt, 1H); 7.63 (d, 1H); 7.71 t, 2H); 7.80 (t, 1H); 7.92 (d, 1H); 8.12 (m, 1H); 9.05 (s, 1H), 13.2 (s, 1H).

[0101] MS (m/z) ES: 389 (MH–, 100); 369 (30).

Example 5

(2,4-Difluoro-phenyl)-[3-(2,4-dimethoxy-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

[0102]



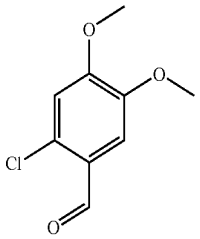
[0103] 1H-NMR (400 MHz; DMSO): 3.82 (s, 3H); 3.84 (s, 3H); 6.64 (dd, 1H); 6.72 (d, 1H); 6.78 (d, 1H); 7.10 (bt, 1H); 7.32 (bt, 1H); 7.50 (d, 1H); 7.83 (d, 1H); 8.18 (m, 1H); 8.94 (s, 1H); 13.2 (s, 1H).

[0104] MS (m/z) ES: 381 (MH−, 100); 361 (50).

[0105] Aldehydes 1-5 and 8 (scheme 2) are prepared as follows before being converted into the products of Example 6-10 according to scheme 1 by analogy to the experimental procedures described for Example 1.

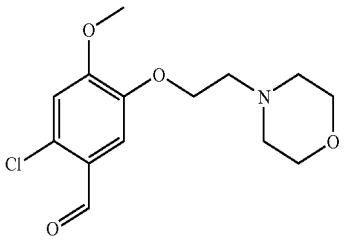
Scheme 2

1



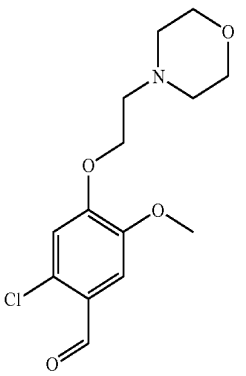
(used in Ex. 6)

2



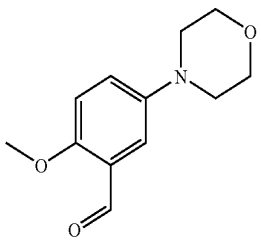
(Ex. 10)

3



(Ex. 9)

4



(Ex. 7)

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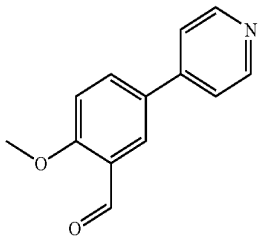
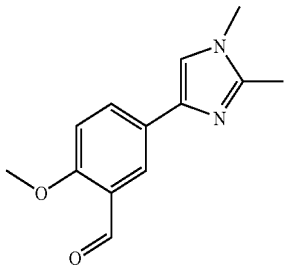
5



(Ex. 8)

8



(Ex. 11)

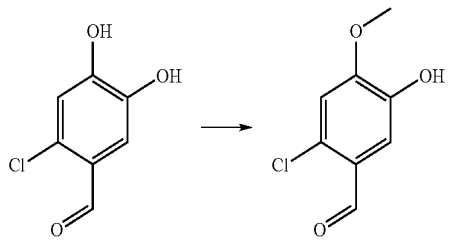
L.L. Miller et al: *J. Org. Chem.* 1978, 43(8), 1580-6.

Preparation of aldehyde 1: according to L. L. Miller et al *J. Org. Chem* 1978, 43(8), 1580-6.

Preparation of 2-chloro-4-methoxy-5-(2-morpholin-4-yl-ethoxy)-benzaldehyde (2)

a) 2-Chloro-4-methoxy-5-hydroxybenzaldehyde

[0106]



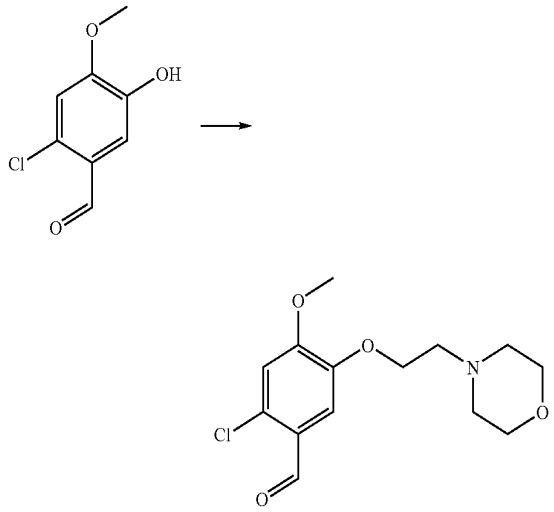
[0107] 2-Chloro-4,5-dihydroxybenzaldehyde (Kaiser, C. et al in *J. Org. Chem.* 1974, 17(10), 1071-5) (5.7 g; 33.1 mmol), MeI (2.0 ml; 33.1 mmol) and K_2CO_3 (4.6 g; 33.1 mmol) are refluxed in acetone (250 ml) for 1.5 hours. Acetone is evaporated and the residue taken up in TBME and extracted three times with TBME. The combined organic phases are dried over Na_2SO_4 and evaporated to dryness. Purification via chromatography (acetone/hexanes 15/85) yields in the first fraction 2-chloro-4,5-dimethoxybenzaldehyde (1.4 g; 23%), followed by the title compound 2-chloro-4-methoxy-5-hydroxybenzaldehyde (2.45 g; 40%; colorless crystals), 2-chloro-4-hydroxy-5-methoxybenzaldehyde (0.23 g; 3.8%) and 2-chloro-4,5-dihydroxybenzaldehyde (2.11 g; 37% unreacted starting material).

[0108] 1H-NMR (400 MHz; $CHCl_3$): 3.90 (s, 3H); 5.52 (s, 1H); 6.81 (s, 1H); 7.37 (s, 1H); 10.22 (s, 1H).

[0109] MS (m/z) ES−: 187 (30); 185 (MH−, 100).

b) 2-Chloro-4-methoxy-5-(2-morpholin-4-yl-ethoxy)-benzaldehyde (2)

[0110]



[0111] 2-Chloro-4-methoxy-5-hydroxybenzaldehyde (500 mg; 2.7 mmol), N-(2-chloroethyl)morpholin.HCl (5100 mg; 2.7 mmol) and K_2CO_3 (830 mg; 6 mmol) are refluxed in acetonitrile (3 ml) for 3 hours. The solvent is evaporated, the residue taken up in acetone (100 ml), filtered, concentrated until the title compound separated as slightly yellow crystals (487 mg; 60%).

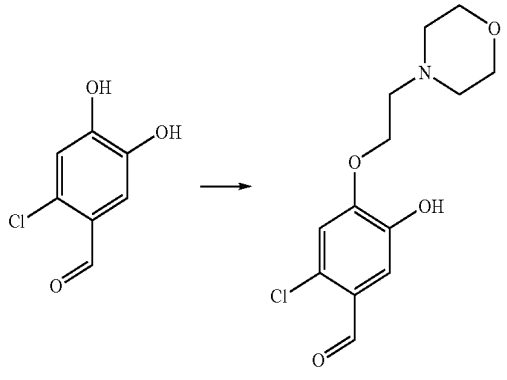
[0112] 1H-NMR (400 MHz; DMSO): 2.50 (bt, 4H); 2.72 (t, 2H); 3.58 (bt, 4H); 3.92 (s, 3H); 4.15 (t, 2H); 7.20 (s, 1H); 7.40 (s, 1H); 10.21 (s, 1H). Regiochemistry is proven by ROESY.

[0113] MS (m/z) EI: 299 (M+, 60); 100 (100).

Preparation of 2-chloro-5-methoxy-4-(2-N-morpholinylethyloxy)benzaldehyde (3)

a) 2-Chloro-5-hydroxy-4-(2-N-morpholinylethyloxy) benzaldehyde

[0114]



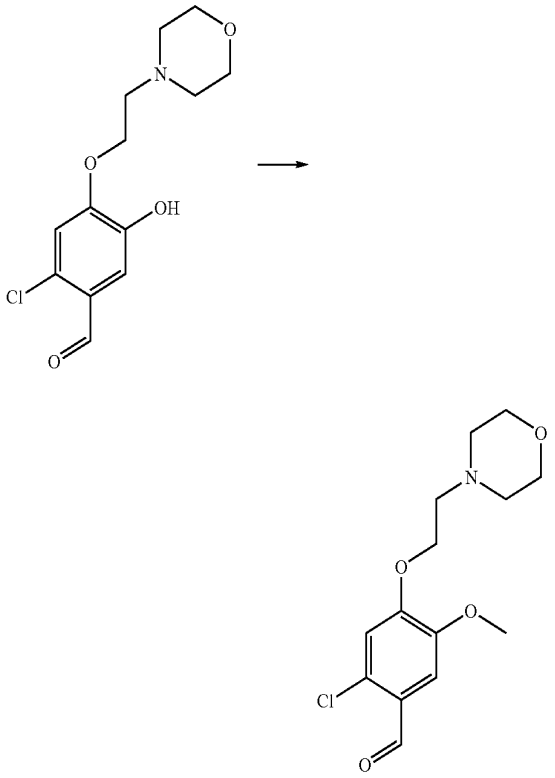
[0115] 2-Chloro-4,5-dihydroxybenzaldehyde Kaiser, C. et al in *J. Org. Chem.* 1974, 17(10), 1071-5) (500 mg; 2.9 mmol), N-(2-chloroethyl)morpholin.HCl (540 mg; 2.9 mmol), K_2CO_3 (880 mg; 6.4 mmol) are refluxed in acetonitrile (3 ml) for 3 hours, cooled, poured on 1N HCl and extracted with ethyl acetate twice. The aqueous phase is made basic by adding a saturated solution of $NaHCO_3$ and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4, evaporated to dryness yielding the title compound as slightly colored crystals (208 mg; 25%).

[0116] 1H-NMR (400 MHz; DMSO): 2.50 (bt, 4H); 2.73 (bt, 2H); 3.59 (bt, 4H); 4.25 (t, 2H); 7.22 (s, 1H); 7.27 (s, 1H); 10.17 (s, 1H).

[0117] MS (m/z) Cm: 286 (MH+, 100).

b) 2-Chloro-5-methoxy-4-(2-N-morpholinylethy-loxy)benzaldehyde (3)

[0118]



[0119] 2-Chloro-5-hydroxy-4-(2-N-morpholinylethyloxy) benzaldehyde (2.54 g: 8.9 mmol) in acetone (60 ml) is refluxed for 1 hour with MeI (0.56 ml; 8.9 mml) and K_2CO_3 (1.2 g; 8.9 mmol). The reaction mixture is diluted with water (100 ml) and 2N NaOH (20 ml) and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4, evaporated to dryness and purified via chromatography (SiO_2; acetone/hexanes 4/6>1/1) to yield the title compound as yellow crystals (850 mg; 32%)

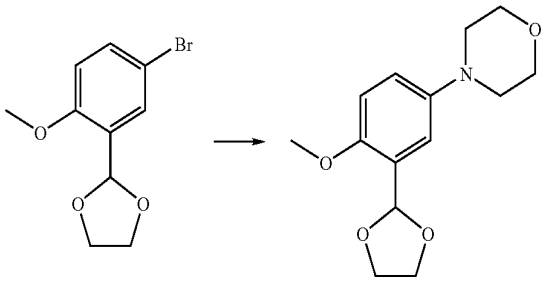
[0120] 1H-NMR (400 MHz; DMSO): 2.50 (m, 4H); 2.73 (t, 2H); 3.58 (t, 4H); 3.83 (s, 3H); 4.23 (t, 2H); 7.26 (s, 1H); 7.35 (s, 1H); 10.20 (s, 1H).

[0121] MS (m/z) Cm: 286 (MH+, 100).

Preparation of
2-methoxy-5-N-morpholinylbenzaldehyde (4)

a) 2-(1,3-dioxolan-2-yl)-4-N-morpholinylanisole

[0122]



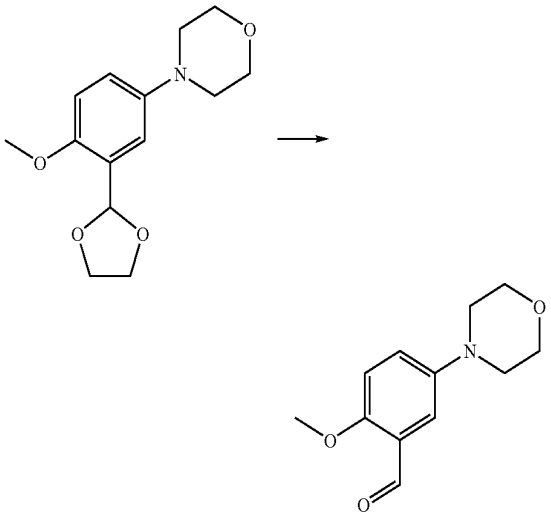
[0123] 2-(1,3-Dioxolan-2-yl)-4-bromoanisole (Hall C. et al: *J. Organomet. Chem.* 1998, 561(1-2), 209-219) (2.6 g; 10 mmol), morpholine (2.1 g; 24 mmol), NaOtBu (2.7 g; 28 mmol), $Pd2(dba)_3$ (46 mg; 0.05 mmol) and tri-o-tolylphosphine (61 mg; 0.2 mmol) are refluxed in dioxane (40 ml) for 1 hour poured on water and extracted with ethyl acetate three times. The combined organic phases are washed with water, dried over Na_2SO_4, evaporated to dryness and purified via chromatography (SiO_2; cyclohexane/acetone 85/15) to yield the title compound as yellow crystals (500 mg; 19%).

[0124] 1H-NMR (400 MHz; DMSO): 3.00 (bt, 4H); 3.77 (s, 3H); 3.78 (bt, 4H); 3.92 (m, 2H); 4.06 (m, 2H); 5.95 (s, 1H); 6.96 (s, 2H); 7.03 (s, 1H).

[0125] MS (m/z) EI: 265 (M+, 100); 250 (5); 207 (25); 135 (50).

b) 2-Methoxy-5-N-morpholinylbenzaldehyde (4)

[0126]



[0127] 2-(1,3-Dioxolan-2-yl)-4-N-morpholinylanisole (265 mg; 1 mmol) is treated with acetone/H_2SO_4 (10 ml/215 mg) for 10 min at room temperature. The reaction mixture is poured on 2N Na_2CO_3 and extracted with ethyl acetate twice. The combined organic phases are washed with water, dried over Na_2SO_4, evaporated to dryness and purified via chromatography (SiO_2; cyclohexane/acetone 85/15) to yield the title compound as yellow oil (200 mg; 90%).

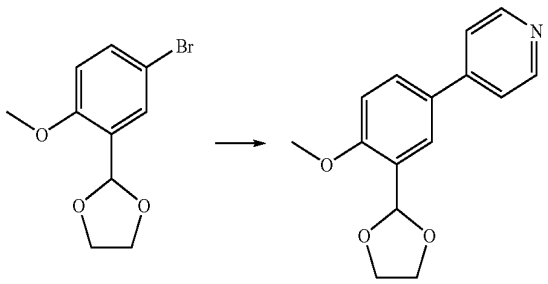
[0128] 1H-NMR (400 MHz; DMSO): 3.08 (bt, 4H); 3.76 (bt, 4H); 3.88 (s, 3H); 7.19 (d, 1H); 7.20 (s, 1H); 7.47 (dd, 1H); 10.35 (s, 1H).

[0129] MS (m/z) EI: 221 (M+; 100); 206 (25); 163 (80); 148 (20); 134 (20); 117 (15).

Preparation of
2-methoxy-5-(4-pyridinyl)benzaldehyde (5)

a) 2-(1,3-Dioxolan-2-yl)-4-(4-pyridinyl)anisole

[0130]



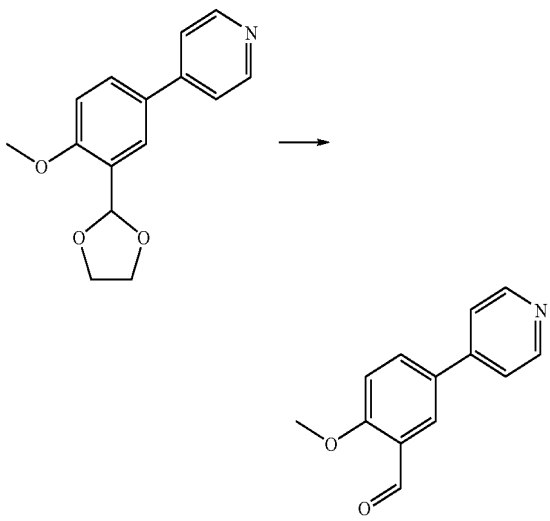
[0131] 2-(1,3-Dioxolan-2-yl)-4-bromoanisole (Hall C. et al: *J. Organomet. Chem.* 1998, 561(1-2), 209-219) (500 mg; 0.19 mmol) dissolved in xylene (10 ml) is combined with 4-trimethylstannylpyridine (560 mg; 0.23 mmol) and $PdCl_2(PPh_3)_2$ (140 mg; 0.019 mmol) and refluxed for 15 min. The reaction mixture is diluted with toluene, decanted and purified via chromatography (SiO_2; acetone/hexanes 2/8>4/6) to yield the title compound (346 mg; 70%) as a viscous oil.

[0132] 1H-NMR (400 MHz; DMSO): 3.87 (s, 3H); 3.95 (m, 2H); 4.10 (m, 2H); 6.03 (s, 1H); 7.20 (d, 1H); 7.67 (d, 2H); 7.82 (d, 1H); 7.85 (d, 1H); 8.58 (d, 2H).

[0133] MS (m/z) EI: 257 (M+, 100).

b) 2-Methoxy-5-(pyridinyl)benzaldehyde (5)

[0134]



[0135] 2-(1,3-Dioxolan-2-yl)-4-(4-pyridinyl)anisole (100 mg; 0.39 mmol) is refluxed with acetone/H_2SO_4conc (6 ml/90 mg; 0.8 mmol) for 10 min. The reaction mixture is

poured on 2N Na_2CO_3 and extracted with ethyl acetate three times. The combined organic phases are washed with water, dried over Na_2SO_4, evaporated to dryness and yielded the title compound as a yellow oil (79 mg; 95%).

