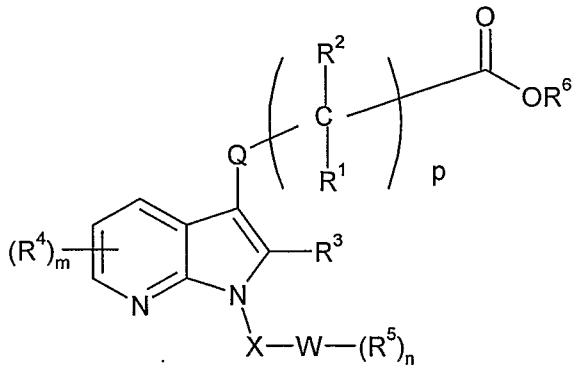
ORGANIC COMPOUNDS

The present invention relates to organic compounds, their preparation and their use as pharmaceuticals.

In a first aspect, the present invention provides compounds of formula (I)



(I)

in free or salt form, wherein

Q is a bond or a C_1-C_{10}-alkylene group optionally substituted by halogen;

R^1 and R^2 are, independently, H, halogen or C_1-C_8-alkyl, or

R^1 and R^2, together with the carbon atom to which they are attached, form a divalent C_3-C_8-cycloaliphatic group;

R^3 is H, C_1-C_8-alkyl, a C_3-C_{15}-carbocyclic group, C_1-C_8-haloalkyl, alkoxy C_1-C_8 alkyl, C_1-C_8-hydroxyalkyl;

R^4 and R^5 are, independently, halogen, C_1-C_8-alkyl, C_1-C_8-haloalkyl, a C_3-C_{15}-carbocyclic group, nitro, cyano, C_1-C_8-alkylsulfonyl, C_1-C_8-alkylsulfinyl, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkoxy, C_1-C_8-haloalkoxy, carboxy, carboxy-C_1-C_8-alkyl, amino, C_1-C_8-alkylamino, di(C_1-C_8-alkyl)amino, SO_2NH_2, (C_1-C_8-alkylamino)sulfonyl, di(C_1-C_8-alkyl)aminosulfonyl, aminocarbonyl, C_1-C_8-alkylaminocarbonyl, di(C_1-C_8-alkyl)aminocarbonyl or a 4- to 10-membered heterocyclic group having one or more heteroatoms selected from the group consisting of oxygen, nitrogen and sulphur;

R^6 is H or C_1-C_8-alkyl;

W is a C_6-C_{15}-aromatic carbocyclic group or a 4- to 10-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur;

X is -SO_2-, -CH_2-, -CON(C_1-C_8-alkyl)-, -CH(C_1-C_8-alkyl)- or a bond;

m and n are each, independently, an integer from 0-3; and

p is 1.

Terms used in the specification have the following meanings:

"Optionally substituted", as used herein, means the group referred to can be substituted at one or more positions by any one or any combination of the radicals listed thereafter.

"Halogen" or "halo" may be fluorine, chlorine, bromine or iodine; preferably it is bromine or chlorine or fluorine.

"C_1-C_8-alkyl" denotes straight-chain or branched C_1-C_8-alkyl, which may be, e.g., methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, straight- or branched-pentyl, straight- or branched-hexyl, straight- or branched-heptyl or straight- or branched-octyl. Preferably, C_1-C_8-alkyl is C_1-C_4-alkyl.

"C_3-C_{15}-carbocyclic group", as used herein, denotes a carbocyclic group having 3- to 15-ring carbon atoms, e.g., a monocyclic group, either cycloaliphatic, such as a C_3-C_8-cycloalkyl, e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; or aromatic, such as phenyl; or a bicyclic group, such as bicyclooctyl, bicyclononyl including indanyl and indenyl, and bicyclodecyl including naphthyl. Preferably the C_3-C_{15}-carbocyclic group is a C_3-C_{10}-carbocyclic group, e.g., phenyl or naphthyl. The C_3-C_{15}-carbocyclic group can be substituted with 1-3 substituents or unsubstituted. Preferred substituents include halo, cyano, amino, nitro, carboxy, C_1-C_8-alkyl, C_1-C_8-halo-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkylcarbonyl, C_1-C_8-alkylsulfonyl, $-SO_2NH_2$, (C_1-C_8-alkylamino)-sulfonyl, di(C_1-C_8-alkyl)aminosulfonyl, aminocarbonyl, C_1-C_8-alkylaminocarbonyl and di(C_1-C_8-alkyl)aminocarbonyl, a C_3-C_{10}-carbocyclic group and a 5- to 12-membered heterocyclic group having at least one ring heteroatom selected from nitrogen, oxygen and sulphur.

"C_6-C_{15}-aromatic carbocyclic group", as used herein, denotes an aromatic group having 6- to 15-ring carbon atoms, e.g., phenylene, naphthylene or anthrylene. The C_6-C_{15}-aromatic group can be substituted with 1-3 substituents or can be unsubstituted. Preferred substituents include halo, cyano, amino, nitro, carboxy, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkylcarbonyl, C_1-C_8-alkylsulfonyl, $-SO_2NH_2$, (C_1-C_8-alkylamino)-sulfonyl, di(C_1-C_8-alkyl)aminosulfonyl, aminocarbonyl, C_1-C_8-alkylaminocarbonyl and di(C_1-C_8-alkyl)aminocarbonyl, a C_3-C_{15}-carbocyclic group and a 5- to 12-membered heterocyclic group having at least one ring heteroatom selected from nitrogen, oxygen and sulphur.

"Divalent C_3-C_8-cycloaliphatic" denotes cycloalkylene having 3- to 8-ring carbon atoms, e.g., a monocyclic group, such as a cyclopropylene, cyclobutylene, cyclopentylene,

cyclohexylene, cycloheptylene or cyclooctylene, any of which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups; or a bicyclic group, such as bicycloheptylene or bicyclooctylene. Preferably "C_3-C_8-cycloalkylene" is C_3-C_5-cycloalkylene, e.g., cyclopropylene, cyclobutylene or cyclopentylene.

"C_1-C_8-alkoxy" denotes straight-chain or branched C_1-C_8-alkoxy which may be, e.g., methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy, *tert*-butoxy, straight- or branched-pentoxy, straight- or branched-hexyloxy, straight- or branched-heptyloxy or straight- or branched-octyloxy. Preferably, C_1-C_8-alkoxy is C_1-C_4-alkoxy.