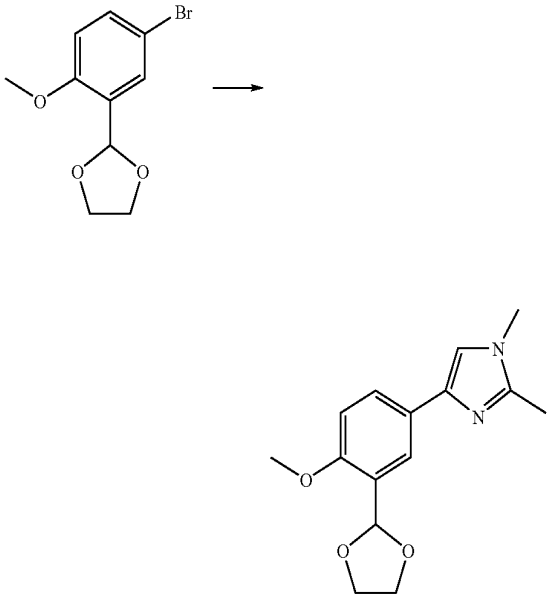
[0136] 1H-NMR (400 MHz; DMSO): 4.02 (s, 3H); 7.43 (d, 1H); 7.75 (d, 2H); 8.10 (d, 1H); 8.17 (dd, 1H); 8.63 (d, 2H); 10.42 (s, 1H).

[0137] MS (m/z) EI: 213 (M+, 100); 196 (30); 167 (25); 115 (15).

5-(1,2-Dimethyl-1.H.-imidazol-4-yl)-2-methoxy-benzaldehyde (8)

a) 4-(3-[1,3]Dioxolan-2-yl-4-methoxy-phenyl)-1,2-dimethyl-1.H.-imidazole

[0138]



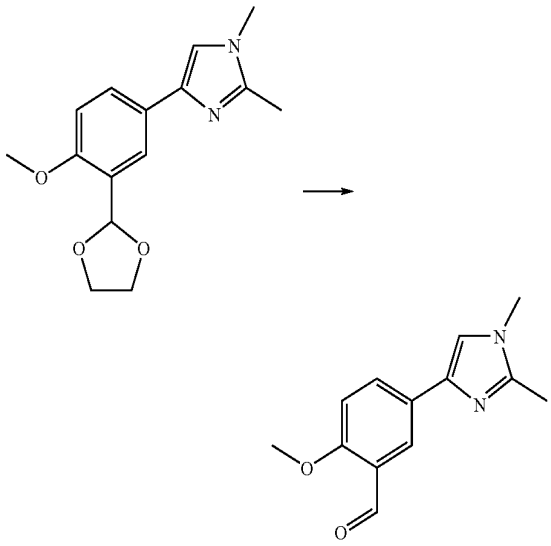
[0139] 1,2-Dimethyl-1.H.-imidazole (4.8 g, 50 mmol), 2-(5-bromo-2-methoxy-phenyl)-[1,3]dioxolane (6.5 g, 25 mmol), $Pd(OAc)_2$ (140 mg, 0.625 mmol), PPh_3 (327 mg, 1.25 mmol) and Cs_2CO_3 (8.15 g; 25 mmol) are dissolved in DMF (50 ml) and heated to 145 C for Sh under argon. The reaction mixture is poured on saturated NaCl-solution and extracted with EtOAc 3 times. The organic phases are dried over Na_2SO_4, evaporated to dryness and purified via chromatography (SiO_2, Acetone/EtOH 9/1) to yield the title compound as a clear oil (4.0 g; 58%).

[0140] 1H-NMR (400 MHz; DMSO-d6): 2.33 (s, 3H); 3.46 (s, 3H); 3.82 (s, 3H); 3.92 (m, 2H); 4.05 (m, 2H); 6.02 (s, 1H); 6.78 (s, 1H); 7.12 (d, 1H); 7.40 (m, 2H).

[0141] MS (m/z) ES+: 275 (MH+, 100).

b) 5-(1,2-Dimethyl-1.H.-imidazol-4-yl)-2-methoxy-benzaldehyde

[0142]



[0143] 4-(3-[1,3]Dioxolan-2-yl-4-methoxy-phenyl)-1,2-dimethyl-1.H.-imidazole (4.0 g, 14.5 mmol) is dissolved in acetone/H_2SO_4conc (264 ml/3.2 g) and stirred for 3 h at room temperature. Acetone is partially evaporated and the residue dissolved in EtOAc, washed with 2N Na_2CO_3 and water, dried over Na_2SO_4 and evaporated to dryness. The crude product is recrystallised from TBME/hexanes to yield the title compound as colorless crystals (2.8 g, 83%).

[0144] 1H-NMR (400 MHz; DMSO-d6): 2.34 (s, 3H); 3.49 (s, 3H); 3.96 (s, 3H); 6.85 (s, 1H); 7.34 (d, 1H); 7.66 (d, 1H); 7.73 (dd, 1H); 10.38 (s, 1H).

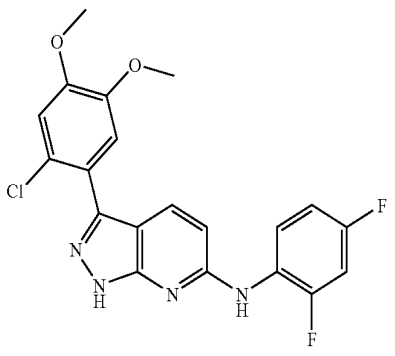
[0145] MS (m/z) EI: 230 (M+, 100), 215 (10(187 (40).

[0146] Aldehydes 1-6 are converted into the compounds of Examples 6-11 according to scheme 1 using the general procedure described for example 1.

Example 6

[3-(2-Chloro-4,5-dimethoxy-phenyl)-1.H.-pyrazolo [3,4-.b.]pyridin-6-yl]-(2,4-difluoro-phenyl)-amine

[0147]



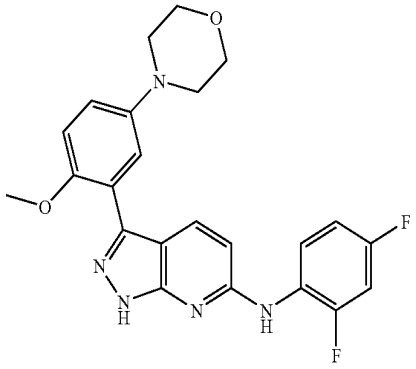
[0148] 1H-NMR (400 MHz; DMSO): 3.80 (s, 3H); 3.87 (s, 3H); 6.83 (d, 1H); 7.11 (m, 2H); 7.19 (s, 1H); 7.35 (bt, 1H); 7.84 (d, 1H); 8.17 (m, 1H); 9.03 (s, 1H); 13.20 (s, 1H).

[0149] MS (m/z) Cm: 415 (MH−, 100); 367 (50); 322 (40); 255 (15); 209 (80).

Example 7

(2,4-Difluoro-phenyl)-[3-(2-methoxy-5-morpholin-4-yl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

[0150]



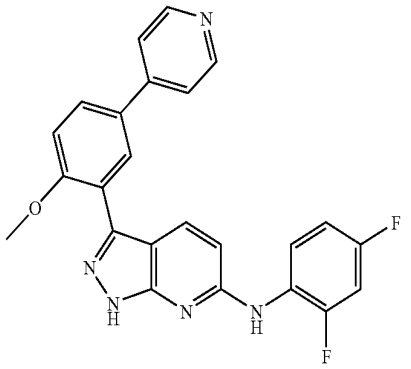
[0151] 1H-NMR (400 MHz; DMSO): 3.03 (m, 4H); 3.78 (m, 7H); 6.80 (d, 1H); 7.03 (dd, 1H); 7.10 (m, 2H); 7.18 (d, 1H); 7.33 (m, 1H); 7.87 (d, 1H); 8.18 (m, 1H); 8.97 (s, 1H); 13.2 (s, 1H).

[0152] MS (m/z) ES: 438 (M+, 100); 330 (20).

Example 8

(2,4-Difluoro-phenyl)-[3-(2-methoxy-5-pyridin-4-yl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

[0153]



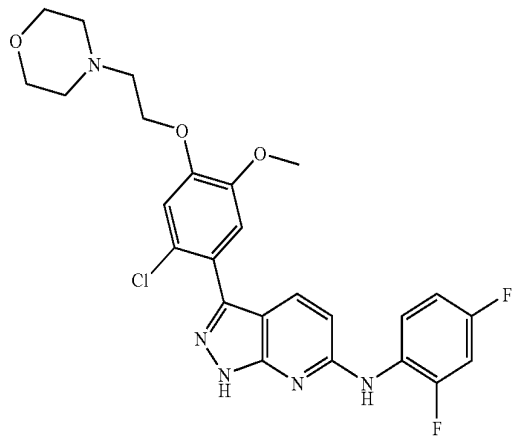
[0154] 1H-NMR (400 MHz; DMSO): 3.93 (s, 3H); 6.82 (d, 1H); 7.12 (m, 1H); 7.33 (m, 2H); 7.75 (d, 2H); 7.91 (m, 2H); 8.00 (d, 1H); 8.20 (m, 1H); 8.62 (d, 2H); 9.01 (s, 1H); 13.2 (s, 1H).

[0155] MS (m/z) ES: 430 (MH+, 100); 317 (10).

Example 9

{3-[2-Chloro-5-methoxy-4-(2-morpholin-4-yl-ethoxy)-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-(2,4-difluoro-phenyl)-amine

[0156]



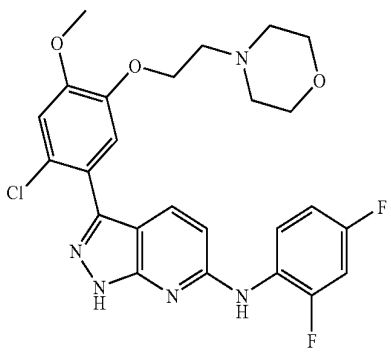
[0157] 1H-NMR (400 MHz; DMSO): 2.53 (bs, 4H); 2.75 (t, 2H); 3.62 (t, 4H); 3.82 (s, 3H); 4.20 (t, 2H); 6.84 (d, 1H); 7.10 (s, 1H); 7.13 (bd, 1H); 7.24 (s, 1H); 7.35 (dt, 1H); 7.84 (d, 1H); 8.17 (m, 1H); 9.05 (s, 1H); 13.10 (s, 1H).

[0158] MS (m/z) ES+: 516 (MH+, 100).

Example 10

{3-[2-Chloro-4-methoxy-5-(2-morpholin-4-yl-ethoxy)-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-(2,4-difluoro-phenyl)-amine

[0159]



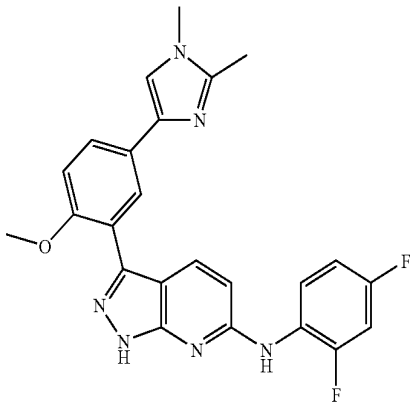
[0160] 1H-NMR (400 MHz; DMSO): 2.47 (t, 4H); 2.70 (t, 2H); 3.58 (t, 4H); 3.88 (s, 3H); 4.13 (t, 2H); 6.83 (d, 1H); 7.12 (bd, 1H); 7.16 (s, 1H); 7.19 (s, 1H); 7.33 (m, 1H); 7.84 (d, 1H); 8.18 (m, 1H); 9.05 (s, 1H); 13.20 (2, 1H).

[0161] MS (m/z) ES+: 516 (MH+, 100).

Example 11

(2,4-Difluoro-phenyl)-{3-[5-(1,2-dimethyl-1.H.-imidazol-4-yl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-amine

[0162]

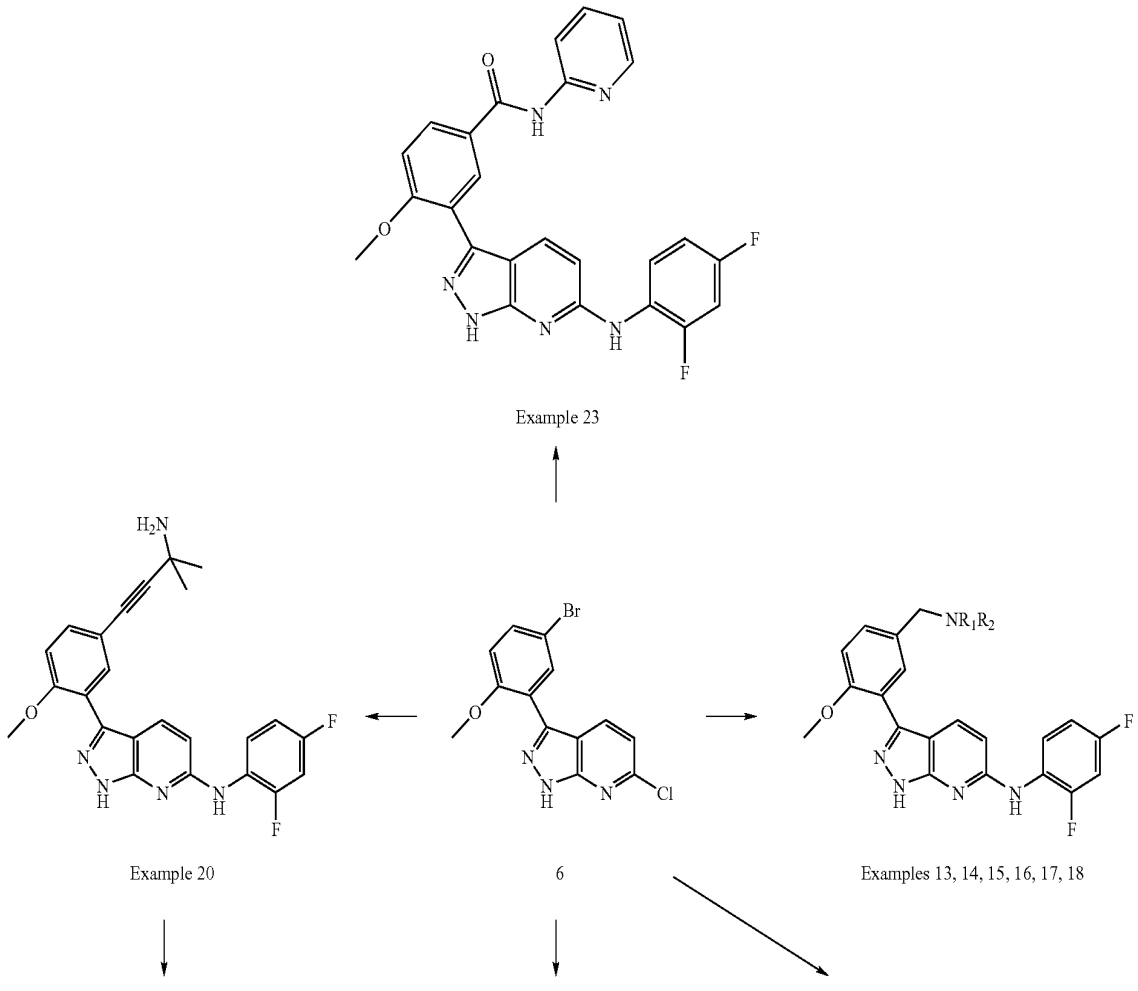


[0163] 1H-NMR (400 MHz; DMSO): 2.33 (s, 3H); 3.52 (s, 3H); 3.87 (s, 3H); 6.78 (d, 1H); 6.82 (s, 1H); 7.09 (bt, 1H); 7.26 (d, 1H); 7.34 (dt, 1H); 7.43 (dd, 1H); 7.57 (d, 1H); 7.87 (d, 1H); 8.18 (m, 1H); 8.98 (s, 1H, NH); 13.12 (s, 1H, NH).

[0164] MS (m/z) ES+: 447 (MH+, 100).

[0165] The common precursor for the compounds in Example 12-22 (scheme 3) is bromide 6, which is prepared according to scheme 1 from commercially available 5-bromo-2-methoxybenzaldehyde and 2,6-dichloropyridine in 3 steps following the general procedure described for Example 1c. Compound 6 is converted according to scheme 3 into aldehyde 7, which serves as precursor for the amines in Examples 13-18. Compound 6 is further transformed into the piperazine analogue in Example 22 and into the primary amines in Examples 20 and 21.

Scheme 3 (Examples 12-22)



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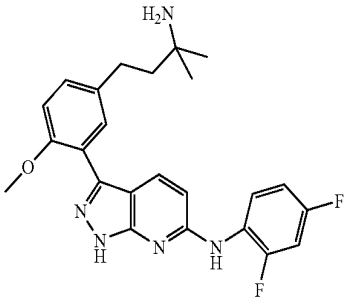
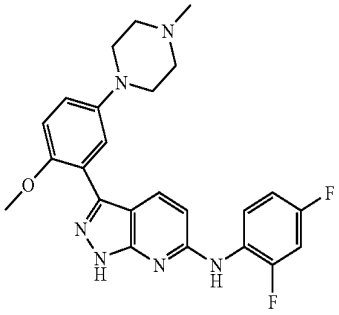
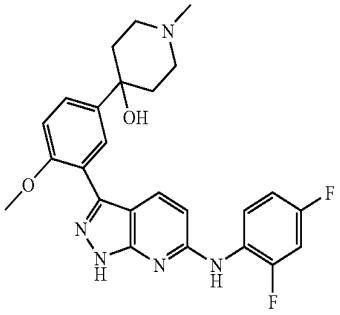


Example 21



Example 22



Example 12

Compound 6: 3-(5-Bromo-2-methoxy-phenyl-6-chloro-1.H.-pyrazolo[3,4-.b.]pyridine

[0166] Prepared from commercially available 5-bromo-2-methoxybenzaldehyde in three steps according to scheme 1 following the general procedure described for 6-chloro-3-(2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridine (1c).

[0167] 1H-NMR (400 MHz; DMSO): 3.87 (s, 3H); 7.21 (d, 1H); 7.29 (d, 1H); 7.63 (dd, 1H); 7.78 (d, 1H); 8.25 (d, 1H).

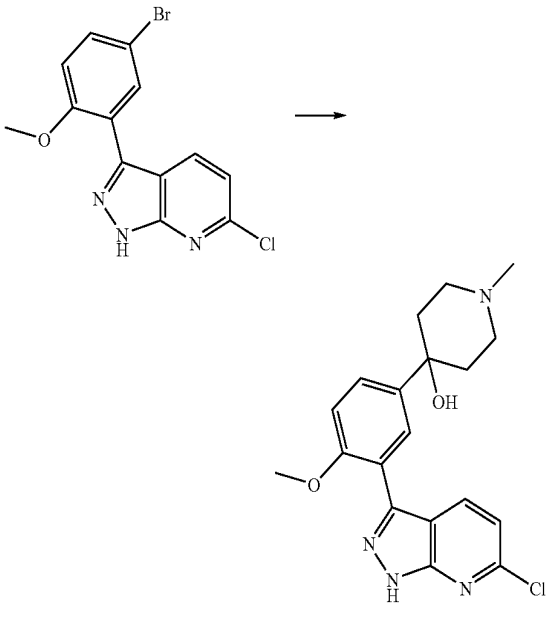
[0168] MS (m/z) Cm: 338 (MH−, 100); 255 (20); 173 (25); 155 (50).