"C_1-C_8-haloalkyl" and "C_1-C_8-haloalkoxy" denote C_1-C_8-alkyl and C_1-C_8-alkoxy as hereinbefore defined substituted by one or more halogen atoms, preferably one, two or three halogen atoms, preferably fluorine, bromine or chlorine atoms. Preferably, C_1-C_8-haloalkyl is C_1-C_4-alkyl substituted by one, two or three fluorine, bromine or chlorine atoms. Preferably, C_1-C_8-haloalkoxy is C_1-C_4-alkoxy substituted by one, two or three fluorine, bromine or chlorine atoms.

"C_1-C_8-alkylsulfonyl", as used herein, denotes C_1-C_8-alkyl as hereinbefore defined linked to -SO_2-. Preferably C_1-C_8-alkylsulfonyl is C_1-C_4-alkylsulfonyl, especially methylsulfonyl.

"C_1-C_8-alkylsulfinyl", as used herein, denotes C_1-C_8-alkyl as hereinbefore defined linked to –SO-. Preferably C_1-C_8-alkylsulfinyl is C_1-C_4-alkylsulfinyl, especially methylsulfinyl.

"Amino-C_1-C_8-alkyl" and "amino-C_1-C_8-alkoxy" denote amino attached by a nitrogen atom to C_1-C_8-alkyl, e.g., NH_2-(C_1-C_8)-, or to C_1-C_8-alkoxy, e.g., NH_2-(C_1-C_8)-O-, respectively, as hereinbefore defined. Preferably, amino-C_1-C_8-alkyl and amino-C_1-C_8-alkoxy are, respectively, amino-C_1-C_4-alkyl and amino-C_1-C_4-alkoxy.

"Amino-(hydroxy)-C_1-C_8-alkyl" denotes amino attached by a nitrogen atom to C_1-C_8-alkyl and hydroxy attached by an oxygen atom to the same C_1-C_8-alkyl. Preferably, amino-(hydroxy)-C_1-C_8-alkyl is amino-(hydroxy)-C_2-C_4-alkyl.

"Carboxy-C_1-C_8-alkyl" and "carboxy-C_1-C_8-alkoxy" denote carboxy attached by a carbon atom to C_1-C_8-alkyl or C_1-C_8-alkoxy, respectively, as hereinbefore defined. Preferably, carboxy-C_1-C_8-alkyl and carboxy-C_1-C_8-alkoxy are, respectively, carboxy-C_1-C_4-alkyl and carboxy-C_1-C_4-alkoxy.

"C_1-C_8-alkylcarbonyl", "C_1-C_8-alkoxycarbonyl "and "C_1-C_8-haloalkylcarbonyl" denote C_1-C_8-alkyl, C_1-C_8-alkoxy or C_1-C_8-haloalkyl, respectively, as hereinbefore defined attached by a carbon atom to a carbonyl group. "C_1-C_8-alkoxycarbonyl" denotes C_1-C_8-alkoxy as hereinbefore defined wherein the oxygen of the alkoxy group is attached to the carbonyl carbon. Preferably, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl and C_1-C_8-haloalkylcarbonyl are, respectively, C_1-C_4-alkylcarbonyl, C_1-C_4-alkoxycarbonyl and C_1-C_4-haloalkylcarbonyl.

"C_1-C_8-alkylamino" and "di(C_1-C_8-alkyl)amino" denote C_1-C_8-alkyl as hereinbefore defined attached by a carbon atom to an amino group. The C_1-C_8-alkyl groups in di(C_1-C_8-alkyl)amino may be the same or different. Preferably, C_1-C_8-alkylamino and di(C_1-C_8-alkyl)amino are, respectively, C_1-C_4-alkylamino and di(C_1-C_4-alkyl)amino.

"C_1-C_8-alkylaminocarbonyl" and "di(C_1-C_8-alkyl)aminocarbonyl" denote C_1-C_8-alkylamino and di(C_1-C_8-alkyl)amino, respectively, as hereinbefore defined attached by a nitrogen atom to the carbon atom of a carbonyl group. Preferably, C_1-C_8-alkylamino-carbonyl and di(C_1-C_8-alkyl)-aminocarbonyl are, respectively, C_1-C_4-alkylaminocarbonyl and di(C_1-C_4-alkyl)-aminocarbonyl.

"Di(C_1-C_8-alkyl)amino-C_1-C_8-alkyl" and "di(C_1-C_8-alkyl)amino-C_1-C_8-alkoxy" denote di(C_1-C_8-alkyl)amino as hereinbefore defined attached by a nitrogen atom to the carbon atom of a C_1-C_8-alkyl or a C_1-C_8-alkoxy group, respectively. Preferably, di(C_1-C_8-alkyl)-amino-C_1-C_8-alkyl and di(C_1-C_8-alkyl)amino-C_1-C_8-alkoxy are, respectively, di(C_1-C_4-alkyl)-amino-C_1-C_4-alkyl and di(C_1-C_4-alkyl)amino-C_1-C_4-alkoxy.

"4- to 10-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur", as used herein, may be monocyclic or bicyclic, e.g., furan, tetrahydrofuran, pyrrole, pyrrolidine, pyrazole, imidazole, triazole, isotriazole, tetrazole, thiadiazole, isothiazole, oxadiazole, pyridine, oxazole, isoxazole, pyrazine, pyridazine, pyrimidine, piperidine, piperazine, morpholine, triazine, oxazine, thiazole, quinoline, isoquinoline, benzothiophene, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, benzofuran, indole, indazole or benzimidazole. Preferred heterocyclic groups include piperazine, morpholine, imidazole, isotriazole, pyrazole, pyridine, furan, oxazole, isoxazole, thiazole, tetrazole, benzothiophene, benzoxazole, benzothiazole and benzofuran. The 4- to 10-membered heterocyclic group can be unsubstituted or substituted. Preferred substituents include halo, cyano, oxo, hydroxy, carboxy, nitro, C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl, hydroxy-C_1-C_8-alkyl, C_1-C_8-haloalkyl, amino-C_1-C_8-alkyl, amino(hydroxy)C_1-C_8-alkyl and C_1-C_8-alkoxy optionally substituted by aminocarbonyl. Especially preferred substituents include halo, oxo, C_1-C_4-

alkyl, C_1-C_4-alkylcarbonyl, hydroxy-C_1-C_4-alkyl, C_1-C_4-haloalkyl, amino-C_1-C_4-alkyl and amino(hydroxy)C_1-C_4-alkyl.