Example 12

4-{3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl]-4-methoxy-phenyl}-1-methyl-piperidin-4-ol

a) 4-[3-(6-Chloro-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl)-4-methoxy-phenyl]-1-methyl-piperidin-4-ol

[0169]



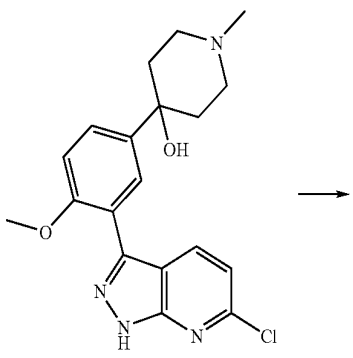
[0170] nBuLi (1.46 ml; 2.33 mmol of a 1.6M solution in hexane) is slowly added at −78° C. to a solution of 3-(5-bromo-2-methoxy-phenyl)-6-chloro-1.H.-pyrazolo[3,4-.b.]pyridine (compound 6) (400 mg; 1.2 mmol) in THF (10 ml). The yellow solution is stirred at −78° C. for 10 min, then N-methyl-4-piperidone (0.272 ml; 2.4 mmol) in THF (0.5 ml) is added rapidly. After stirring for another 10 min at −78° C., the reaction mixture is poured on an aqueous NaCl solution and extracted with ethyl acetate three times. The combined organic phases are washed with water, dried over Na_2SO_4, evaporated to dryness and yielded the title compound as a yellow foam, which crystallised upon taking up in ether (280 mg; 62%).

[0171] 1H-NMR (400 MHz; DMSO): 1.63 (bd, 2H); 1.97 (dt, 2H); 2.22 (s, 3H); 2.37 (bt, 2H); 2.53 (bt, 2H); 3.83 (s, 3H); 4.77 (s, 1H, OH); 7.15 (d, 1H); 7.20 (bd, 1H); 7.51 (dd, 1H); 7.78 (d, 1H); 8.19 (d, 1H).

[0172] MS (m/z) ES+: 373 (MH+; 100).

b) 4-{3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl]-4-methoxy-phenyl}-1-methyl-piperidin-4-ol

[0173]



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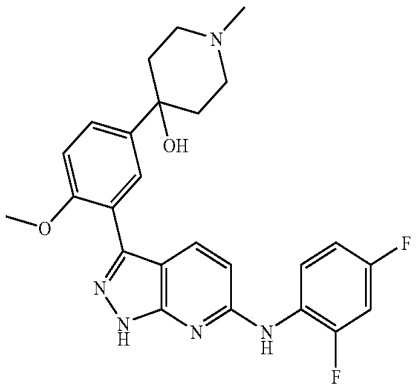


[0174] 4-[3-(6-Chloro-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl)-4-methoxy-phenyl]-1-methyl-piperidin-4-ol (280 mg; 0.75 mmol) and 2,4-difluoroaniline (3 ml; 29 mmol) are dissolved in hot dioxane, combined with NaOtBu (280 mg; 2.9 mmol), $Pd(OAc)_2$ (25 mg; 0.11 mol) and R-(+)-BINAP (25 mg; 0.04 mmol) and refluxed for 30 min. The reaction mixture is poured on water/NaCl and extracted with ethyl acetate three times. The combined organic phases are washed with water, dried over Na_2SO_4, evaporated to dryness and purified via chromatography (SiO_2; TBME/MeOH/NH_3conc 80/20/2) to yield the title compound as brownish crystals (180 mg; 52%)

[0175] 1H-NMR (400 MHz; DMSO): 1.64 (bd, 2H); 1.96 (dt, 2H); 2.22 (s, 3H); 2.37 (bt, 2H); 2.53 (bt, 2H); 3.83 (s, 3H); 4.73 (s, 1H); 6.80 (d, 1H); 7.11 (m, 2H); 7.33 (dt, 1H); 7.48 (dd, 1H); 7.72 (d, 1H); 7.87 (d, 1H); 8.20 (m, 1H); 8.97 (s, 1H); 13.10 (s, 1H).

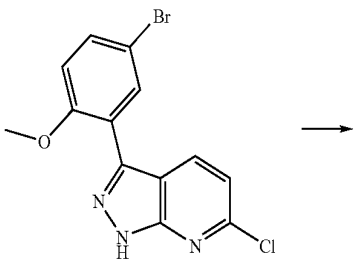
[0176] MS (m/z) ES+: 466 (MH+, 100).

Example 13

(2,4-Difluoro-phenyl)-[3-(2-methoxy-5-methylaminomethyl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

a) 3-(6-Chloro-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl)-4-methoxy-benzaldehyde

[0177]



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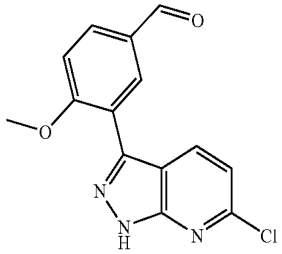


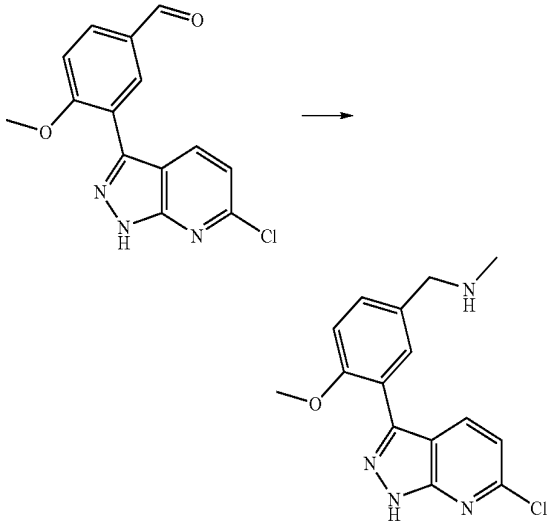
[0178] 3-(5-Bromo-2-methoxy-phenyl)-6-chloro-1.H.-pyrazolo[3,4-.b.]pyridine-(compound 6) (1 g; 2.9 mmol) in THF (50 ml) is cooled to −78° C. and treated with nBuLi (3.7 ml; 5.9 mml of a 1.6M solution in hexane). After 10 min at −78° C. DMF (0.455 ml; 6.6 mmol) is introduced and stirring continued for 10 min. The reaction mixture is warmed to −30 C, poured on water/NaCl and extracted with TBME three times. The combined organic phases are washed with water, dried over Na_2SO_4, evaporated to dryness and purified via chromatography (SiO2; acetone/hexanes 1/9>2/8) to yield the desired aldehyde (270 mg; 31%) as colorless crystals and debrominated starting material (330 mg)

[0179] 1H-NMR (400 MHz; DMSO): 4.00 (s, 3H); 7.31 (d, 1H); 7.46 (d, 1H); 8.06 (dd, 1H); 8.21 (s, 1H); 8.27 (d, 1H); 10.00 (s, 1H); 14.10 (s, 1H, NH).

[0180] MS (m/z) EI: 287 (M+, 100); 271 (15); 258 (25).

b) [3-(6-Chloro-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl)-4-methoxy-benzyl]-methyl-amine

[0181]



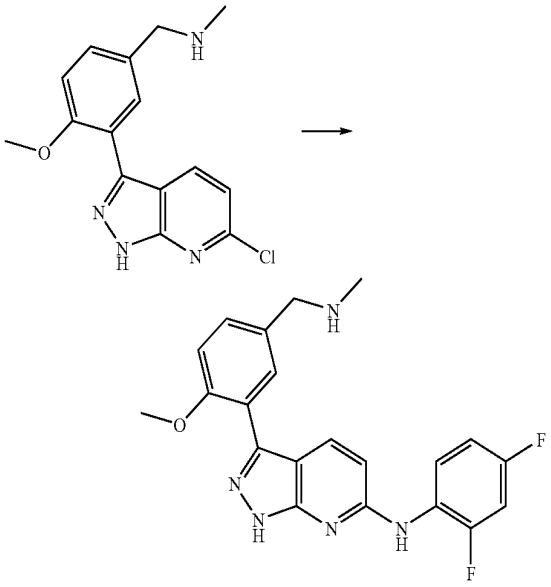
[0182] 3-(6-Chloro-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl)-4-methoxy-benzaldehyde (270 mg; 0.94 mmol) is dissolved in EtOH (75 ml), warmed to 40° C. and combined with a 10% solution of $MeNH_2$ in EtOH (4.5 ml). After stirring at 40° C. for 2 min, $NaBH_4$ (54 mg; 1.4 mmol) in EtOH (2 ml) is added and stirring continued for 5 min. The reaction mixture was poured on water/NaCl and extracted with TBME three times. The combined organic phases are washed with water, dried over Na_2SO_4, evaporated to dryness and purified via chromatography (SiO_2; TBME/MeOH/NH_3conc 80(18/2) to yield the title compound as a colorless foam (140 mg; 49%).

[0183] 1H-NMR (400 MHz; DMSO): 2.31 (s, 3H); 3.68 (s, 2H); 3.85 (s, 3H); 7.18 (bt, 1H); 7.25 (s, 1H); 7.43 (bs, 1H); 7.60 (s, 1H); 8.22 (s, 1H).

[0184] MS (m/z) EI: 302 (M+, 40); 272 (50); 139 (40).

c) (2,4-Difluoro-phenyl)-[3-(2-methoxy-5-methylaminomethyl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

[0185]



[0186] The Buchwald reaction is carried out by analogy to Example 12b) and yields the desired compound as a colorless foam in 10% yield.

[0187] 1H-NMR (400 MHz; DMSO): 2.28 (s, 3H); 3.63 (s, 2H); 3.82 (s, 3H); 6.80 (d, 1H); 7.11 (m, 2H); 7.32 (m, 2H); 7.54 (d, 1H); 7.88 (d, 1H); 8.20 (m, 1H); 8.98 (s, 1H); 13.05 (s, 1H).

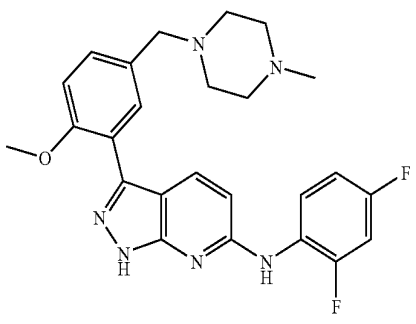
[0188] MS (m/z) ES+: 396 (MH+, 20); 365 (100).

[0189] Compounds of Examples 14-18 are prepared from 3-(6-Chloro-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl)-4-methoxy-benzaldehyde (Example 13a) by a reductive amination followed by a Buchwald reaction by analogy to Example 13:

Example 14

(2,4-Difluoro-phenyl)-{3-[2-methoxy-5-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-amine

[0190]



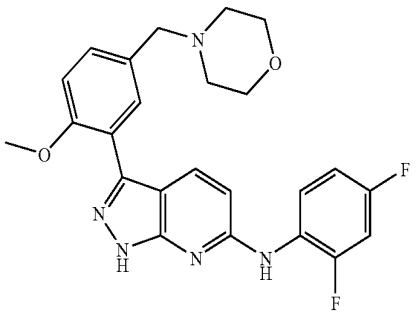
[0191] 1H-NMR (400 MHz; DMSO): 2.17 (s, 3H); 2.24-2.48 (m, 8H); 3.43 (s, 2H); 3.82 (s, 3H); 6.80 (d, 1H); 7.11 (m, 2H); 7.29-7.38 (m, 2H); 7.53 (s, 1H); 7.88 (d, 1H); 8.18 (m, 1H); 8.98 (s, 1H); 13.2 (s, 1H).

[0192] MS (m/z) ES+: 465 (MH+, 100); 365 (20).

Example 15

(2,4-Difluoro-phenyl)-[3-(2-methoxy-5-morpholin-4-ylmethyl-phenyl)-1H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

[0193]



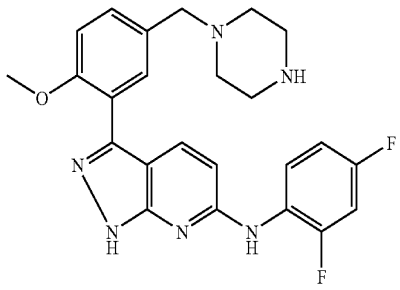
[0194] 1H-NMR (400 MHz; DMSO): 2.38 (bs, 4H); 3.47 (s, 2H); 3.59 (bs, 4H); 3.84 (s, 3H); 6.80 (d, 1H); 7.12 (m, 2H); 7.33 (m, 2H); 7.56 (d, 1H); 7.88 (d, 1H); 8.19 (m, 1H); 8.97 (s, 1H); 13.2 (s, 1H).

[0195] MS (m/z) ES+: 452 (MH+, 100); 365 (50); 330 (10); 289 (10).

Example 16

(2,4-Difluoro-phenyl)-[3-(2-methoxy-5-piperazin-1-ylmethyl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

[0196]



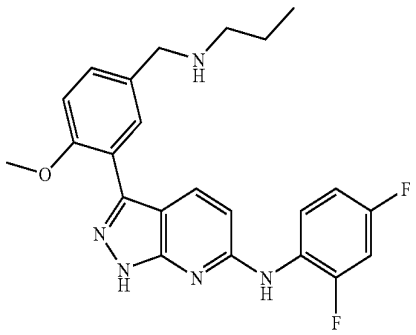
[0197] 1H-NMR (400 MHz; DMSO): 2.31 (m, 4H); 2.67 (m, 4H); 3.41 (s, 2H); 3.83 (s, 3H); 6.80 (d, 1H); 7.11 (m, 2H); 7.28-7.37 (m, 2H); 7.52 (d, 1H); 7.88 (d, 1H); 8.18 (m, 1H); 8.97 (s, 1H); 13.10 (s, 1H).

[0198] MS (m/z) ES+: 451 (MH+, 100); 365 (20).

Example 17

(2,4-Difluoro-phenyl)-[3-(2-methoxy-5-propylaminoethyl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine

[0199]



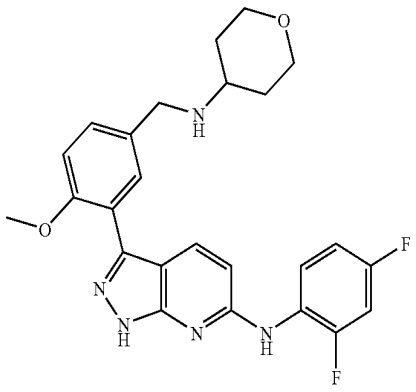
[0200] 1H-NMR (400 MHz; DMSO): 0.88 (t, 3H); 1.44 (q, 2H); 2.47 (t, 2H); 3.69 (s, 2H); 3.83 (s, 3H); 6.82 (d, 1H); 7.12 (m, 2H); 7.35 (m, 2H); 7.56 (d, 1H); 7.88 (d, 1H); 8.21 (m, 1H); 8.98 (s, 1H, NH); 13.09 (s, 1H, NH).

[0201] MS (m/z) ES+: 422 (MH+, 100).

Example 18

(2,4-Difluoro-phenyl)-(3-{2-methoxy-5-[(tetrahydropyran-4-ylamino)-methyl]-phenyl}-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl)-anine

[0202]



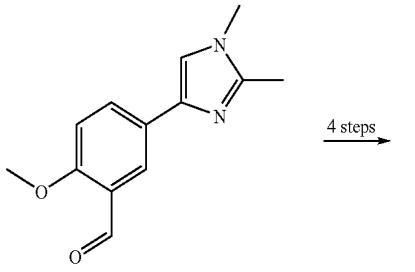
[0203] 1H-NMR (400 MHz; DMSO): 1.22-1.47 (m, 2H); 1.82 (bd, 2H); 2.63 (m, 1H); 3.30 (m, 2H); 3.75 (bs, 2H); 3.87 (m, 2H); 3.83 (s, 3H); 6.81 (d, 1H); 7.12 (m, 2H); 7.31-7.40 (m, 2H); 7.58 (d, 1H); 7.88 (d, 1H); 8.13-8.23 (m, 1H); 8.98 (s, 1H, NH); 13.09 (s, 1H, NH).

[0204] MS (m/z) ES+: 466 (MH+, 100).

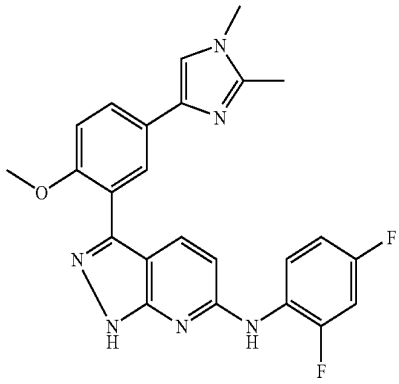
Example 19

(2,4-Difluoro-phenyl)-{3-[5-(1,2-dimethyl-1.H.-imidazol-4-yl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-amine

[0205] (2,4-Difluoro-phenyl)-{3-[5-(1,2-dimethyl-1.H.-imidazol-4-yl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl} is prepared in four steps from 5-(1,2-Dimethyl-1.H.-imidazol-4-yl)-2-methoxy-benzaldehyde (compound 8) and 2,6-dichloropyridine as described in examples 1a)-1d)



compound 8



Example 21

[0206] 1H-NMR (400 MHz; DMSO): 2.33 (s, 3H); 3.52 (s, 3H); 3.87 (s, 3H); 6.78 (d, 1H); 6.82 (s, 1H); 7.08 (bt, 1H); 7.26 (d, 1H); 7.33 (dt, 1H); 7.43 (dd, 1H); 7.57 (5, 1H); 7.87 (d, 1H); 8.13 (m, 1H); 8.98 (s, 1H, NH); 13.12 (s, 1H, NH).

[0207] MS (m/z) ES+: 447 (MH+, 100).