Throughout this specification and in the claims that follow, unless the context requires otherwise, the word "comprise", or variations, such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Where in formula (I), m or n are 2, the two substituents may be the same or different. Where m or n are 3, two or all of the substituents may be the same, or all three may be different.

In another aspect, the present invention provides compounds of formula (I) in free or salt form, wherein

Q is a bond or a C_1-C_{10}-alkylene group optionally substituted by halogen;

R^1 and R^2 are, independently, H, halogen or C_1-C_8-alkyl, or

R^1 and R^2, together with the carbon atom to which they are attached, form a divalent C_3-C_8-cycloaliphatic group;

R^3 is H, C_1-C_8-alkyl, a C_3-C_{15}-carbocyclic group, C_1-C_8-haloalkyl, alkoxy C_1-C_8 alkyl, C_1-C_8-hydroxyalkyl;

R^4 and R^5 are, independently, halogen, C_1-C_8-alkyl, C_1-C_8-haloalkyl, a C_3-C_{15}-carbocyclic group, nitro, cyano, C_1-C_8-alkylsulfonyl, C_1-C_8-alkylsulfinyl, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkoxy, C_1-C_8-haloalkoxy, carboxy, carboxy-C_1-C_8-alkyl, amino, C_1-C_8-alkylamino, di(C_1-C_8-alkyl)amino, SO_2NH_2, (C_1-C_8-alkylamino)sulfonyl, di(C_1-C_8-alkyl)aminosulfonyl, aminocarbonyl, C_1-C_8-alkylaminocarbonyl, di(C_1-C_8-alkyl)aminocarbonyl or a 4- to 10-membered heterocyclic group having one or more heteroatoms selected from the group consisting of oxygen, nitrogen and sulphur;

R^6 is H or C_1-C_8-alkyl;

W is a C_6-C_{15}-aromatic carbocyclic group or a 4- to 10-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur;

X is -SO_2-, -CH_2-, -CON(C_1-C_8-alkyl)-, -CH(C_1-C_8-alkyl)- or a bond;

m and n are each, independently, an integer from 0-3; and

p is 1.

In another aspect, the present invention provides compounds of formula (I) in free or salt form, wherein

Q is a bond;

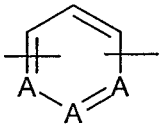
R^1 and R^2 are, independently, H or C_1-C_8-alkyl;

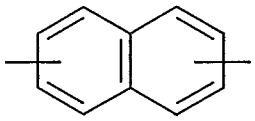
R^3 is C_1-C_8-alkyl;

R^4 and R^5 are, independently, halogen, C_1-C_8-alkyl, C_1-C_8-haloalkyl, a C_3-C_{15}-carbocyclic group, nitro, cyano, C_1-C_8-alkylsulfonyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkoxy or C_1-C_8-haloalkoxy;

R^6 is H or C_1-C_8-alkyl;

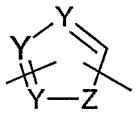
W is a group of formula (W_{a1}) or (W_{a2})



(W_{a1}) or  **(W_{a2})**,

wherein A is, independently, C or N, or

W is a group of formula (W_b);



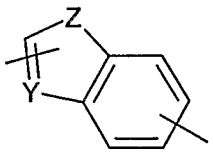
(W_b),

wherein

Y is, independently, C or N; and

Z is N, O or S, or

W is a group of formula (W_c)



(W_c),

wherein

Y is, independently, C or N; and

Z is O or S;

X is $-SO_2-$, $-CH_2-$, $-CH(C_1$-C_8-alkyl$)-$, $-CON(C_1$-C_8-alkyl$)-$ or a bond;

m and n are each, independently, an integer from 0-3; and

p is 1.

In yet another aspect, the present invention provides compounds of formula (I) in free or salt form, wherein

Q is a bond;

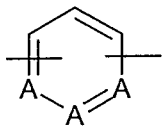
R^1 and R^2 are, independently, H or C_1-C_4-alkyl;

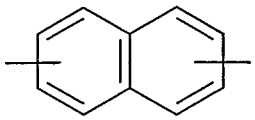
R^3 is C_1-C_4-alkyl;

R^4 and R^5 are, independently, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, C_3-C_{10}-carbocyclic group, C_1-C_4-alkoxycarbonyl, C_1-C_4-alkylsulfonyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy;

R^6 is H or C_1-C_4-alkyl;

W is a group of formula (W_{a1}) or (W_{a2})



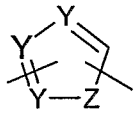
(W_{a1}) or  **(W_{a2})**,

wherein

one A is C or N; and

the other two are each C, or

W is a group of formula (W_b)



(W_b),

wherein

Y is, independently, C or N; and

Z is N, O or S;

X is $-SO_2-$, $-CH_2-$ or $-CH(C_1-C_4\text{-alkyl})-$;

m and n are each, independently, an integer from 0-3; and

p is 1.

In a yet further aspect, the present invention provides for the use of a compound of formula (I) in any of the aforementioned embodiments, in free or salt form, for the manufacture of a medicament for the treatment of an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease.

Salts and Isomers

Many of the compounds represented by formula (I) are capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts. Pharmaceutically acceptable acid addition salts of the compound of formula (I) include those of inorganic acids, e.g., hydrohalic acids, such as hydrochloric acid or hydrobromic

acid; nitric acid; sulphuric acid; phosphoric acid; and organic acids, e.g., aliphatic monocarboxylic acids, such as formic acid, acetic acid, diphenylacetic acid, triphenylacetic acid, caprylic acid, dichloroacetic acid, trifluoroacetic acid, hippuric acid, propionic acid and butyric acid; aliphatic hydroxy acids, such as lactic acid, citric acid, gluconic acid, mandelic acid, tartaric acid or malic acid; dicarboxylic acids, such as adipic acid, aspartic acid, fumaric acid, glutamic acid, maleic acid, malonic acid, sebacic acid or succinic acid; aromatic carboxylic acids, such as benzoic acid, *p*-chlorobenzoic acid, or nicotinic acid; aromatic hydroxy acids, such as *o*-hydroxybenzoic acid, *p*-hydroxybenzoic acid, 1-hydroxy-naphthalene-2-carboxylic acid or 3-hydroxynaphthalene-2-carboxylic acid; and sulfonic acids, such as ethanesulfonic acid, ethane-1,2-disulfonic acid, 2-hydroxyethane-sulfonic acid, methanesulfonic acid, (+)-camphor-10-sulfonic acid, benzenesulfonic acid, naph-thalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid or *p*-toluenesulfonic acid. These salts may be prepared from compounds of formula (I) by known salt-forming procedures.