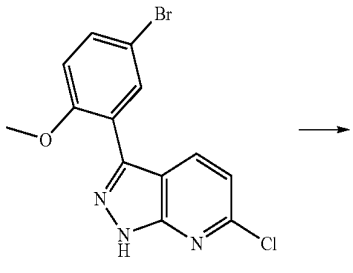
[0208] Example 20 (scheme 3) is prepared in two steps from 3-(5-bromo-2-methoxy-phenyl)-6-chloro-1.H.-pyrazolo[3,4-.b.]pyridine (compound 6) by a Sonogashira coupling with 3-amino-3-methyl-1-butyne followed by a Buchwald reaction. Hydrogenation of the triple bond delivered the compound of Example 21:

Example 20

{3-[5-(3-Amino-3-methyl-but-1-ynyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-(2,4-difluoro-phenyl)-amine

a) 3-[3-(6-Chloro-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl)-4-methoxy-phenyl]-1,1-dimethyl-prop-2-ynylamine

[0209]



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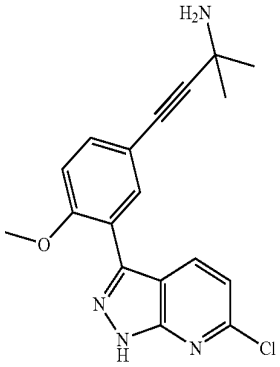


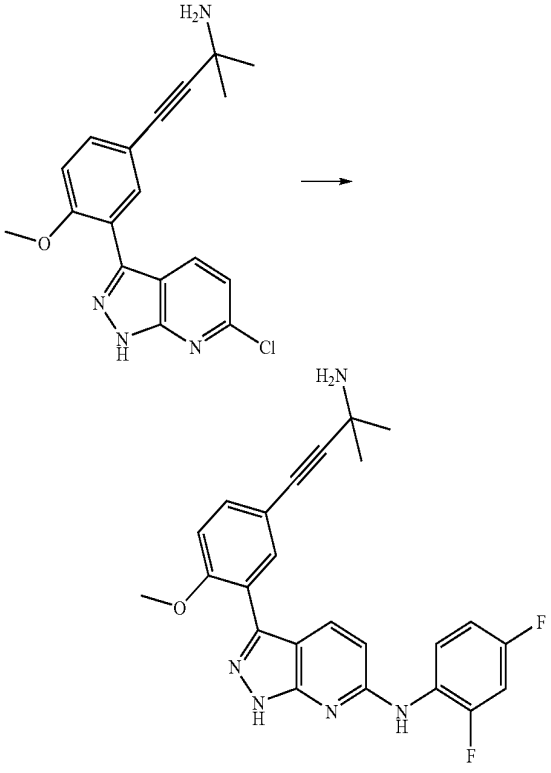
[0210] 3-(5-Bromo-2-methoxy-phenyl)-6-chloro-1.H.-pyrazolo[3,4-.b.]pyridine (compound 6) (1 g; 2.94 mmol), 3-amino-3-methyl-1-butyne (0.35 ml; 3.3 mmol), $PdCl_2(PPh_3)_2$ (210 mg; 0.29 mmol) and CuI (172 mg; 0.29 mmol) are refluxed in triethylamine (140 ml) and dioxane (30 ml) for 3 hours. The reaction mixture is filtered, evaporated and purified via chromatography (SiO_2; TBME/MeOH/NH_3conc 90/9/1) to yield the title compound as a yellow foam (218 mg; 20%).

[0211] 1H-NMR (400 MHz; DMSO): 1.40 (s, 6H); 3.88 (s, 3H); 7.20 (d, 1H); 7.28 (d, 1H); 7.47 (dd, 1H); 7.63 (d, 1H); 8.23 (d, 1H);

[0212] MS (m/z) EI: 340 (M+, 10); 325 (100), 277 (20).

b) {3-[5-(3-Amino-3-methyl-but-1-ynyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-(2,4-difluoro-phenyl)-amine

[0213]



[0214] 3-[3-(6-Chloro-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl)-4-methoxy-phenyl]-1,1-dimethyl-prop-2-ynylamine (350 mg; 1.02 mmol) in dioxane (7 ml) is combined with 2,4-difluoroaniline (3 ml; 19.3 mmol), NaOtBu (350 mg; 3.6 mmol), $Pd(OAc)_2$ (70 mg; 0.308 mol) and R-(+)-BINAP (70 mg; 0.112 mmol) and refluxed for 1 hour. The reaction mixture is poured on 2N HCl and extracted with ethyl acetate three times. The combined organic phases are made basic with 2N NaOH and extracted three times with ethyl acetate. The combined organic phases are dried over Na_2SO_4 and evaporated to dryness. The residue is further purified by dissolving in hot toluene and filtering off the dark precipitate formed after cooling. Toluene is evaporated and the residue recrystallised from ethyl acetate resulting in the title compound as off-white crystals (20 mg; 6%).

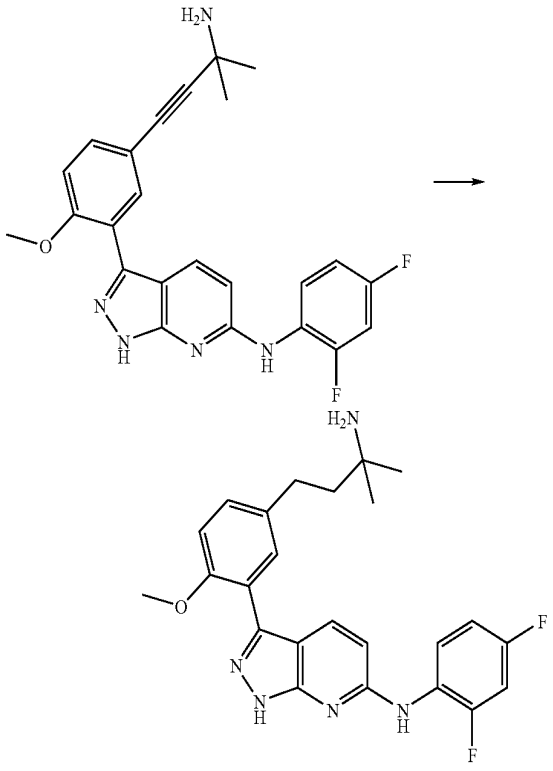
[0215] 1H-NMR (400 MHz; DMSO): 1.39 (s, 6H); 2.06 (bs, 2H); 3.80 (s, 3H); 6.81 (d, 1H); 7.11 (bd, 1H); 7.15 (d, 1H); 7.34 (dt, 1H); 7.40 (d, 1H); 7.59 (d, 1H); 7.88 (d, 1H); 8.18 (m, 1H); 9.00 (s, 1H); 13.17 (s, 1H).

[0216] MS (m/z) ES+: 434 (MH+, 70); 417 (100).

Example 21

{3-[5-(3-Amino-3-methyl-butyl-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-(2,4-difluoro-phenyl)-amine

[0217]



[0218] {3-[5-(3-Amino-3-methyl-but-1-ynyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-(2,4-difluoro-phenyl)-amine (50 mg; 0.11 mmol) is dissolved in EtOH (100 ml) and hydrogenated over 10% Pd/C (100 mg) for 1 hour.

The reaction mixture is filtered, evaporated and yields the title compound as colorless crystals (30 mg; 60%) after recrystallisation from ether/hexanes.

[0219] 1H-NMR (400 MHz; DMSO): 1.08 (s, 6H); 1.53-1.60 (m, 4H); 2.58-2.63 (m, 2H); 3.81 (s, 3H); 6.80 (d, 1H); 7.03-7.14 (m, 2H); 7.22 (d, 1H); 7.32 (bt, 1H); 7.43 (s, 1H); 7.87 (d, 1H); 8.19 (m, 1H); 8.90 (s, 1H); 13.10 (s, 1H).

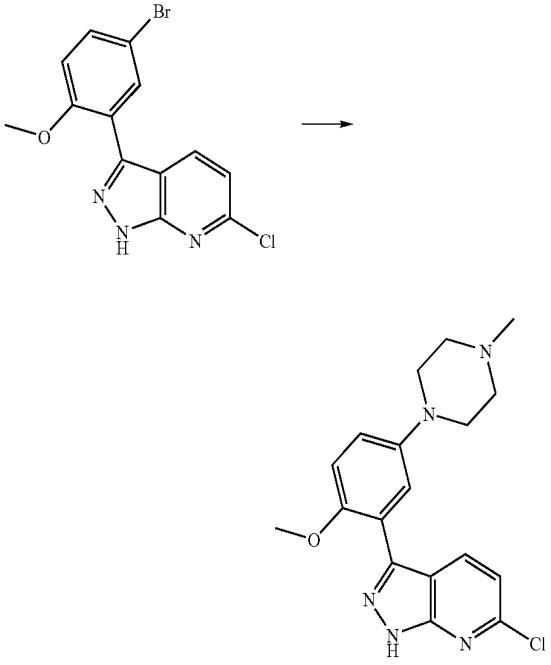
[0220] MS (m/z) ES+: 438 (MH+, 100); 421 (20); 192 (10); 180 (50).

Example 22

(2,4-Difluoro-phenyl)-{3-[2-methoxy-5-(4-methyl-piperazin-1-yl)-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-amine

a) 6-Chloro-3-[2-methoxy-5-(4-methyl-piperazin-1-yl)-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridine

[0221]



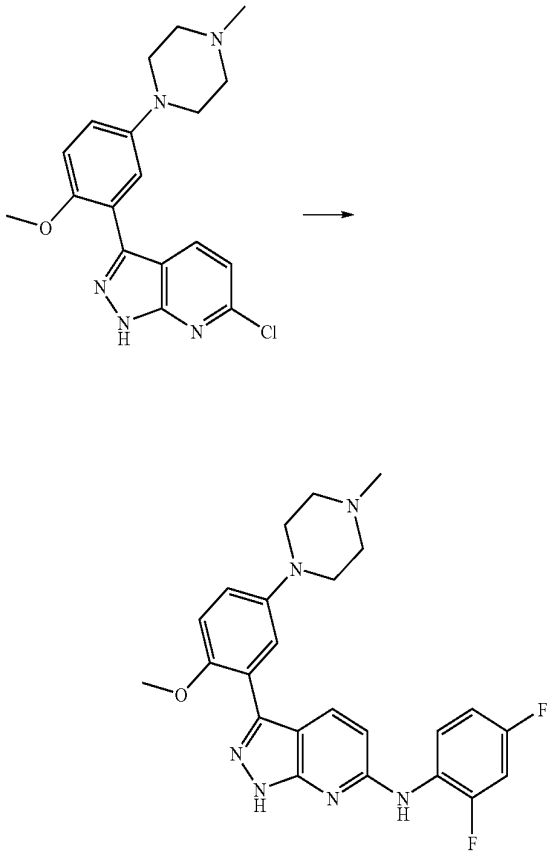
[0222] 3-(5-Bromo-2-methoxy-phenyl)-6-chloro-1.H.-pyrazolo[3,4-.b.]pyridine (compound 6) (200 mg; 0.588 mmol) NaOtBu (224 mg; 2.3 mmol), $Pd(OAc)_2$ (20 mg; 0.08 mol) and R-(+)-BINAP (20 mg; 0.03 mmol) and N-methylpiperazine (0.1 ml; 1 mmol) are refluxed in dioxane (4 ml) for 3 hours. TBME (20 ml) is added to the reaction mixture, filtered from the precipitate and purified via chromatography (SiO_2; TBME/MeOH/NH_3conc 90/10/1) to yield the title compound (40 mg; 19%) after recrystallisation from ether/hexanes.

[0223] 1H-NMR (400 MHz; DMSO): 2.24 (s, 3H); 2.48 (bt, 4H); 3.10 (bt, 4H); 3.78 (s, 3H); 7.05-7.11 (m, 2H); 7.20 (d, 1H); 7.28 (d, 1H); 8.20 (d, 1H); 13.90 (bs, 1H).

[0224] MS (m/z) Cm: 358 (MH+, 100); 324 (10).

b) (2,4-Difluoro-phenyl)-{3-[2-methoxy-5-(4-methyl-piperazin-1-yl)-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-amine (Example 8)

[0225]



[0226] 6-Chloro-3-[2-methoxy-5-(4-methyl-piperazin-1-yl)-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridine (186 mg; 0.52 mmol) in dioxane (4 ml) is combined with 2,4-difluoroaniline (3 ml; 19.3 mmol), NaOtBu (186 mg; 1.9 mmol), $Pd(OAc)_2$ (40 mg; 0.175 mol) and R-(+)-BINAP (40 mg; 0.063 mmol) and refluxed for 1 hour. The reaction mixture is taken up in 2N HCl and washed with ethyl acetate twice. The aqueous layer is made basic with 2N NaOH and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4, filtered and evaporated to dryness to yield a dark residue, which is crystallised twice from hot toluene to render the title compound as slightly colored crystals (45 mg; 20%).

[0227] 1H-NMR (400 MHz; DMSO): 2.23 (s, 3H); 2.45 (m, 4H); 3.07 (m, 4H); 3.77 (s, 3H); 6.79 (d, 1H); 7.01 (dd, 1H); 7.05-7.14 (m, 2H); 7.18 (d, 1H); 7.33 (m, 1H); 7.85 (d, 1H); 8.19 (m, 1H); 8.96 (s, 1H); 13.2 (s, 1H).

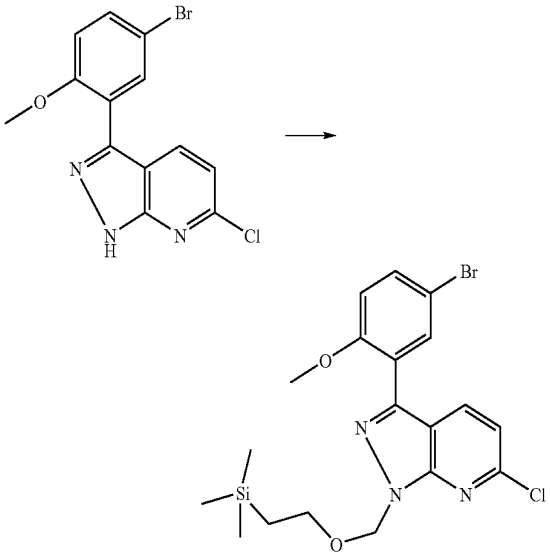
[0228] MS (m/z) Cm: 451 (MH+, 100).

Example 23

3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl]-4-methoxy-.N.-pyridin-2-yl-benzamide

a) 3-(5-Bromo-2-methoxy-phenyl-6-chloro-1-(2-trimethylsilanyl-ethoxymethyl)-1.H.-pyrazolo[3,4-.b.]pyridine

[0229]



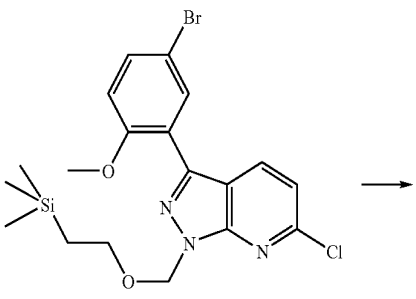
[0230] 3-(5-Bromo-2-methoxy-phenyl)-6-chloro-1.H.-pyrazolo[3,4-.b.]pyridine (6.8 g; 20 mmol) is dissolved in THF (240 ml) and treated at −78 C with KN(TMS)2 (5.25 g; 25 mmol). After stirring for 15 minutes at −78 C, (2-chloromethoxy-ethyl)-trimethyl-silane (4.47 ml; 25 mmol) is added and stirring continued for 15 minutes at −78 C. The reaction mixture is warmed to 0 C, poured on water/NaCl and extracted with TBME three times. The combined organic phases are dried over Na_2SO_4 and evaporated to dryness. Purification via chromatography (SiO_2; TBME/cyclohexane 10/90) yields the title compound as a colorless foam (6.0 g; 64%), which is eluted before its isomer 3-(5-bromo-2-methoxy-phenyl)-6-chloro-2-(2-trimethylsilanyl-ethoxymethyl)-2.H.-pyrazolo[3,4-.b.]pyridine (3.2 g; 34%).

[0231] 1H-NMR (400 MHz; DMSO): −0.08 (s, 9H); 0.88 (t, 2H); 3.68 (t, 2H); 3.88 (s, 3H); 5.81 (s, 2H); 7.23 (d, 1H); 7.40 (d, 1H); 7.68 (dd, 1H); 7.76 (d, 1H); 8.28 (d, 1H).

[0232] MS (m/z) ES+: 470 (MH+; 100).

b) 3-[6-Chloro-1-(2-trimethylsilanyl-ethoxymethyl)-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl]-4-methoxy-benzoic acid

[0233]



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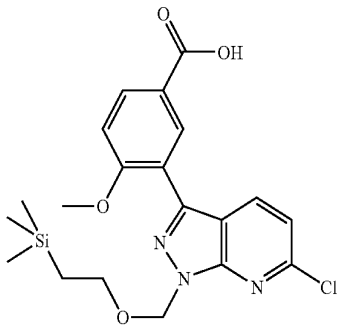


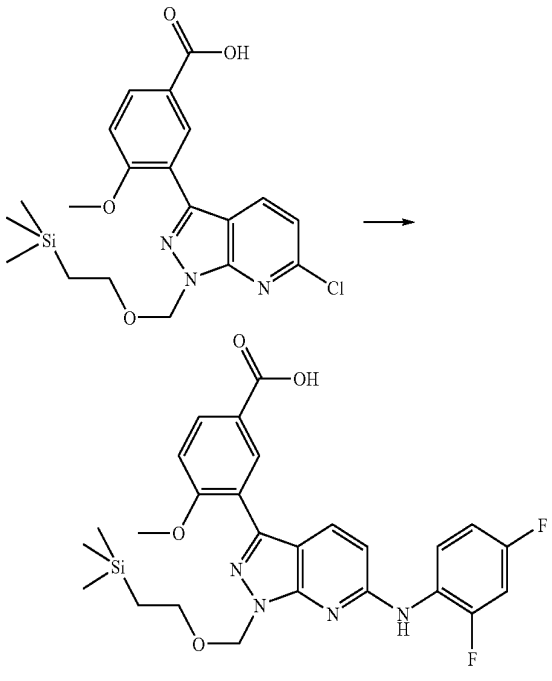
[0234] 3-(5-Bromo-2-methoxy-phenyl)-6-chloro-1-(2-trimethylsilanyl-ethoxymethyl)-1.H.-pyrazolo[3,4-.b.]pyridine (3 g; 6.38 mmol) in THF (90 ml) is cooled to −78 C and treated with nBuLi (4.4 ml; 7.02 mmol of a 1.6M solution in hexane). Stirring is continued for 10 minutes, then CO_2-gas is introduced during 5 minutes. The reaction mixture is stirred for 10 minutes at −78 C, then poured on 0.1 M HCl-solution and extracted with EtOAc three times. The organic phases are washed with brine, dried over Na_2SO_4 and evaporated to dryness. Purification via chromatography (SiO_2, acetone/hexanes/HOAc 20/80/1) yields the title compound (3.2 g; 58%) as colorless crystals.

[0235] 1H-NMR (400 MHz; DMSO): −0.08 (s, 9H); 0.88 (t, 2H); 3.68 (t, 2H); 3.95 (s, 3H); 5.82 (s, 2H); 7.33 (d, 1H); 7.38 (d, 1H); 8.09 (dd, 1H); 8.22 (d, 1H); 8.30 (d, 1H).