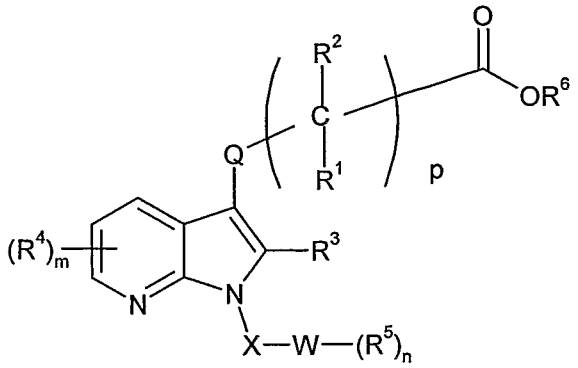
Compounds of formula (I) which contain acidic, e.g., carboxyl, groups, are also capable of forming salts with bases, in particular, pharmaceutically acceptable bases, such as those well-known in the art; suitable such salts include metal salts, particularly, alkali metal or alkaline earth metal salts, such as sodium, potassium, magnesium, calcium or zinc salts; or salts with ammonia or pharmaceutically acceptable organic amines or heterocyclic bases, such as benethamine, benzathine, diethanolamine, ethanolamine, 4(2-hydroxy-ethyl)morpholine,1-(2-hydroxyethyl)pyrrolidine, *N*-methyl glucamine, piperazine, triethanol-amine or tromethamine. These salts may be prepared from compounds of formula (I) by known salt-forming procedures.

In those compounds where there is an asymmetric carbon atom or an axis of chirality the compounds exist in individual optically active isomeric forms or as mixtures thereof, e.g., as racemic or diastereomeric mixtures. The present invention embraces both individual optically active *R* and *S* isomers, as well as mixtures, e.g., racemic or diastereomeric mixtures, thereof.

Specific preferred compounds of formula (I) are described hereinafter in the Examples.

The invention also provides a process for the preparation of compounds of formula (I), in free or salt form, which comprises the steps of:

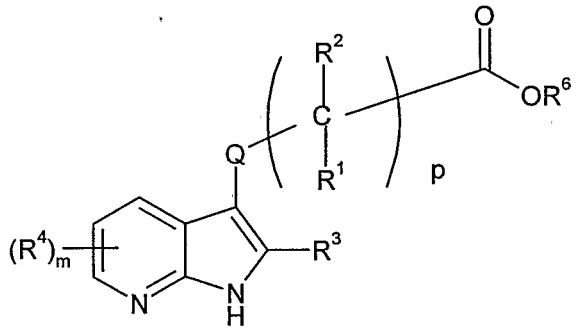
(i) (A) for the preparation of compounds of formula (I), wherein R^6 is H, cleaving the ester group -$COOR^6$ in a compound of formula (I),



(I)

where R^6 is C_1-C_8-alkyl and Q, R^1, R^2, R^3, R^4, R^5, W, X, m, n and p are as hereinbefore defined; or

(B) for the preparation of compounds of formula (I), wherein R^6 is C_1-C_8-alkyl, reacting a compound of formula (II)



(II)

wherein

R^6 is C_1-C_8-alkyl; and

Q, R^1, R^2, R^3, R^4, m, n and p are as hereinbefore defined with a compound of formula (III)

$$G—X—W—(R^5)_n \qquad \textbf{(III)},$$

wherein

G is a leaving moiety, e.g., a halogen atom or an arylsulfonate group; and

R^5, W, X and n are as hereinbefore defined; or

(C) for the preparation of compounds of formula (I),

wherein

R^6 is C_1-C_8-alkyl;

R^1 is H or C_1-C_8-alkyl;

R^2 is C_1-C_8-alkyl; and

p is 1, reacting a compound of formula (I),

where

R^1 is H or C_1-C_8-alkyl; and

R^2 is H, with a compound of formula R^A G,

where

R^A is C_1-C_8-alkyl; and

G is as hereinbefore defined; and

(ii) recovering the resultant compound of formula (I) in free or salt form.

Process variant (A) may be carried out using known methods (or analogously as hereinafter described in the Examples) for cleavage of carboxylic ester groups and can be carried out *in situ* after preparation of a compound of formula (I), where R^6 is C_1-C_8-alkyl. For example, the compound of formula (I), where R^6 is C_1-C_8-alkyl, which is conveniently in solution in a polar organic solvent or a mixture thereof with water, may be reacted with an aqueous inorganic base, such as NaOH or LiOH to hydrolyse the ester group; where the base is NaOH, the reaction may be carried out at a temperature of 10-40°C, conveniently ambient temperature, while when the base is LiOH the reaction may be started at -5°C to 5°C and then continued at 10-40°C, conveniently ambient temperature. Alternatively, the compound of formula (I), where R^6 is C_1-C_8-alkyl, which is conveniently in solution in an organic solvent, such as CH_2Cl_2, may be reacted with a Lewis acid, such as boron tribromide to effect ester cleavage; the reaction may conveniently be carried out at 50-60°C, e.g., with the aid of microwave irradiation.

Process variant (B) may be carried out using known procedures or analogously as hereinafter described in the Examples. For example, the compound of formula (II) may be reacted with a sulfonyl halide of formula (III),

where

G is halogen;

X is $-SO_2-$; and

R^5, W and n are as hereinbefore defined,

in the presence of an organic base, such as 2-*tert*-butylimino-1,3-dimethyl-2 lambda*5*-[1,3,2]diazaphosphinan-2-yl)-diethyl-amine (BEMP); the reaction may be carried out in an organic solvent, e.g., a polar aprotic solvent, such as *N,N*-dimethylformamide (DMF) and may be carried out at 10-40°C, conveniently at ambient temperature. In another example, the compound of formula (II) may be reacted with a compound of formula (III),

where

G is halogen;

X is $-CH_2-$; and

R^5, W and n are as hereinbefore defined,

in the presence of an organic base, such as BEMP, e.g., in a polar aprotic solvent, such as *N,N*-DMF; the reaction may be carried out at 10-40°C, conveniently at ambient temperature. In a further example, the compound of formula (II) may be reacted with a compound of formula (III),

where

G is halogen;

X is $-CH_2-$;

W is of formula (W_a),

where

one A is N; and

the other two are C; and

R^5 and n are as hereinbefore defined,

in the form of a salt, such as a hydrohalide, in the presence of an inorganic base, such as NaH or an organic base, such as BEMP, e.g., in a polar aprotic solvent, such as *N,N*-DMF; the reaction may be carried out at 10-40°C, conveniently at ambient temperature. In yet another example, the compound of formula (II) may be reacted with a compound of formula (III),

where

G is arylsulfonate;

X is $-CH_2-$; and

R^5, W and n are as hereinbefore defined,

in the presence of an organic base, such as BEMP, e.g., in a mixture of a polar aprotic solvent, such as *N,N*-DMF and an ethereal solvent; the reaction may be carried out at 10-40°C, conveniently at ambient temperature. In a yet further example, the compound of formula (II) may be reacted with a compound of formula (III),

where

G is halogen; X is a bond;

W is phenylene or naphthylene; and

R^5 and n are as hereinbefore defined,

in the presence of a metal compound catalyst, e.g., a transition metal complex formed *in situ* from a metal salt, such as CuI and a diamine, and an inorganic base, such as sodium

phosphate; the reaction is preferably carried out in an organic solvent, e.g., a polar aprotic solvent, such as dioxane; the reaction temperature may be from 140-180°C, preferably from 150-170°C.

Process variant (C) may be carried out using known procedures for α-alkylation of carboxylic esters, or analogously, e.g., as hereinafter described in the Examples. The reaction is conveniently carried out in the presence of an inorganic base, .e.g., lithium diisopropyl amide, followed by addition of an alkyl iodide, e.g., methyl iodide. The reaction temperature may be from about -90°C to about -60°C, but conveniently at -78°C.

Compounds of formula (II) are known or may be obtained by known methods, e.g., as described in U.S. Patent No. 3,320,268, or analogously as hereinafter described in the Examples. Compounds of formula (III) are known or may be obtained by known methods, or analogously, as hereinafter described in the Examples.

The compounds of formula (I) in free form may be converted into salt form, and vice versa, in a conventional manner. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallisation. Compounds of formulae (I) and (II) can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as enantiomers, may be obtained in a conventional manner, e.g., by fractional crystallisation, chiral HPLC resolution or asymmetric synthesis from correspondingly asymmetrically substituted, e.g., optically active, starting materials.

Pharmaceutical Use and Assay

Compounds of formulae (I) and (II) and their pharmaceutically acceptable salts, hereinafter referred to alternatively as "agents of the invention", are useful as pharmaceuticals. In particular, the compounds have good CRTh2 receptor antagonist activity and may be tested in the following assays.

Filtration binding assay protocol

The binding of CRTh2 antagonists is determined using membranes prepared from human CRTh2-expressing Chinese Hamster Ovary cells (CHO.K1-CRTh2). To produce cell membranes CHO.K1-CRTh2 cells cultured in roller bottles are harvested using cell dissociation buffer (Invitrogen). The cells are pelleted by centrifugation (167 *g*, 5 min). The cell pellet is incubated in hypotonic buffer (15 mM Tris-OH, 2 mM $MgCl_2$, 0.3 mM EDTA, 1 mM EGTA, 1x Complete™ tablet) at 4°C for 30 min. At 4°C cells are homogenized using a Polytron® (IKA Ultra Turrax T25) for 5 bursts of 1 second. The homogenate is centrifuged

(Beckman Optima TM TL Ultracentrifuge, 48000 *g*, 30 min at 4°C). The supernatant is discarded and the membrane pellet resuspended in homogenisation buffer (75 mM Tris-OH, 12.5 mM MgCl2, 0.3 mM EDTA, 1 mM EGTA, 250 mM Sucrose, 1x Complete™ tablet. Membrane preparations are aliquoted and stored at 80°C. The protein content is estimated using Bradford Protein Assay Dye (Bio Rad).

The binding of [^{3}H]-PGD_2 (157 Ci/mmol) to CHO.K1-CRTh2 membranes is determined in the absence (total binding) and presence (non-specific binding) of unlabelled PGD_2 (1 μM). Subtraction of the cpm (counts per minute) of [^{3}H]-PGD_2 binding in presence of excess unlabelled PGD_2 from that observed in the absence of excess unlabelled PGD_2 is defined as specific binding. Active CRTh2 antagonists are able to compete with [^{3}H]-PGD_2 for binding to the CRTh2 receptor and are identified in a decrease in the number of cpm bound.

The assay is performed in Greiner U-bottomed 96 well-plates, in a final volume of 100 μl per well. CHO.K1-CRTh2 membranes were diluted in assay buffer (10mM HEPES-KOH (pH 7.4), 1 mM EDTA and 10 mM $MnCl_2$) and 10 μg are added to each well. [^{3}H]-PGD_2 is diluted in assay buffer and added to each well at a final concentration of 2.5 nM. To determine non-specific binding, [^{3}H]-PGD_2 binding to the CRTh2 receptor is competed with using unlabelled PGD_2 at a final well concentration of 1 μM. The experiment is done in triplicate, with reagents added to the wells as follows:

- 25 μL assay buffer for total binding or

- 25 μL PGD_2 to determine non-specific binding

- 25 μL [^{3}H]PGD_2

- 50 μL membranes

- 25 μL test compound in DMSO/assay buffer

The plates are incubated at room temperature on a shaker for 1 hour, and then harvested (Tomtec Harvester 9600) onto GF/C filter plates using wash buffer (10 mM HEPES-KOH, pH 7.4). The plate is dried for 2 hours, prior to addition of Micro-Scint 20™ (50 μL) and sealing with TopSeal-S™. Plates are then counted using a Packard Top Count instrument, Plates are then read on the Packard Topcount with the 3H Scintillation program (1 min per well).

Ki (dissocation constant for the inhibition) values for the CRTh2 antagonists are reported. Ki values are determined using Sigma Plot™ software, using the Cheng-Prussoff equation.

$Ki = IC_{50} / 1+ [S]/Kd$

where S is the concentration of radioligand and Kd is the dissociation constant.

CRTH2 cAMP functional assay protocol

This assay is conducted in CHO.K1-CRTh2 cells. cAMP is generated in the cell by stimulating cells with 5 μM forskolin, an adenylate cyclase activator. PGD_2 is added to activate the CRTh2 receptor which results in the attenuation of the forskolin-induced cAMP accumulation. Potential CRTh2 antagonists are tested for their ability to inhibit the PGD_2-mediated attenuation of the forskolin-induced cAMP accumulation in CHO.K1-CRTh2 cells.