[0236] MS (m/z) ES−: 432 (MH−; 100).

c) 3-[6-(2,4-Difluoro-phenylamino)-1-(2-trimethylsilanyl-ethoxymethyl-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl]-4-methoxy-benzoic acid

[0237]



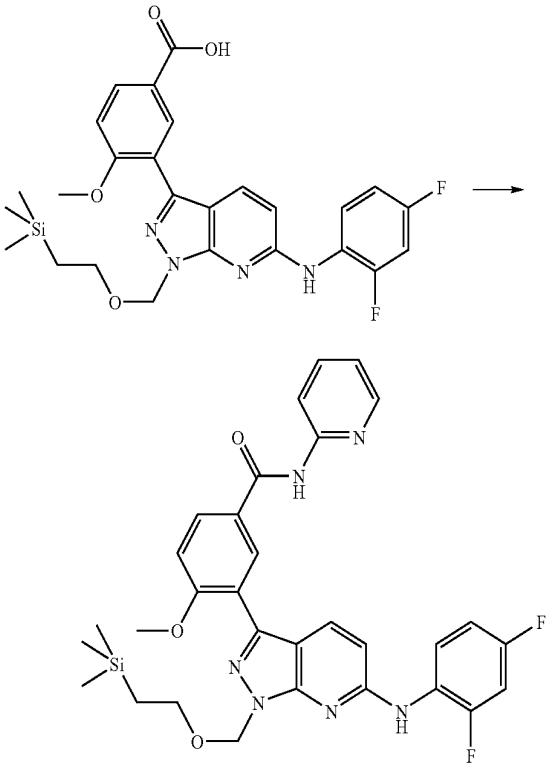
[0238] 3-[6-Chloro-1-(2-trimethylsilanyl-ethoxymethyl)-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl]-4-methoxy-benzoic acid (3.2 g; 7.39 mmol), R-(+)-BINAP (229 mg; 0.369 mmol), $Pd(OAc)_2$ (248 mg; 1.1 mmol), PPh_3 (503 mg; 1.9 mmol), 2,4-difluoroaniline (18.7 ml; 184 mmol) and NaOtBu (1.77 g; 18.47 mmol) are dissolved in dioxane (50 ml) and heated to 130 C for 15 minutes. The reaction mixture is poured on brine and extracted with EtOAc twice. The combined organic phases are washed with 0.1N HCl and water, dried over Na_2SO_4 and evaporated to dryness. The crude product was purified via chromatography (SiO_2, Acetone/cyclohexane/HOAc 20/80/1) to yield the title compound as yellowish crystals (3.4 g; 87%).

[0239] 1H-NMR (400 MHz; DMSO): −0.08 (s, 9H); 0.85 (t, 2H); 3.62 (t, 2H); 3.93 (s, 3H); 5.68 (s, 2H); 6.90 (d, 1H); 7.11 (dt, 1H); 7.28-7.38 (m, 2H); 7.92 (d, 1H); 8.03 (dd, 1H); 8.23 (d, 1H); 8.35-8.45 (m, 1H); 9.20 (s, 1H).

[0240] MS (m/z) ES−: 525 (MH−; 100).

d) 3-[6-(2,4-Difluoro-phenylamino)-1-(2-trimethylsilanyl-ethoxymethyl)-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl]-4-methoxy-.N.-pyridin-2-yl-benzamide

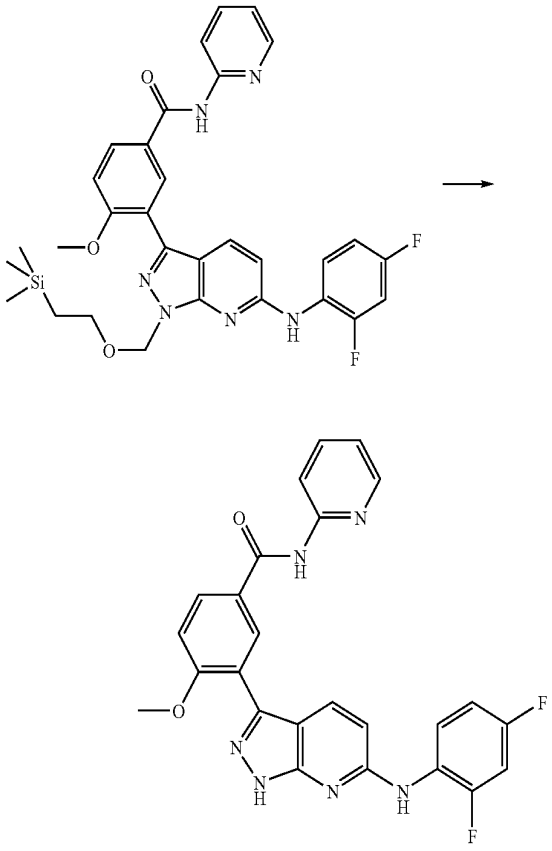
[0241]



[0242] 3-[6-(2,4-Difluoro-phenylamino)-1-(2-trimethylsilanyl-ethoxymethyl)-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl]-4-methoxy-benzoic acid (1.1 g; 2.08 mmol) and 1,1'-carbonyldiimidazole (674 mg; 4.16 mmol) are dissolved in THF (7 ml) and refluxed for 5 minutes until gas evolution ceases. The reaction mixture is cooled to 35 C and 2-aminopyridine (1.17 g; 12.48 mmol) added. After heating at 80 C for 5 minutes the reaction mixture is evaporated and kept at 130 C for 30 minutes. Purification via chromatography (SiO_2, acetone/hexanes 25/75) yielded the crude title compound as colorless crystals (1.0 g), which is used in the next step.

e) 3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl]-4-methoxy-.N.-pyridin-2-yl-benzamide

[0243]



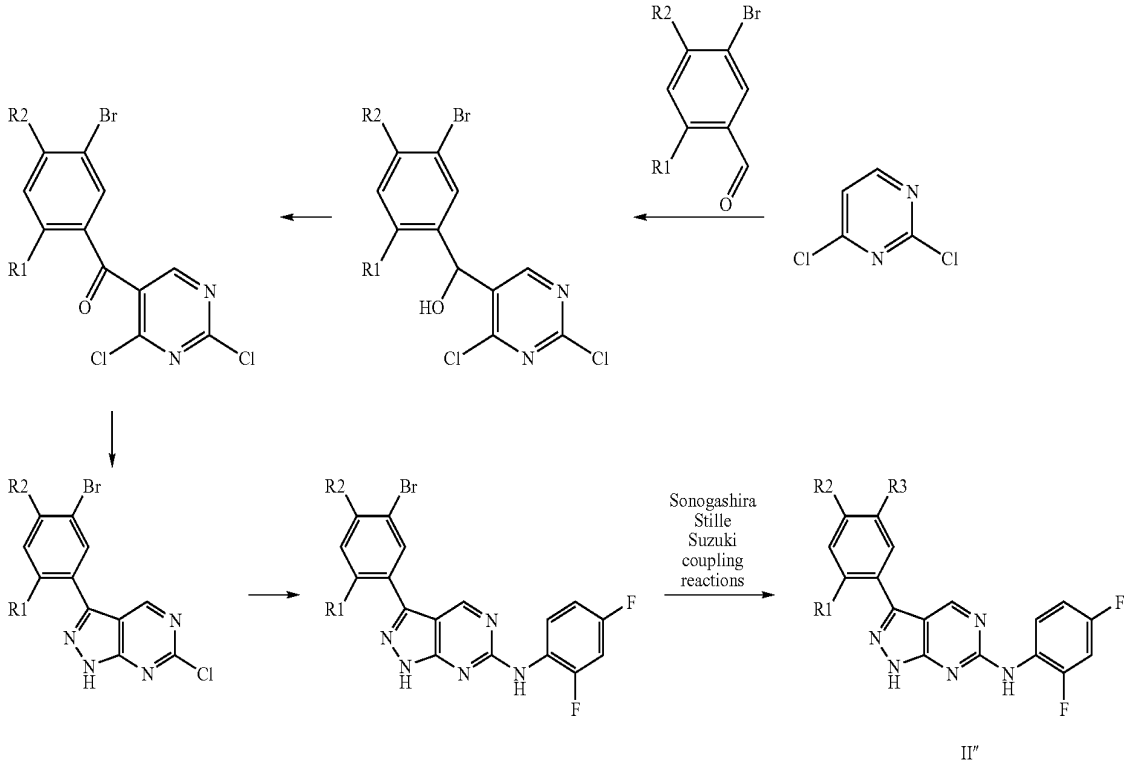
[0244] 3-[6-(2,4-Difluoro-phenylamino)-1-(2-trimethylsilanyl-ethoxymethyl)-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl]-4-methoxy-.N.-pyridin-2-yl-benzamide (1.0 g; 1.66 mol) in EtOH/HCl conc (100 ml; 1:1) is kept at room temperature for 15 minutes, poured on a saturated solution of Na_2CO_3 (300 ml) and extracted with EtOAc/THF (10:1). The combined organic phases are washed with Na_2CO_3 saturated and brine, evaporated to dryness and purified via chromatography (SiO2, acetone/hexanes 3070>100/0) to yield the title compound as white crystals (680 mg; 86%).

[0245] 1H-NMR (400 MHz; DMSO): 3.95 (s, 3H); 6.82 (d, 1H); 7.08-7.18 (m, 2H); 7.29 (d, 1H); 7.35 (dt, 1H); 7.84 (dt, 1H); 7.91 (d, 1H); 8.13-8.23 (m, 3H); 8.30 (d, 1H); 8.40 (d, 1H); 9.01 (s, 1H, NH); 10.75 (s, 1H, NH); 13.20 (s, 1H, NH).

[0246] MS (m/z) ES+: 473 (MH+, 100).

Scheme 4

3-Phenyl-1.H.-pyrazolo[3,4-.d.]pyrimidines of the type II″ are prepared as follows:



II″

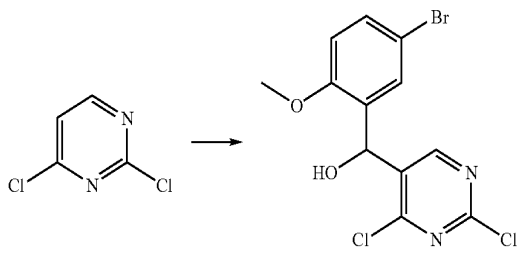
[0247] The synthesis of compounds of type II" is exemplified in example 24:

Example 24

{3-[5-(3-Amino-3-methyl-but-1-ynyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl}-(2,4-difluoro-phenyl)-amine

a) (5-Bromo-2-methoxy-phenyl)-(2,4-dichloro-pyridin-5-yl)-methanol

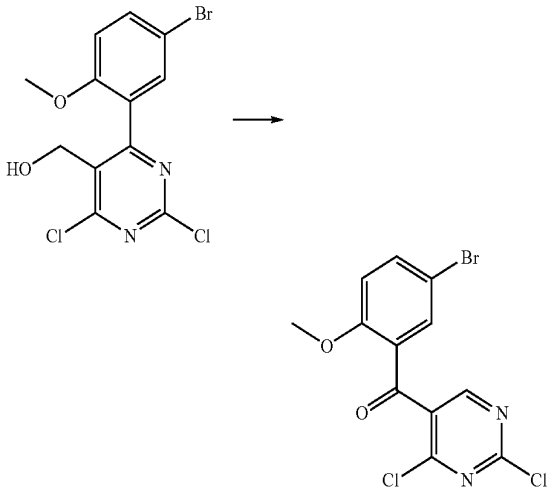
[0248]



[0249] nBuLi (31.25 ml; 50 mmol of a 1.6M solution in hexanes; 50 mmol) is added at −50 C to a solution of diisopropylamine (7.7 ml; 50 mmol) in THE/isopentane (75 ml/20 ml), stirred for 10 minutes at −50 C, then cooled to −100 C. 2,4-Dichloropyrimidine (3.72 g; 25 mmol) in THF (45 ml) is added and stirred at −100 C for 15 minutes. 5-Bromo-o-anisaldehyde (3.22 g; 15 mmol) in TH (15 ml) is added at −100 C to the black reaction mixture, stirred for 10 minutes at −78 C, poured on brine and extracted with TBME three times. The combined organic phases are dried over Na_2SO_4, evaporated and purified via chromatography (SiO_2, cyclohexane/TBME 7/3) to yield the title compound as yellow oil (2.2 g; 40%), which is used in the next step.

b) (5-Bromo-2-methoxy-phenyl)-(2,4-dichloro-pyrimidin-5-yl)-methanone

[0250]



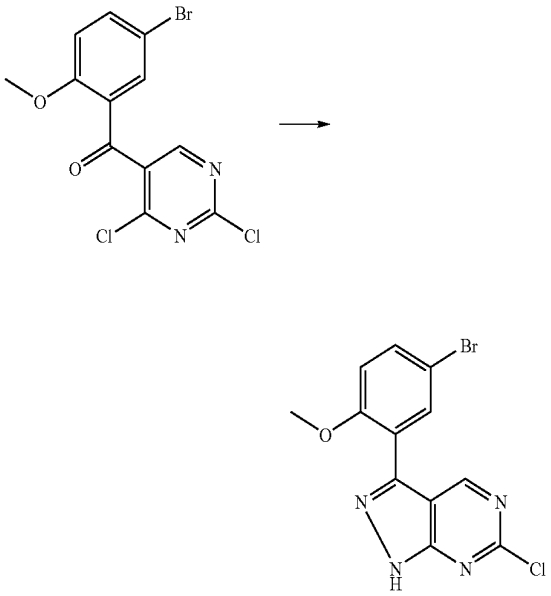
[0251] (5-Bromo-2-methoxy-phenyl)-(2,4-dichloro-pyrimidin-5-yl)-methanol (2.2 g; 6 mmol) is dissolved in acetone (190 ml) and treated with 3 portions of MnO_2 (3×2.1 g) added in 15 minutes intervals. The mixture was filtered, evaporated, recrystallised from TBME/hexanes to yield the title compound as yellow crystals (1.5 g; 68%).

[0252] 1H-NMR (400 MHz; DMSO): 3.70 (s, 3H); 7.23 (d, 1H); 7.90 (m, 2H); 8.93 (s, 1H).

[0253] MS (m/z) EI: 362 (M+, 100); 327 (25); 215 (75); 213 (80).

c) 3-(5-Bromo-2-methoxy-phenyl-6-chloro-1.H.-pyrazolo[3,4-.d.]pyrimidine

[0254]



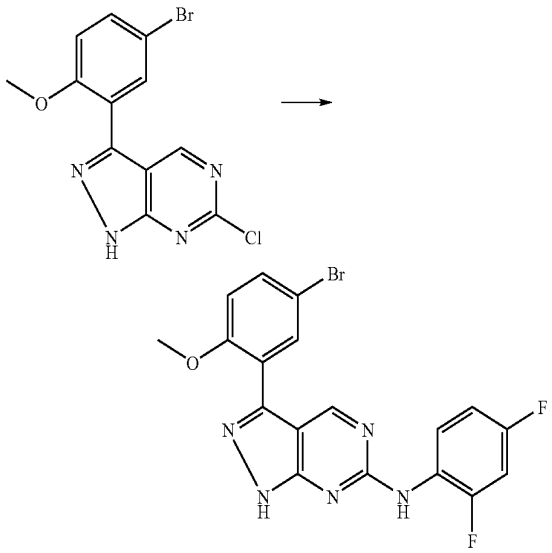
[0255] (5-Bromo-2-methoxy-phenyl)-(2,4-dichloro-pyrimidin-5-yl)-methanone (3.0 g; 8.2 mmol) is dissolved in warm EtOH (240 ml) and cooled to 30 C. A solution of $H_2NNH_2.H_2O$ (3.26 ml; 18.2 mmol of a 24% solution in water) in 2N HCl (10.8 ml; 21.75 mmol) is added at 30 C under stirring. $NaHCO_3$ (49.4 ml; 57.2 mmol; saturated solution) is added, the resulting precipitate stirred for 15 minutes, the reaction mixture poured on water and extracted with TBME twice. The combined organic phases are washed with brine, dried over Na_2SO_4 and evaporated to dryness to yield the title compound as a solid, which is purified via recrystallisation from TBME (2.2 g; 75%)

[0256] 1H-NMR (400 MHz; DMSO): 3.92 (s, 3H); 7.25 (d, 1H); 7.68 (dd, 1H); 7.88 (d, 1H); 9.28 (s, 1H); 14.50 (s, 1H, NH).

[0257] MS (m/z) ES−: 339 (MH−, 100); 249 (50).

d) [3-(5-Bromo-2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl]-(2,4-difluoro-phenyl)-amine

[0258]



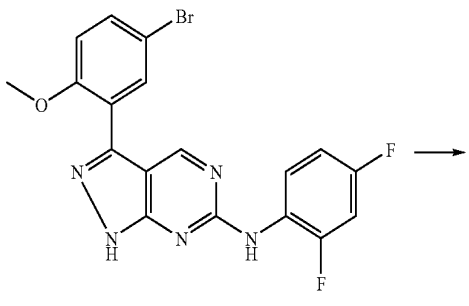
[0259] 3-(5-Bromo-2-methoxy-phenyl)-6-chloro-1.H.-pyrazolo[3,4-.d.]pyrimidine (8.6 g; 25 mmol) and 2,4-difluoroaniline (25 ml) are heated to 150 C. After 5 minutes a precipitation is formed; heating is continued for another 10 minutes. The reaction mixture is cooled and diluted with hexanes (800 ml), filtered, and the solid washed and triturated with water. The greenish product is dissolved in 1.5 liters of hot EtOAc/THF/EtOH (1:1:1) and concentrated to ~100 ml of volume. The resulting precipitate is diluted with TBME/hexanes (100 ml/200 ml) and filtered to yield the title compound as greenish crystals (9.7 g; 89%).

[0260] 1H-NMR (400 MHz; DMSO): 3.91 (s, 3H); 7.12 (bt, 1H); 7.20 (d, 1H); 7.35 (bt, 1H); 7.63 (dd, 1H); 7.73 (m, 1H); 7.81 (d, 1H); 8.97 (s, 1H); 9.38 (s, 1H, NH); 13.50 (s, 1H, NH).