For each concentration value on the dose-response curve, test compounds are prepared in assay stimulation buffer (HBSS, 5 mM HEPES, 10 μM IBMX ± 0.1% human serum albumin) containing DMSO (3% vol/vol) and 5 μL/well is added to an assay plate (384 well white optiplate).

CHO.K1-CRTh2 cultured in tissue culture flasks are washed with PBS and harvested with dissociation buffer. Cells are washed with PBS and resuspended in stimulation buffer to a concentration of 0.4×10^6 / mL and added to the assay plate (10 μL/well).

The assay plate is incubated at room temperature on a shaker for 15 minutes.

A mix of agonist (10 nM Prostaglandin D_2) and 5 μM forskolin is prepared in assay stimulation buffer and added to the assay plate (5 μL/well).

In addition, a cAMP standard is serially diluted in assay stimulation buffer and added to separate empty wells on the assay plate (20 μL/well). The cAMP standard allows for the quantification of cAMP generated in CHO.K1-CRTH2 cells.

The assay plate is incubated at room temperature on a shaker for 60 minutes.

Cell lysis buffer (Lysis buffer: Milli-Q H_20, 5 mM HEPES, 0.3% Tween-20, 0.1% human serum albumin) is added to a bead mix (containing Alphascreen™ anti-cAMP acceptor beads 0.06 units/μL, Alphascreen™ streptavidin-coated donor beads 0.06

units/μL, biotinylated cAMP 0.06 units/μL, 10μM IBMX) is prepared under darkened conditions 60 minutes prior to addition to the assay plate. The resulting lysis mix is added to all wells of the assay plate (40 μL/well).

The assay plate is sealed with Topseal-S™ and incubated in the dark at room temperature on a shaker for 45 minutes. The plate is then counted using a Packard Fusion™ instrument.

The resulting counts per minute are converted to nM cAMP by using the prepared cAMP standard curve. IC_{50} values (concentration of CRTh2 antagonist required to inhibit 50% of the PGD_2-mediated attenuation of forskolin-induced cAMP accumulation in CHO.K1-CRTh2 cells) are then determined using Prism™ software.

Compounds of the Examples herein below generally have Ki values in the SPA binding assay below 1 μM. For example, the compounds of Examples 3, 18, 31, 54, 59, 84, 90, 92, 93, 94, 95, 96, 97, 99, 100, 102, 103, 105, 112, 115, 117, 119, 122, 125, 127, 129, 130, and 148 have Ki values of 0.048, 0.090, 0.122, 0.037, 0.033 0.10, 0.003, 0.022, 0.008, 0.007, 0.004, 0.029, 0.011, 0.012, 0.005, 0.056, 0.035, 0.098, 0.031, 0.045, 0.025, 0.029, 0.147, 0.027, 0.043, 0.043, 0.050, and 0.064 μM respectively.

Compounds of the Examples herein below generally have IC_{50} values in the functional assay below 1 μM. For example, the compounds of Examples 3, 18, 31, 54, 59 and 84 have IC_{50} values of 0.276, 0.171, 0.178, 0.168, 0.150, 0.084, 0.014, 0.040, 0.022, 0.016, 0.019, 0.021, 0.013, 0.019, 0.009, 0.091, 0.041, 0.046, 0.026, 0.080, 0.021, 0.064, 0.144, 0.095, 0.031, 0.143, 0.060, and 0.131μM respectively.

Compounds of formulae (I) and (II), in free or salt form, are antagonists of the G-protein-coupled chemoattractant receptor CRTh2, expressed on Th2 cells, eosinophils and basophils. PGD_2 is the natural ligand for CRTh2. Thus, antagonists which inhibit the binding of CRTh2 and PGD_2 are useful in the treatment of allergic and anti-inflammatory conditions. Treatment in accordance with the invention may be symptomatic or prophylactic.

Accordingly, agents of the invention are useful in the treatment of inflammatory or obstructive airways diseases, resulting, e.g., in reduction of tissue damage, airways inflammation, bronchial hyperreactivity, remodelling or disease progression. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic

(allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitis asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g., of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g., of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e., therapy for or intended to restrict or abort symptomatic attack when it occurs, e.g., anti-inflammatory (e.g., corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may, in particular, be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g., between the hours of about 4-6 a.m., i.e., at a time normally substantially distant from any previously administered symptomatic asthma therapy.

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular, other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis including, e.g., aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Having regard to their anti-inflammatory activity, in particular, in relation to inhibition of eosinophil activation, agents of the invention are also useful in the treatment of eosinophil related disorders, e.g., eosinophilia, in particular, eosinophils-related disorders of the airways, e.g., involving morbid eosinophilic infiltration of pulmonary tissues including

hypereosinophilia as it effects the airways and/or lungs, as well as, e.g., eosinophil-related disorders of the airways consequential or concomitant to Löffler's syndrome; eosinophilic pneumonia; parasitic, in particular, metazoan, infestation including tropical eosinophilia; bronchopulmonary aspergillosis; polyarteritis nodosa including Churg-Strauss syndrome; eosinophilic granuloma; and eosinophil-related disorders affecting the airways occasioned by drug-reaction.

Agents of the invention are also useful in the treatment of inflammatory or allergic conditions of the skin, e.g., psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphisus, epidermolysis bullosa acquisita and other inflammatory or allergic conditions of the skin.

Agents of the invention may also be used for the treatment of other diseases or conditions, in particular, diseases or conditions having an inflammatory component, e.g., treatment of diseases and conditions of the eye, such as conjunctivitis, keratoconjunctivitis sicca and vernal conjunctivitis; diseases affecting the nose including allergic rhinitis; and inflammatory disease, in which autoimmune reactions are implicated or having an autoimmune component or aetiology, including autoimmune hematological disorders, e.g., hemolytic anemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia; systemic lupus erythematosus; polychondritis; sclerodoma; Wegener granulamatosis; dermatomyositis; chronic active hepatitis; myasthenia gravis; Steven-Johnson syndrome; idiopathic sprue; autoimmune inflammatory bowel disease, e.g., ulcerative colitis and Crohn's disease; endocrine opthalmopathy; Grave's disease; sarcoidosis; alveolitis; chronic hypersensitivity pneumonitis; multiple sclerosis; primary billiary cirrhosis; 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 minal change nephropathy.

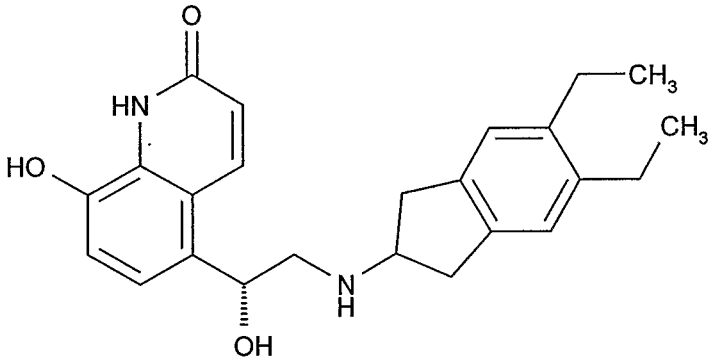
Other diseases or conditions which may be treated with agents of the invention include septic shock; rheumatoid arthritis; osteoarthritis; proliferative diseases, such as cancer; atherosclerosis; allograft rejection following transplantation; stroke; obesity; restenosis; diabetes, e.g., diabetes mellitus type I (juvenile diabetes) and diabetes mellitus type II; diarrhoeal diseases; ischemia/reperfusion injuries; retinopathy, such as diabetic retinopathy or hyperbaric oxygen-induced retinopathy; and conditions characterised by elevated intraocular pressure or secretion of ocular aqueous humor, such as glaucoma.

The effectiveness of an agent of the invention in inhibiting inflammatory conditions, e.g., in inflammatory airways diseases, may be demonstrated in an animal model, e.g., a mouse or rat model, of airways inflammation or other inflammatory conditions, e.g., as described by Szarka et al., *J Immunol Methods*, Vol. 202, pp. 49-57 (1997); Renzi et al., *Am Rev Respir Dis*, Vol. 148, pp. 932-939 (1993); Tsuyuki et al., *J Clin Invest*, Vol. 96, pp. 2924-2931 (1995); Cernadas et al., *Am J Respir Cell Mol Biol*, Vol. 20, pp. 1-8 (1999); and Williams and Galli, *J Exp Med*, Vol. 192, pp. 455-462 (2000).

The agents of the invention are also useful as co-therapeutic agents for use in combination with other drug substances, such as anti-inflammatory, bronchodilatory or antihistamine drug substances, particularly in the treatment of obstructive or inflammatory airways diseases, such as those mentioned hereinbefore, e.g., as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. An agent of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance. Accordingly the invention includes a combination of an agent of the invention as hereinbefore described with an anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substance, said agent of the invention and said drug substance being in the same or different pharmaceutical composition.

Such anti-inflammatory drugs include steroids, in particular, glucocorticosteroids, such as budesonide, beclamethasone dipropionate, fluticasone propionate, ciclesonide or mometasone furoate; or steroids, described in WO 02/88167, WO 02/12266, WO 02/100879, WO 02/00679 (especially those of Examples 3, 11, 14, 17, 19, 26, 34, 37, 39, 51, 60, 67, 72, 73, 90, 99 and 101), WO 03/035668, WO 03/048181, WO 03/062259, WO 03/064445 and WO 03/072592; non-steroidal glucocorticoid receptor agonists, such as those described in WO 00/00531, WO 02/10143, WO 03/082280, WO 03/082787, WO 03/104195 and WO 04/005229; LTB4 antagonists, such as those described in U.S. Patent No. 5,451,700; LTD4 antagonists, such as montelukast and zafirlukast; PDE4 inhibitors, such as cilomilast (Ariflo® GlaxoSmithKline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene), SelCID(TM) CC-10004 (Celgene), KW-4490 (Kyowa Hakko Kogyo), WO 03/104204, WO 03/104205, WO 04/000814, WO 04/000839 and WO 04/005258 (Merck), as well as those described in WO 98/18796 and WO 03/39544; A2a agonists, such as those described in EP 1052264, EP 1241176, EP 409595A2, WO 94/17090, WO 96/02543, WO

96/02553, WO 98/28319, WO 99/24449, WO 99/24450, WO 99/24451, WO 99/38877, WO 99/41267, WO 99/67263, WO 99/67264, WO 99/67265, WO 99/67266, WO 00/23457, WO 00/77018, WO 00/78774, WO 01/23399, WO 01/27130, WO 01/27131, WO 01/60835, WO 01/94368, WO 02/00676, WO 02/22630, WO 02/96462 and WO 03/086408; A2b antagonists, such as those described in WO 02/42298; and beta (β)-2-adrenoceptor agonists, such as albuterol (salbutamol), metaproterenol, terbutaline, salmeterol, fenoterol, procaterol, and especially, formoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula (I) of WO 00/75114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



and pharmaceutically acceptable salts thereof, as well as compounds (in free or salt or solvate form) of formula (I) of WO 04/16601. Further β-2-adrenoreceptor agonists include compounds, such as those described in WO 99/64035, WO 01/42193, WO 01/83462, WO 02/066422, WO 02/070490, WO 02/076933, WO 2004/011416 and US 2002/0055651.

Such bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular, ipratropium bromide, oxitropium bromide, tiotropium salts and CHF 4226 (Chiesi), but also those described in WO 01/04118, WO 02/51841, WO 02/53564, WO 03/00840, WO 03/87094, WO 04/05285, WO 02/00652, WO 03/33495, WO 03/53966, EP 0424021, US 5171744 and US 3714357.

Such co-therapeutic antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride.

Combinations of agents of the invention and steroids, β-2 agonists, PDE4 inhibitors or LTD4 antagonists may be used, e.g., in the treatment of COPD or, particularly, asthma. Combinations of agents of the invention and anticholinergic or antimuscarinic agents,

PDE4 inhibitors, dopamine receptor agonists or LTB4 antagonists may be used, e.g., in the treatment of asthma or, particularly, COPD.

Other useful combinations of agents of the invention with anti-inflammatory drugs are those with antagonists of chemokine receptors, e.g., CCR-1, CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9, CCR-10, CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5; particularly useful are CCR-3 antagonists, such as those described in WO 2002/026723, especially 4-{3-[(*S*)-4-(3,4-dichlorobenzyl)-morpholin-2-ylmethyl]-ureidomethyl}-benzamide and those described in WO 2003/077907, WO 2003/007939 and WO 2002/102775.