[0261] MS (m/z) ES−: 432, 430 (MH−; 100).

e) {3-[5-(3-Amino-3-methyl-but-1-ynyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl}-(2,4-difluoro-phenyl)-amine

[0262]



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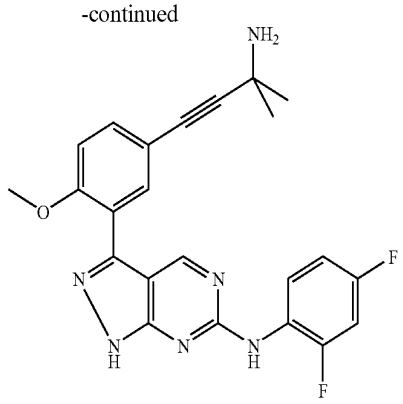


[0263] [3-(5-Bromo-2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl]-(2,4-difluoro-phenyl)-amine (648 mg; 1.5 mmol) and 1,1-dimethyl-prop-2-ynylamine (1.5 ml; 15 mmol), $PdCl_2(PPh_3)_2$ (105 mg; 0.15 mmol), CuI (114 mg; 0.6 mmol), Cs_2CO_3 (487 mg; 1.5 mmol) are dissolved in Huenigs base (150 ml) and heated to 130 C for 1 h. The reaction mixture is evaporated, taken up in TBME/EtOH, filtered and the filtrate purified via chromatography (SiO_2, TBME/MeOH 95/5>TBME/MeOH/NH_3conc 90/9/1) to yield the title compound as yellow-brown crystals (100 mg; 15%).

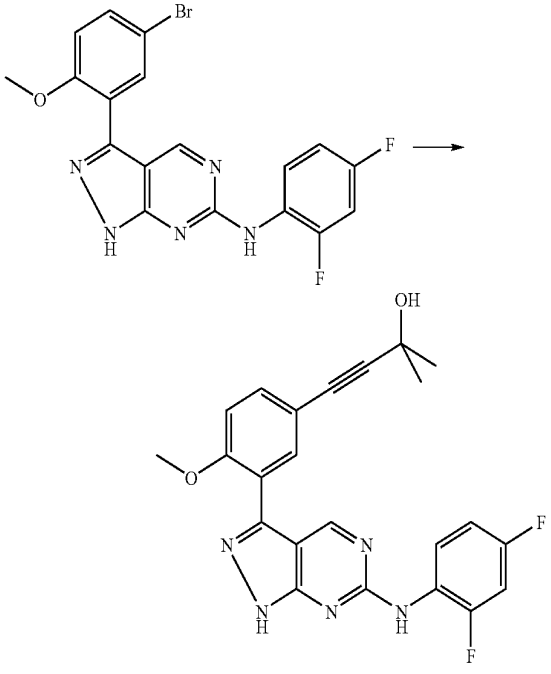
[0264] 1H-NMR (400 MHz; DMSO): 1.40 (s, 6H); 2.14 (bs, 2H, NH_2); 3.90 (s, 3H); 7.11 (bt, 1H); 7.19 (d, 1H); 7.33 (bt, 1H); 7.42 (d, 1H); 7.66 (s, 1H); 7.72 (m, 1H); 8.94 (s, 1H); 9.23 (s, 1H); 13.45 (s, 1H, NH).

[0265] MS (m/z) ES−: 433 (M-H; 100).

Example 25

4-{3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo [3,4-.d.]pyrimidin-3-yl]-4-methoxy-phenyl}-2-methyl-but-3-yn-2-ol

[0266]



[0267] [3-(5-Bromo-2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl]-(2,4-difluoro-phenyl)-amine (3.04 g; 7 mmol), 2-methyl-but-3-yn-2-ol (2.83 ml; 28 mmol), Et_3N (16 ml), DMF (28 ml), $PdCl_2(PPh_3)_2$ (981 mg; 40 mmol) and CuI (266 mg; 1.4 mmol) are heated to 100 C for 1 hour. The reaction mixture is evaporated, taken up in toluene (100 ml), filtered and the filtrate purified by chromatography (SiO_2, toluene/TBME 70/30>toluene/TBME 50/50) to yield the title compound as yellow solid, which is recrystallised from toluene/hexanes/TBME (1.6 g; 52%).

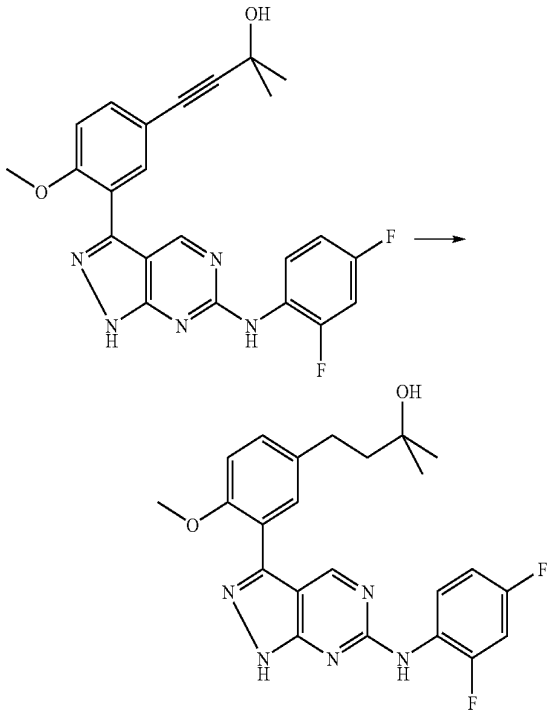
[0268] 1H-NMR (400 MHz; DMSO): 1.49 (s, 6H); 3.93 (s, 3H); 5.43 (s, 1H, OH); 7.12 (dt, 1H); 7.21 (d, 1H); 7.35 (dt, 1H); 7.49 (dd, 1H); 7.71 (d, 1H); 7.72-7.78 (m, 1H); 8.97 (s, 1H); 9.23 (s, 1H, NH); 13.35 (s, 1H, NH).

[0269] MS (m/z) ES+: 436 (MH+; 100).

Example 26

4-{3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo [3,4-.d.]pyrimidin-3-yl]-4-methoxy-phenyl}-2-methyl-butan-2-ol

[0270]



[0271] 4-{3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo[3,4-.d.]pyrimidin-3-yl]-4-methoxy-phenyl}-2-methyl-but-3-yn-2-ol (1.0 g; 2.3 mmol) is dissolved in EtOH (150 ml) and hydrogenated under normal pressure over Pd/C (10%; 400 mg) for 4 hours. The reaction is filtered, evaporated and purified via chromatography (SiO_2, acetone/hexanes 2/8) to yield the title compound as white solid, which is crystallised from acetone/TBME (700 mg; 70%).

[0272] 1H-NMR (400 MHz; DMSO): 1.17 (s, 6H); 1.62-1.70 (m, 2H); 2.61-2.68 (m, 2H); 3.86 (s, 3H); 4.25 (s, 1H, OH),

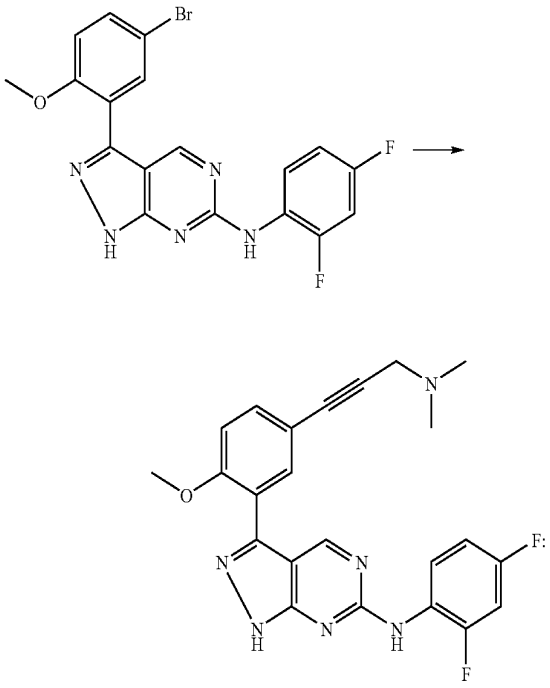
7.10-7.15 (m, 2H); 7.28 (dd, 1H); 7.33 (dt, 1H); 7.52 (d, 1H); 7.71-7.78 (m, 1H); 8.93 (s, 1H); 9.20 (s, 1H, NH); 13.30 (s, 1H, NH).

[0273] MS (m/z) ES+: 440 (MH+; 100).

Example 27

(2,4-Difluoro-phenyl)-{3-[5-(3-dimethylamino-prop-1-ynyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.d.] pyrimidin-6-yl}-amine

[0274]



[0275] [3-(5-Bromo-2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl]-(2,4-difluoro-phenyl)-amine (1 g; 2.3 mmol), R-BINAP (100 mg; 1.6 mmol), CuI (75 mg; 0.39 mmol), $Pd(OAc)_2$ (100 mg; 0.44 mmol), PPh_3 (175 mg; 0.66 mmol), NaOtBu (444 mg; 4.6 mmol) and dimethyl-prop-2-ynyl-amine (5.3 ml; 46 mmol) are dissolved in diethyleneglycol dimethylether (100 ml) and heated in an autoclave at 135 C for 1 hour. The reaction mixture is evaporated, dissolved in 2N HCl, washed with EtOAc, the aqueous phase alkalised with Na_2CO_3conc, filtered and extracted with EtOAc three times. The combined organic phases are dried over Na_2SO_4, evaporated to dryness and purified via chromatography (SiO_2, acetone/hexanes 4/6>100/0>TBME/MeOH/NH_3conc 90/10/1) to yield the pure title compound after recrystallisation from methylene chloride (447 mg; 45%).

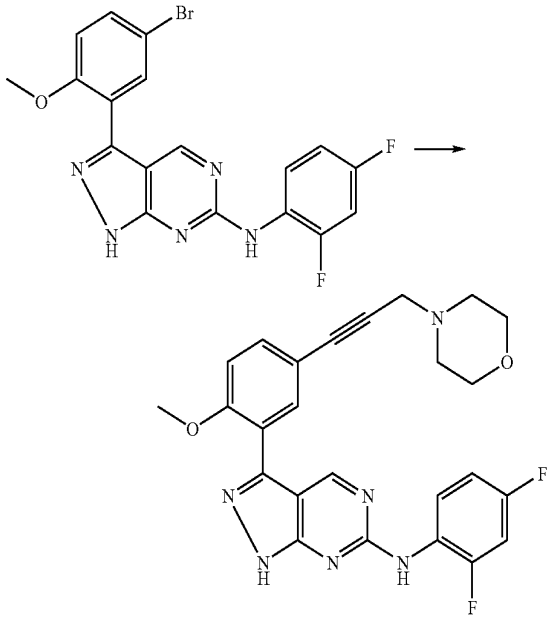
[0276] 1H-NMR (400 MHz; DMSO): 2.24 (s, 6H); 3.44 (s, 2H); 3.90 (s, 3H); 7.10 (dt, 1H); 7.21 (d, 1H); 7.32 (dt, 1H); 7.70 (d, 1H); 7.50 (dd, 1H); 7.74 (m, 1H); 8.92 (s, 1H); 9.21 (s, 1H, NH); 13.45 (bs, 1H, NH).

[0277] MS (m/z) ES+: 435 (MH+, 100).

Example 28

(2,4-Difluoro-phenyl)-{3-[2-methoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-phenyl]-1.H.-pyrazolo[3,4-.d.] pyridin-6-yl}-amine

[0278]



[0279] The title compounds is obtained from [3-(5-bromo-2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl]-(2,4-difluoro-phenyl)-amine and 4-prop-2-ynyl-morpholine in analogy to example 27 in 70% yield as colorless crystals.

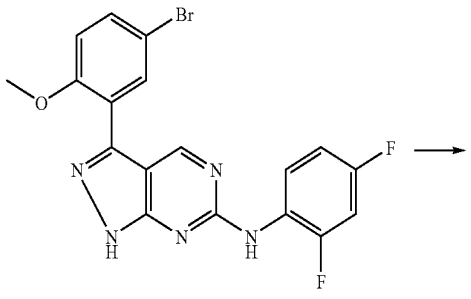
[0280] 1H-NMR (400 MHz; DMSO): 2.53 (bt, 4H); 3.50 (s, 2H); 3.61 (bt, 4H); 3.91 (s, 3H); 7.11 (dt, 1H); 7.22 (d, 1H); 7.32 (dt, 1H); 7.51 (dd, 1H); 7.71 (dd, 2H); 8.93 (s, 1H); 9.23 (s, 1H, NH); 13.45 (s, 1H, NH).

[0281] MS (m/z) ES+: 477 (MH+, 40), 390 (100).

Example 29

(2,4-Difluoro-phenyl)-(3-{2-methoxy-5-[3-(4-methyl-piperazin-1-yl)-prop-1-ynyl]-phenyl}-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl)-amine

[0282]



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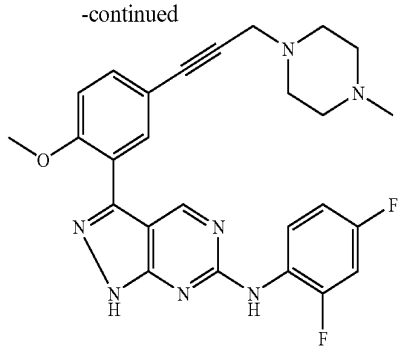


[0283] The title compound is obtained from [3-(5-bromo-2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl]-(2,4-difluoro-phenyl)-amine and 1-methyl-4-prop-2-ynyl-piperazine in analogy to example 27 in 75% yield as colorless crystals.

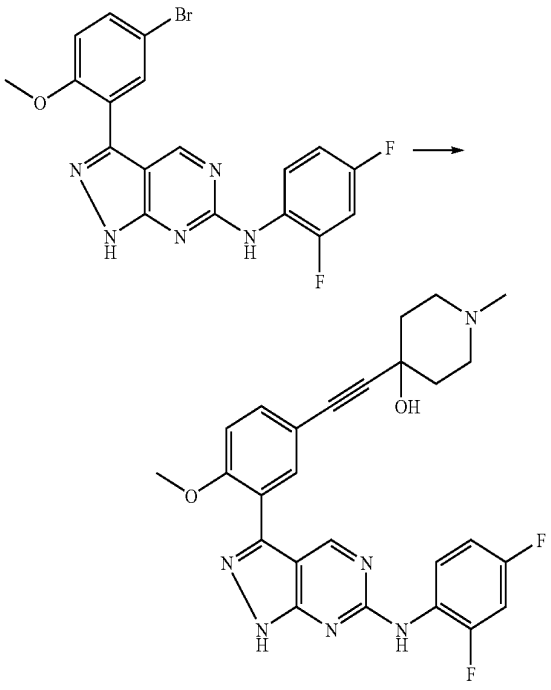
[0284] 1H-NMR (400 MHz; DMSO): 2.15 (s, 3H); 2.34 (bs, 4H); 2.53 (bs, 4H); 3.51 (s, 2H); 3.90 (s, 3H); 7.10 (dt, 1H); 7.21 (d, 1H); 7.32 (dt, 1H); 7.49 (dd, 1H); 7.70 (d, 1H); 7.72 (m, 1H); 8.93 (s, 1H, NH); 9.22 (s, 1H, NH); 13.45 (bs, 1H, NH).

[0285] MS (m/z) ES+: 490 (MH+, 100).

Example 30

4-{3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo [3,4-.d.]pyrimidin-3-yl]-4-methoxy-phenylethynyl}-1-methyl-piperidin-4-ol

[0286]



[0287] [3-(5-Bromo-2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl]-(2,4-difluoro-phenyl)-amine (1.38 g; 3.2 mmol), 4-ethynyl-1-methyl-piperidin-4-ol (0.9 g; 6.5 mmol), $PdCl_2(PPh_3)_2$ (0.43 g; 0.6 mmol), Cs_2CO_3 (2.7 g; 8.3 mmol) and CuI (133 mg; 0.7 mmol) are dissolved in diethylene glycol dimethyl ether (32 ml) and N,N-diisopropylethylamine (16 ml) and heated to 140° C. for 15 minutes. The reaction mixture is filtered, evaporated and purified via chromatography (SiO_2, EtOAc/MeOH/NH_3conc 95/4.5/0.5>90/9/1) to yield the title compound, which is crystallised from EtOH/TBME (900 mg; 54%).

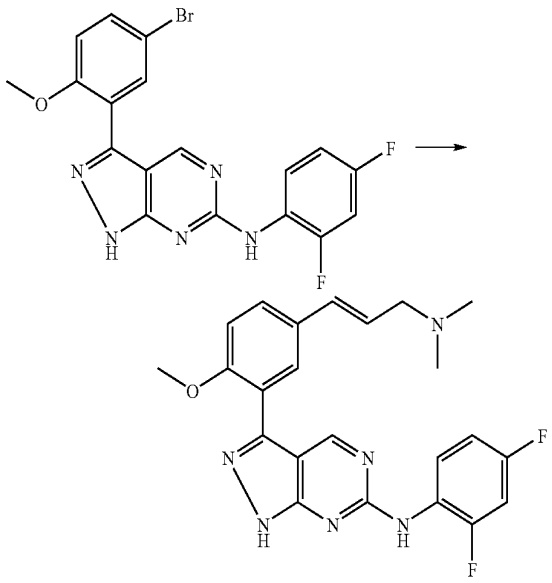
[0288] 1H-NMR (400 MHz; DMSO): 1.72 (m, 2H); 1.83 (m, 2H); 2.16 (s, 3H); 2.26 (m, 2H); 2.54 (m, 2H); 3.91 (s, 3H); 5.50 (s, 1H, OH); 7.11 (dt, 1H); 7.22 (d, 1H); 7.32 (dt, 1H); 7.48 (dd, 1H); 7.69 (d, 1H); 7.72 (m, 1H); 8.93 (s, 1H); 9.24 (s, 1H, NH); 13.44 (bs, 1H, NH)

[0289] MS (m/z) ES+: 491 (MH+, 100).

Example 31

(2,4-Difluoro-phenyl)-{3-[5-((E)-3-dimethylamino-propenyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.d.] pyrimidin-6-yl}-amine

[0290]



[0291] Dimethyl-((E)-3-tributylstannanyl-allyl)-amine (312 mg, 0.83 mmol) and [3-(5-bromo-2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl]-(2,4-difluoro-phenyl)-amine (200 mg, 0.69 mmol) are added to a solution of $Pd(OAc)_2$ (15 mg, 0.07 mmol) and PPh_3 (75 mg, 0.2 mmol) in diethylene glycol dimethyl ether (16 ml) and heated to 130 C under argon for 40 minutes. The reaction mixture is evaporated to dryness and purified via a first chromatography (SiO_2, acetone/hexanes 6/4>9/1>acetone/MeOH 9/1) followed by a second chromatography (SiO_2, TBME/MeOH/NH_3conc 95/5/0.5>90/10/1) to yield the title compound as pale yellow crystals (60 mg; 20%).

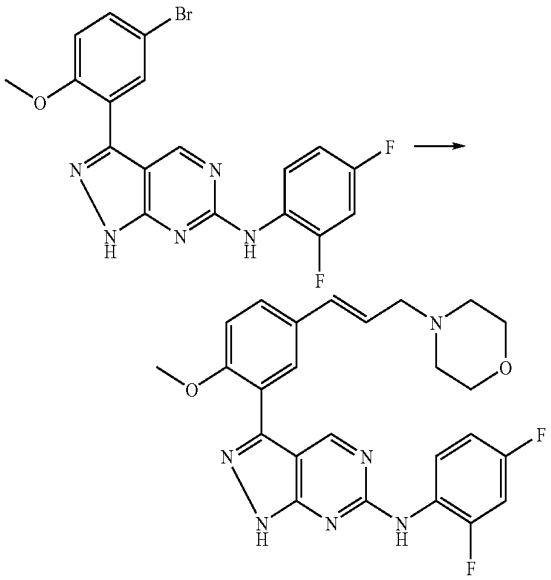
[0292] 1H-NMR (400 MHz; DMSO): 2.16 (s, 6H); 3.01 (bd, 2H); 3.88 (s, 3H); 6.19 (dt, 1H); 6.52 (d, 1H); 7.10 (bt, 1H); 7.17 (d, 1H); 7.32 (bt, 1H); 7.52 (bd, 1H); 7.71-7.80 (m, 2H); 8.91 (s, 1H); 9.20 (bs, 1H, NH); 13.40 (s, 1H, NH).

[0293] MS (m/z) ES+: 424 (MH+, 100).

Example 32

(2,4-Difluoro-phenyl)-{3-[2-methoxy-5-((E)-3-morpholin-4-yl-propenyl)-phenyl]-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl}-amine

[0294]



[0295] The title compound is obtained from 4-((E)-3-tributylstannanyl-allyl)-morpholine and [3-(5-bromo-2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl]-(2,4-difluoro-phenyl)-amine as colorless crystals in analogy to example 30 in 47% yield.

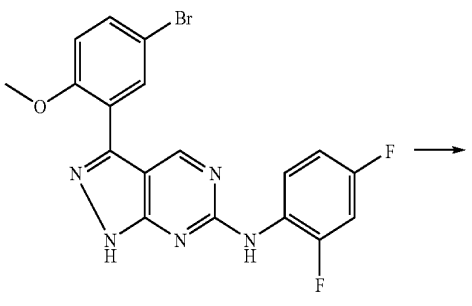
[0296] 1H-NMR (400 MHz; DMSO): 2.39 (bs, 4H); 3.07 (bd, 2H); 3.58 (bt, 4H); 3.88 (s, 3H); 6.21 (dt, 1H); 6.54 (d, 1H); 7.11 (dt, 1H); 7.17 (d, 1H); 7.33 (dt, 1H); 7.55 (dd, 1H); 7.71 (m, 2H); 8.91 (s, 1H); 9.21 (s, 1H, NH); 13.40 (s, 1H, NH).

[0297] MS (m/z) ES+: 479 (MH+, 100).

Example 33

(2,4-Difluoro-phenyl)-(3-{2-methoxy-5-[(E)-3-(4-methyl-piperazin-1-yl-propenyl]-phenyl}-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl)-amine

[0298]



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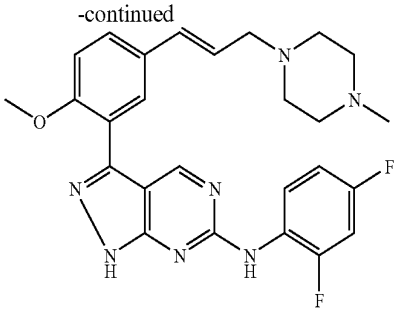


[0299] The title compound is obtained from 1-methyl-4-((E)-3-tributylstannanyl-allyl)-piperazine and [3-(5-bromo-2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl]-(2,4-difluoro-phenyl)-amine as colorless crystals in analogy to example 31 in 10% yield.

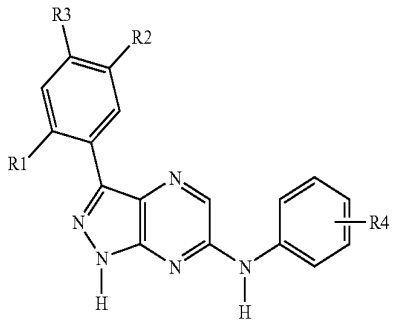
[0300] 1H-NMR (400 MHz; DMSO: 2.14 (s, 3H); 2.25-2.50 (m, 8H); 3.07 (d, 2H); 3.87 (s, 3H); 6.18 (dt, 1H); 6.52 (d, 1H); 7.11 (dt, 1H); 7.17 (d, 1H); 7.32 (dt, 1H); 7.52 (dd, 1H); 7.70-7.78 (m, 2H); 8.91 (s, 1H); 9.22 (s, 1H, NH); 13.40 (s, 1H, NH).

[0301] MS (m/z) ES+: 492 (MH+, 100).

Scheme 5

[0302] The synthesis of phenyl-(3-phenyl-1.H.-pyrazolo[3,4-.b.]pyrazin-6-yl)-amines of type I'''

I'''



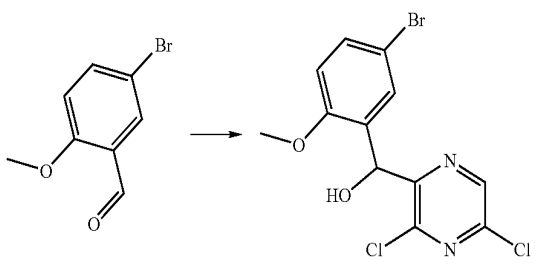
is exemplified in Examples 33 and 35:

Example 34

4-{3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo[3,4-.b.]pyrazin-3-yl]-4-methoxy-phenyl}-2-methyl-but-3-yn-2-ol

a) (5-Bromo-2-methoxy-phenyl)-(3,5-dichloro-pyrazin-2-yl)-methanol

[0303]



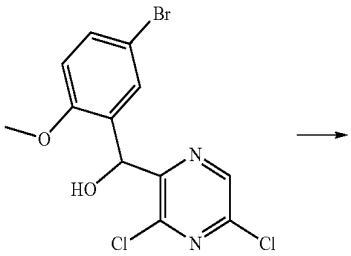
[0304] Tetramethylpiperidine (5.25 ml; 30.75 mmol) in THF (450 ml) is cooled to −15 C and treated with nBuLi (18.7 ml; 30 mmol of a 1.6M solution in hexanes) for 10 minutes and then cooled to −90 C. 2,6-Dichloro-pyrazine (3.34 g; 22.5 mmol) in THF (45 ml) is added within a minute and the red-brown reaction mixture stirred for 30 seconds at −90 C to −100 C. 5-Bromo-2-methoxy-benzaldehyde (3.2 g; 15 mmol) in THF (45 ml) is added at −90 C within one minute and the reaction stirred at −78 C for 10 minutes. The black reaction mixture is poured on brine and extracted twice with TBME. The combined organic phases are washed with water, dried over Na_2SO_4, filtered and evaporated to dryness. Purification via chromatography (SiO_2, toluene) delivers the title compound as colorless crystals (3 g; 55%).

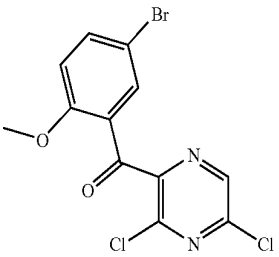
[0305] 1H-NMR (400 MHz; DMSO: 3.62 (s, 3H); 6.25 (s, 1H); 6.90 (d, 1H); 7.45 (dd, 1H); 7.70 (d, 1H); 8.71 (s, 1H).

[0306] MS (m/z) EI: 364 (M+, 90); 333 (65); 215 (100).

b) (5-Bromo-2-methoxy-phenyl)-(3,5-dichloro-pyrazin-2-yl)-methanone

[0307]





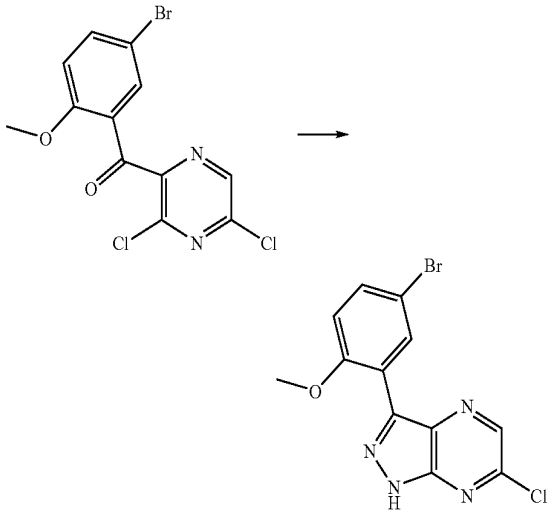
[0308] (5-Bromo-2-methoxy-phenyl)-(3,5-dichloro-pyrazin-2-yl)-methanol (9 g; 24.7 mmol) in acetone (800 ml) is treated for 15 minutes at room temperature with Jones reagent (53 ml; 123 mmol of a 2.33 mol solution). Acetone (−700 ml) is distilled off and the residue poured on saturated Na_2CO_3 and extracted with EtOAc twice. The combined organic phases are dried over Na_2SO_4, filtered and evaporated to dryness to yield the title compound as white crystals (7.9 g; 88%).

[0309] 1H-NMR (400 MHz; DMSO): 3.62 (s, 3H); 6.71 (d, 1H); 7.83-7.93 (m, 2H); 8.90 (s, 1H).

[0310] MS (m/z) EI: 362 (M+, 30); 331 (30); 213 (100).

c) 3-(5-Bromo-2-methoxy-phenyl)-6-chloro-1.H.-pyrazolo[3,4-.b.]pyrazine

[0311]



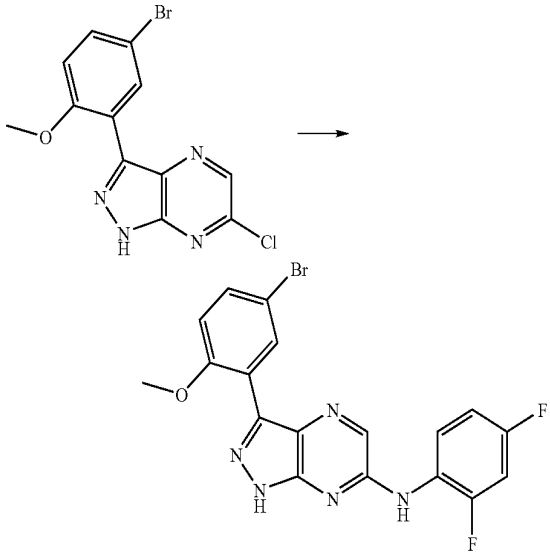
[0312] (5-Bromo-2-methoxy-phenyl)-(3,5-dichloro-pyrazin-2-yl)-methanone (7.9 g; 21.8 mmol) is dissolved in warm (50 C) MeOH (790 ml) and treated with $H_2NNH_2.H_2O$ (2.37 ml; 48 mmol of a 98% solution in water). After 1 hour at 50 C a second portion of $H_2NNH_2.H_2O$ (1.2 ml; 24 mmol of a 98% solution in water) is added and stirring continued for 30 minutes. Filtration of the yellow solid delivers the title compound (2.66 g; 36%).

[0313] 1H-NMR (400 MHz; DMSO): 3.83 (s, 3H); 6.70 (d, 1H); 7.65 (dd, 1H); 7.95 (bs, 1H); 8.75 (s, 1H).

[0314] MS (m/z) ES− 339 (MH−; 100).

d) [3-(5-Bromo-2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.b.]pyrazin-6-yl]-(2,4-difluoro-phenyl)-amine

[0315]



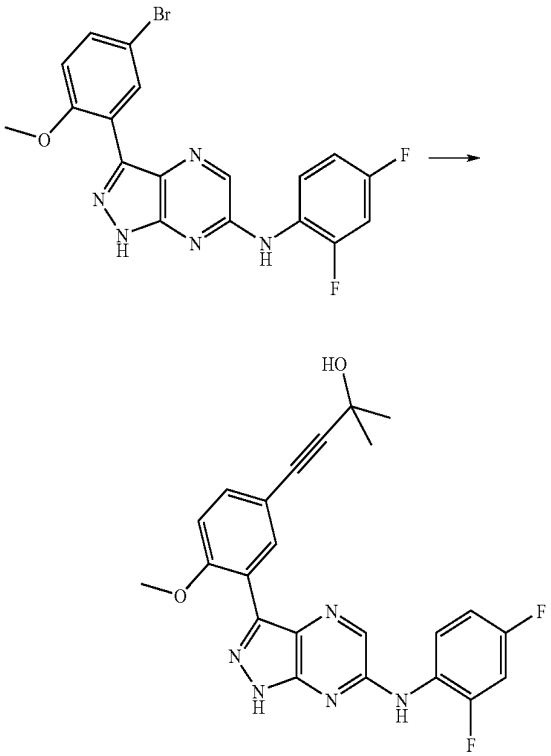
[0316] 3-(5-Bromo-2-methoxy-phenyl)-6-chloro-1.H.-pyrazolo[3,4-.b.]pyrazine (2.8 g; 8.27 mmol) and 2,4-difluoroaniline (16.5 ml) are heated at 175 C for 1 hour. The reaction mixture—originally a suspension—forms a solution, then precipitates again. Hexane (500 ml) is added to the cooled reaction, the precipitate filtered off, dissolved in EtOAc/THF (500 ml 4:1) and washed with water (400 ml). The aqueous phase is extracted with EtOAc, the combined organic phases dried over Na_2SO_4 and evaporated to dryness to yield the title compound, which is crystallised from EtOAc/TBME (3.3 g; 91%).

[0317] 1H-NMR (400 MHz; DMSO): 3.81 (s, 3H); 7.13-7.22 (m, 2H); 7.41 (dt, 1H); 7.62 (dd, 1H); 7.85 (s, 1H); 8.08-8.18 (m, 1H); 8.47 (s, 1H); 9.61 (bs, 1H, NH); 13.50 (s, 1H, NH).

[0318] MS (m/z) ES−: 432 (M+, 100); 430 (100).

d) 4-{3-[6-(2,4-Difluoro-phenylamino-1.H.-pyrazolo[3,4-.b.]pyrazin-3-yl]-4-methoxy-phenyl}-2-methyl-but-3-yn-2-ol

[0319]



[0320] The title compound is obtained in 42% yield from [3-(5-bromo-2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.b.]pyrazin-6-yl]-(2,4-difluoro-phenyl)-amine and 2-methyl-but-3-yn-2-ol in analogy to example 25.

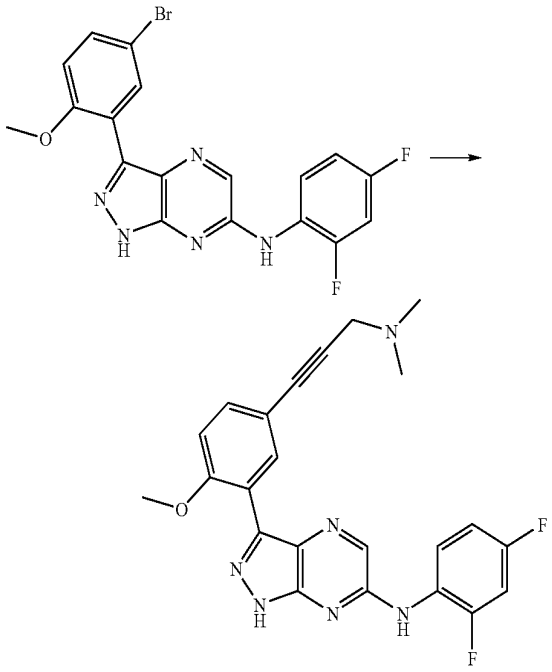
[0321] 1H-NMR (400 MHz; DMSO): 1.48 (s, 6H); 3.84 (bs, 3H); 5.43 (s, 1H, OH); 7.11-7.19 (m, 2H); 7.38 (dt, 1H); 7.45 (d, 1H); 7.70-7.85 (bs, 1H); 8.17 (bs, 1H); 8.37 (s, 1H); 9.55 (bs, 1H, NH); 13.30 (s, 1H, NH).

[0322] MS (m/z) ES−: 434 (MH−; 100).

Example 35

(2,4-Difluoro-phenyl)-{3-[5-(3-dimethylamino-prop-1-ynyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.b.]pyrazin-6-yl}-amine

[0323]



[0324] The title compound is obtained in 20% yield from [3-(5-bromo-2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.b.]pyrazin-6-yl]-(2,4-difluoro-phenyl)-amine and dimethyl-prop-2-ynyl-amine in analogy to example 27.

[0325] 1H-NMR (400 MHz; DMSO): 2.27 (s, 6H); 3.47 (s, 2H); 3.82 (s, 3H); 7.19 (bd, 2H); 7.41 (t, 1H); 7.52 (d, 1H); 7.74 (bs, 1H); 7.78 (bs, 1H); 8.18 (bs, 1H); 9.60 (s, 1H, NH); 13.40 (s, 1H, NH).

[0326] MS (m/z) ES−: 433 (MH−, 100).

[0327] The Agents of the Invention, as defined above, e.g., of formula I, II and V particularly as exemplified, in free or pharmaceutically acceptable acid addition salt form, exhibit pharmacological activity and are useful as pharmaceuticals, e.g. for therapy, in the treatment of diseases and conditions as hereinafter set forth.

[0328] In particular Agents of the Invention possess p38 MAP kinase (Mitogen Activated Protein Kinase) inhibiting activity. Thus the Agents of the Invention act to inhibit production of inflammatory cytokines, such as TNF and IL-1, and also to potentially block the effects of these cytokines on their target cells. These and other pharmacological activities of the Agents of the Invention as may be demonstrated in standard test methods for example as described below:

p38 MAP kinase Assay

[0329] The substrate (GST-ATF-2; a fusion protein comprising amino acids 1-109 of ATF-2 and the GST protein obtained by expression in *E. coli*) is coated onto the wells of microtiter plates (50 µl/well; 1 µg/ml in PBS/0.02% Na azide) overnight at 4° C. The following day, the microtiter plates are washed four times with PBS/0.5% Tween 20/0.02% Na azide and are blocked with PBS/2% BSA/0.02% Na Azide for 1 h at

37° C. Plates are washed again 4 times with PBS/0.5% Tween 20/0.02% Na azide. The kinase cascade reaction is then started by adding the following reactants in 10 μl aliquots to a final reaction volume of 50 μl.

[0330] 1. Agents of the Invention titrated from 10 to 0.001 μM in 10-fold dilutions or solvent (DMSO) or H_2O.

[0331] 2. Kinase buffer (5×); pH 7.4; 125 mM Hepes (Stock at 1M; Gibco #15630-056), 125 mM β-glycerophosphate (Sigma #G-6251): 125 mM $MgCl_2$ (Merck #5833); 0.5 mM Sodium orthovanadate (Sigma #5-6508), 10 mM DTT (Boehringer Mannheim #708992). The (5×) kinase buffer must be prepared fresh the day of the assay from 5× stock solutions kept at RT. DTT is kept at −20° C. and is added as the last reagent.

[0332] 3. His-p38 MAP kinase (10 ng/well; Novartis—a fusion protein comprising full length murine p38 MAP kinase and a His tag, obtained by expression in *E. coli*)

[0333] 4. cold ATP (final concentration 120 μM; Sigma #A-9187)

[0334] 5. Water

[0335] After 1 h at 37° C. the kinase reaction is terminated by washing the plates four times as previously described. Phosphorylated GST-ATF-2 is then detected by adding:

[0336] 1. the PhosphoPlus ATF-2 (Thr71) Antibody (50 μl/well; 1/1000 final dilution in PBS/2% BSA/0.02% Na Azide; New England Biolabs #9221L) for 90 min at RT.

[0337] 2. Biotin labelled goat-anti-rabbit IgG (50 μl/well; 1/3000 final dilution in PBS/2% BSA/0.02% Na Azide; Sigma #B-9642) for 90 min at RT.

[0338] 3. Streptavidin-alkaline phosphatase (50 μl/well; 1/5000 dilution in PBS/2% BSA/0.02% Na Azide; Jackson Immunoresearch #016-050-084) for 30 min at RT.

[0339] 4. Substrate (100 μl/well; Sigma 104 Phosphatase substrate tablets, 5 mg/tablet; #104-105; 1 mg/ml in substrate buffer, Diethanolamine (97 ml/l; Merck #803116)+ $MgCl_2.6H_20$ (100 mg/l; Merck #5833)+Na Azide (0.2 g/l)+HCl 1M to pH 9.8) 30 min at RT.

[0340] After step 1, 2 and 3 the microtiter plates are washed four times with PBS/0.5% Tween 20/0.02% Na azide. After step 4, the plates are read in a Bio-Rad microplate reader in a dual wavelength mode (measurement filter 405 nm and reference filter 490 nm). The background value (without ATP) is subtracted and IC_{50} values are calculated using the Origin computer program (4 parameter logistic function).

[0341] Agents of the Invention typically have IC_{50}s for p38 MAP kinase inhibition in the range from about 100 nM to about 10 nM or less when tested in the above assay.

Assay for Inhibition of TNF-α Release from hPBMCs

[0342] Human peripheral blood mononuclear cells (hPBMCs) are prepared from the peripheral blood of healthy volunteers using ficoll-hypaque density separation according to the method of Hansell et al., J. Imm. Methods (1991) 145: 105. and used at a concentration of 10^5 cells/well in RPMI 1640 plus 10% FCS. Cells are incubated with serial dilutions of the test compounds for 30 minutes at 37° C. prior to the addition of IFNg (100 U/ml) and LPS (5 mg/ml) and subsequently further incubated for three hours. Incubation is terminated by centrifugation at 1400 RPM for 10 min. TNF-α in the supernatant is measured using a commercial ELISA (Innotest hTNFa, available from Innogenetics N.V., Zwijnaarde, Belgium). Agents of the Invention are tested at concentrations of from 0 to 10 mM. Exemplified Agents of the Invention typically suppress TNF release in this assay with an IC_{50} of from about 10 mM to about 100 nM or less when tested in this assay.

Assay for Inhibition of TNF-Production in LPS Stimulated Mice

[0343] Injection of lipopolysaccharide (LPS) induces a rapid release of soluble tumour necrosis factor (TNF-α) into the periphery. This model is be used to analyse prospective blockers of TNF release in vivo.

[0344] LPS (20 mg/kg) is injected i.v. into OF1 mice (female, 8 week old). One (1) hour later blood is withdrawn from the animals and TNF levels are analysed in the plasma by an ELISA method using an antibody to TNF-α. Using 20 mg/kg of LPS levels of up to 15 ng of TNF-α/ml plasma are usually induced. Compounds to be evaluated are given either orally or s.c. 1 to 4 hours prior to the LPS injection. Inhibition of LPS-induced TNF-release is taken as the readout.

[0345] Agents of the Invention typically inhibit TNF production to the extent of up to about 50% or more in the above assay when administered at 10 mg/kg p.o. and up to about 98% or more when administered at 30 mg/kg p.o.

[0346] As indicated in the above assays Agents of the Invention are potent inhibitors of TNF-α release. Accordingly, the Novel Compounds have pharmaceutical utility as follows:

[0347] Agents of the Invention are useful for the prophylaxis and treatment of diseases or pathological conditions mediated by cytokines such as TNFα and IL-1, e.g., inflammatory conditions, autoimmune diseases, severe infections, and organ or tissue transplant rejection, e.g. for the treatment of recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants and for the prevention of graft-versus-host disease, such as following bone marrow transplants.

[0348] Agents of the Invention are particularly useful for the treatment, prevention, or amelioration of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases. Specific auto-immune diseases for which Agents of the Invention may be employed include autoimmune haematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease), endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

[0349] Agents of the Invention are also useful for the treatment, prevention, or amelioration of asthma, bronchitis, pneumoconiosis, pulmonary emphysema, and other obstructive or inflammatory diseases of the airways.

[0350] Agents of the Invention are useful for treating undesirable acute and hyperacute inflammatory reactions which are mediated by TNF, especially by TNFα, e.g., acute infections, for example septic shock (e.g., endotoxic shock and adult respiratory distress syndrome), meningitis, pneumonia; and severe burns; and for the treatment of cachexia or wasting syndrome associated with morbid TNF release, consequent to infection, cancer, or organ dysfunction, especially AIDS-related cachexia, e.g., associated with or consequential to HIV infection.

[0351] Agents of the Invention are also useful for the treatment of neurodegenerative diseases, such as Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis including demyelation and oligodendrocyte loss in multiple sclerosis and inflammatory nervous system diseases, such as neuroinflammatory and stroke.

[0352] Agents of the Invention are particularly useful for treating diseases of bone metabolism including osteoarthritis, osteoporosis and other inflammatory arthritides.

[0353] For the above indications the appropriate dosage will, of course, vary depending, for example, on the particular Agent of the Invention employed, the subject to be treated, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are obtained at daily dosages of from about 1 to about 10 mg/kg/day p.o. In larger mammals, for example humans, an indicated daily dosage is in the range of from about 50 to about 750 mg of an Agent of the Invention administered orally once or, more suitably, in divided dosages two to four times/day.

[0354] The Agents of the Invention may be administered by any conventional route, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Normally for systemic administration oral dosage forms are preferred, although for some indications the Agents of the Invention may also be administered topically or dermally, e.g. in the form of a dermal cream or gel or like preparation or, for the purposes of application to the eye, in the form of an ocular cream, gel or eye-drop preparation; or may be administered by inhalation, e.g., for treating asthma. Suitable unit dosage forms for oral administration comprise e.g. from 25 to 250 mg of Agent of the Invention per unit dosage.

[0355] In accordance with the foregoing the present invention also provides in a further series of embodiments:

A. A method of inhibiting production of soluble TNF, especially TNFα, or of reducing inflammation in a subject (i.e., a mammal, especially a human) in need of such treatment which method comprises administering to said subject an effective amount of an Agent of the Invention, or a method of treating any of the above mentioned conditions, particularly a method of treating an inflammatory or autoimmune disease or condition, e.g. rheumatoid arthritis, or alleviating one or more symptoms of any of the above mentioned conditions.

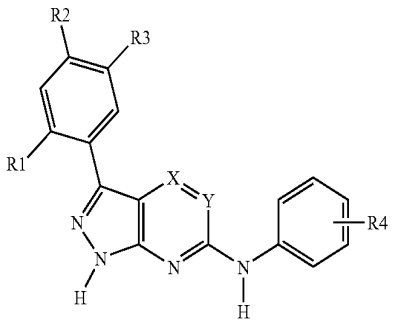
B. An Agent of the Invention for use as a pharmaceutical, e.g. for use as an immunosuppressant or antiinflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

C. A pharmaceutical composition comprising an Agent of the Invention in association with a pharmaceutically acceptable diluent or carrier, e.g., for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

D. Use of an Agent of the Invention in the manufacture of a medicament for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune of inflammatory disease or condition.

1. A compound of formula I

I



wherein

X and Y are independently carbon or nitrogen,

R1 is H, halogen, hydroxy, lower alkoxy, lower alkyl or halo-substituted lower alkyl;

R2 is H, or optionally substituted (heterocyclyl, lower alkyl, lower alkenyl, lower alkynyl or lower alkoxy);

R3 is H, or optionally substituted (heterocyclyl, lower alkyl, lower alkenyl, lower alkynyl or lower alkoxy); or

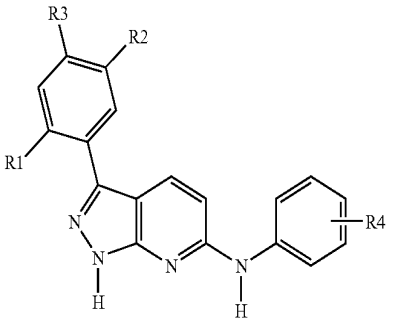
R2 and R3 are linked together to form a 4- to 6-membered heterocyclic ring containing one or more hetero atoms selected from O, S, N or NR, where R is H or lower alkyl;

R4 represents one, two or three halogen substituents which may be the same or different,

or a pharmaceutically-acceptable and -cleavable ester or acid addition salt thereof.

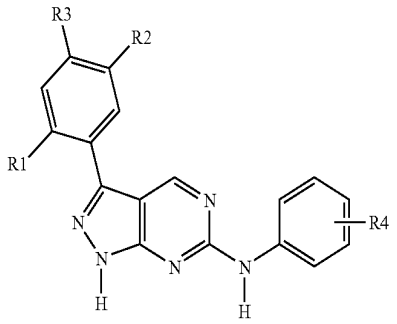
2. A compound according to claim **1** of formulae I', I" or I'"

I'

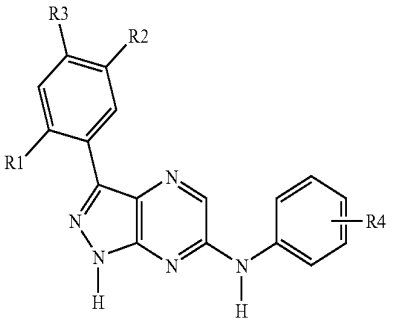


-continued

I''



I'''

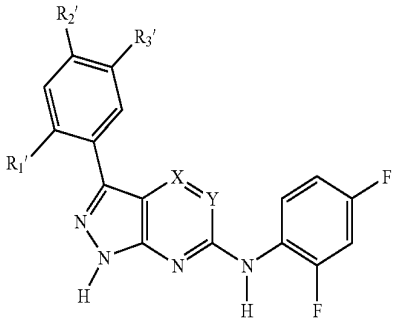


wherein the substituents R1, R2, R3 and R4 are as defined in claim **1**,

or a pharmaceutically-acceptable and -cleavable ester or acid addition salt thereof.

3. A compound of Formulae II

II



Wherein

X and Y are independently carbon or nitrogen,

R1' is halo, C_1-C_4 lower alkyl, C_1-C_4lower alkoxy or halo-substituted C_1-C_4 lower alkyl;

R2' and R3' are, independently of one another, H or optionally substituted (C_1-C_4 lower alkyl, C_1-C_4 lower alkoxy, C_1-C_7alkenyl, C_1-C_7alkynyl, C_5-C_7N-heterocyclyl, C_5-C_7heterocyclylC_1-C_4lower alkoxy, C_5-C_7heterocyclylC_1-C_4lower alkyl, C_5-C_7heterocyclylC_1-C_4lower alkenyl, C_5-C_7heterocyclylC_1-C_4lower alkynyl) wherein the C_5-C_7heterocyclyl optionally contains a second hetero atom and the optional substitution comprises 1 or 2 substituents, separately selected from C_1-C_4 alkyl, halogen, hydroxy, C_1-C_4 alkoxy, or optionally mono- or di-N—C_{1-4}alkyl substituted amino or

R2' and R3' are linked by a methylenedioxy linker or are linked in an imidazole ring optionally substituted by 1 or 2 substituents, separately selected from C_{1-4}alkyl, halogen,

or a pharmaceutically-acceptable and -cleavable ester hydroxy, C_{1-4}alkoxy, or optionally mono- or di-N—C_{1-4}alkyl substituted amino; r or acid addition salt thereof.

4. A compound selected from:

(2,4-Difluoro-phenyl)-[3-(2-methoxy-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine;

[3-(6-Chloro-benzo[1,3]dioxol-5-yl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-(2,4-difluoro-phenyl)-amine;

[3-(2-Chloro-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-(2,4-difluoro-phenyl)-amine;

(2,4-Difluoro-phenyl)-[3-(2-trifluoromethyl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine;

(2,4-Difluoro-phenyl)-[3-(2,4-dimethoxy-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine;

[3-(2-Chloro-4,5-dimethoxy-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-(2,4-difluoro-phenyl)-amine;

(2,4-Difluoro-phenyl)-[3-(2-methoxy-5-morpholin-4-yl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine;

(2,4-Difluoro-phenyl)-{3-[2-methoxy-5-(4-methyl-piperazin-1-yl)-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-amine;

(2,4-Difluoro-phenyl)-[3-(2-methoxy-5-pyridin-4-yl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine;

(2,4-Difluoro-phenyl)-[3-(2-methoxy-5-methylaminomethyl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine;

(2,4-Difluoro-phenyl)-{3-[2-methoxy-5-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-amine;

4-{3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo[3,4-.b.]pyridin-3-yl]-4-methoxy-phenyl}-1-methyl-piperidin-4-ol;

(2,4-Difluoro-phenyl)-[3-(2-methoxy-5-morpholin-4-yl-methyl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine;

(2,4-Difluoro-phenyl)-[3-(2-methoxy-5-piperazin-1-ylmethyl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine;

{3-[5-(3-Amino-3-methyl-but-1-ynyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-(2,4-difluoro-phenyl)-amine;

{3-[5-(3-Amino-3-methyl-butyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-(2,4-difluoro-phenyl)-amine;

{3-[2-Chloro-5-methoxy-4-(2-morpholin-4-yl-ethoxy)-phenyl]-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-(2,4-difluoro-phenyl)-amine;

{3-[2-Chloro-4-methoxy-5-(2-morpholin-4-yl-ethoxy)-phenyl]1.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-(2,4-difluoro-phenyl)-amine;

(2,4-Difluoro-phenyl)-[3-(2-methoxy-5-propylaminomethyl-phenyl)-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl]-amine;

(2,4-Difluoro-phenyl)-(3-{2-methoxy-5-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-1.H.-pyrazolo[3,4-.b.]pyridin-6-yl)-amine;

(2,4-Difluoro-phenyl)-{3-[5-(1,2-dimethyl-1.H.-imidazol-4-yl)-2-methoxy-phenyl]1-.H.-pyrazolo[3,4-.b.]pyridin-6-yl}-amine;

3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo[3,4-.b.] pyridin-3-yl]-4-methoxy-.N.-pyridin-2-yl-benzamide;

{3-[5-(3-Amino-3-methyl-but-1-ynyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl}-(2,4-difluoro-phenyl)-amine;

4-{3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo[3,4-.d.]pyrimidin-3-yl]-4-methoxy-phenyl}-2-methyl-but-3-yn-2-ol;

4-{3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo[3,4-.d.]pyrimidin-3-yl]-4-methoxy-phenyl}-2-methyl-butan-2-ol;

(2,4-Difluoro-phenyl)-{3-[5-(3-dimethylamino-prop-1-ynyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl}-amine;

(2,4-Difluoro-phenyl)-{3-[2-methoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-phenyl]-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl}-amine;

(2,4-Difluoro-phenyl)-(3-{2-methoxy-5-[3-(4-methyl-piperazin-1-yl)-prop-1-ynyl]-phenyl}-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl)-amine;

4-{3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo[3,4-.d.]pyrimidin-3-yl]-4-methoxy-phenylethynyl}-1-methyl-piperidin-4-ol;

(2,4-Difluoro-phenyl)-{3-[5-((E)-3-dimethylamino-propenyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl}-amine;

(2,4-Difluoro-phenyl)-{3-[2-methoxy-5-((E)-3-morpholin-4-yl-propenyl)-phenyl]-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl}-amine

(2,4-Difluoro-phenyl)-(3-{2-methoxy-5-[(E)-3-(4-methyl-piperazin-1-yl)-propenyl]-phenyl}-1.H.-pyrazolo[3,4-.d.]pyrimidin-6-yl)-amine;

4-{3-[6-(2,4-Difluoro-phenylamino)-1.H.-pyrazolo[3,4-.b.]pyrazin-3-yl]-4-methoxy-phenyl}-2-methyl-but-3-yn-2-ol;

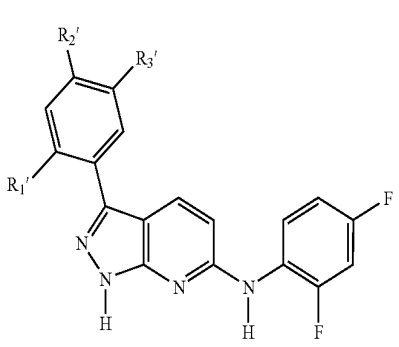
(2,4-Difluoro-phenyl)-{3-[5-(3-dimethylamino-prop-1-ynyl)-2-methoxy-phenyl]-1.H.-pyrazolo[3,4-.b.]pyrazin-6-yl}-amine; and

or a pharmaceutically-acceptable and -cleavable ester or acid addition salt thereof.

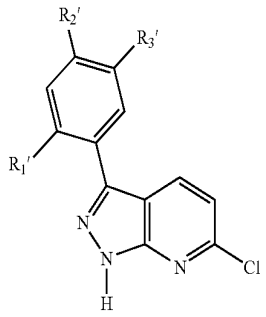
5. A method of inhibiting production of soluble TNF, especially TNFα, or of reducing inflammation in a subject in need of such treatment which method comprises administering to said subject an effective amount of an Agent of the Invention.

6-8. (canceled)

9. A process for the preparation of Agents of the Invention of formula II



wherein R1', R2', and R3' are as defined above, comprising coupling a 6-chloro-3-phenyl-1.H.-pyrazolo[3,4-.b.]pyridine of formula III



wherein R1', R2' and R3' are as defined above, with 2,4-difluoroaniline.

10. All novel compounds, processes, methods and uses substantially as hereinbefore described with particular reference to the Examples.

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