Also especially useful are CCR-5 antagonists, such as Schering-Plough antagonists SC-351125, SCH-55700 and SCH-D; Takeda antagonists, such as *N*-[[4-[[[6,7-dihydro-2-(4-methylphenyl)-5*H*-benzo-cyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-*N,N*-dimethyl-2*H*-pyran-4-aminium chloride (TAK-770); and CCR-5 antagonists, described in US 6166037, WO 00/66558 and WO 00/66559.

The agents of the invention may be administered by any appropriate route, e.g., orally, e.g., in the form of a tablet or capsule; parenterally, e.g., intravenously; by inhalation, e.g., in the treatment of inflammatory or obstructive airways disease; intranasally, e.g., in the treatment of allergic rhinitis; topically to the skin, e.g., in the treatment of atopic dermatitis; or rectally, e.g., in the treatment of inflammatory bowel disease.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) in free form or in the form of a pharmaceutically acceptable salt, optionally together with a pharmaceutically acceptable diluent or carrier therefore. The composition may contain a co-therapeutic agent, such as an anti-inflammatory, bronchodilatory or antihistamine drug as hereinbefore described. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g., patches. Compositions for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

When the composition comprises an aerosol formulation, it preferably contains, e.g., a hydro-fluoro-alkane (HFA) propellant, such as HFA134a or HFA227 or a mixture of these, and may contain one or more co-solvents known in the art, such as ethanol (up to 20% by weight); and/or one or more surfactants, such as oleic acid or sorbitan trioleate;

and/or one or more bulking agents, such as lactose. When the composition comprises a dry powder formulation, it preferably contains, e.g., the compound of formula (I) having a particle diameter up to 10 microns, optionally together with a diluent or carrier, such as lactose, of the desired particle size distribution and a compound that helps to protect against product performance deterioration due to moisture. When the composition comprises a nebulised formulation, it preferably contains, e.g., the compound of formula (I) either dissolved, or suspended, in a vehicle containing water, a co-solvent, such as ethanol or propylene glycol and a stabilizer, which may be a surfactant.

The invention includes:

(a) an agent of the invention in inhalable form, e.g., in an aerosol or other atomizable composition or in inhalable particulate, e.g., micronised form;

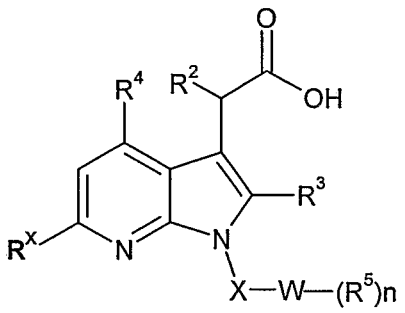
(b) an inhalable medicament comprising an agent of the invention in inhalable form;

(c) a pharmaceutical product comprising such an agent of the invention in inhalable form in association with an inhalation device; and

(d) an inhalation device containing an agent of the invention in inhalable form.

Dosages of agents of the invention employed in practising the present invention will of course vary depending, e.g., on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for oral administration are of the order of 0.01-100 mg/kg.

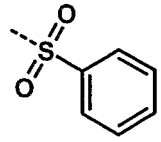
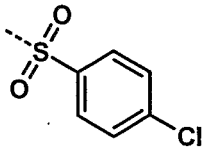
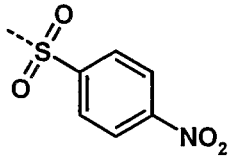
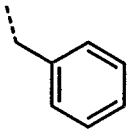
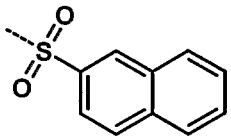
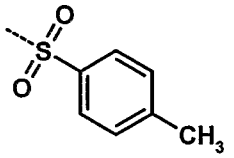
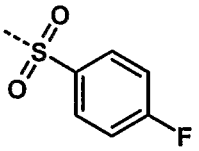
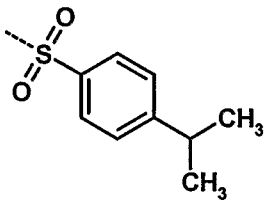
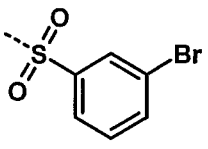
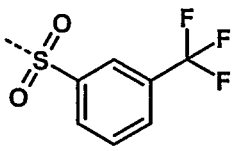
EXAMPLES

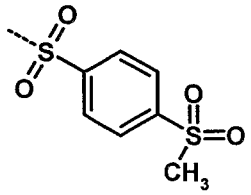
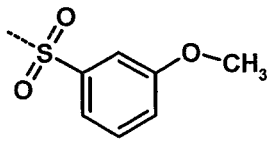
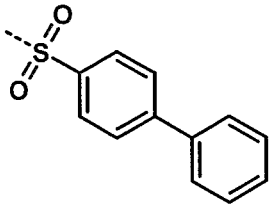
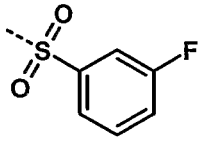
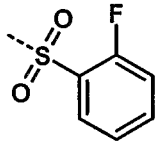
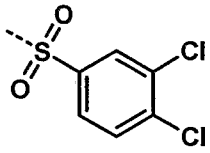
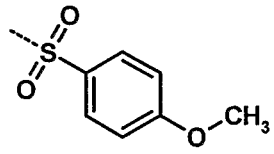
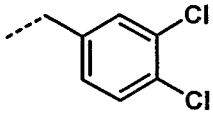
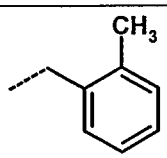
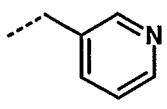


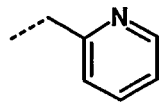
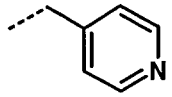
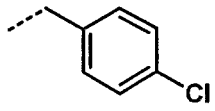
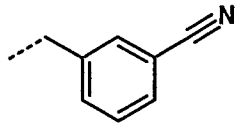
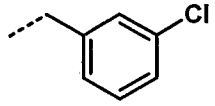
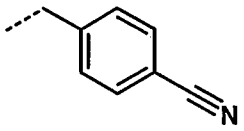
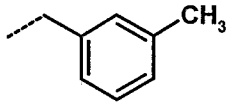
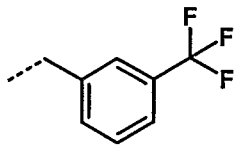
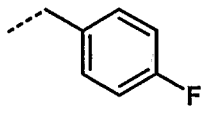
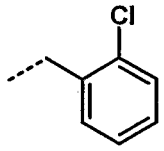
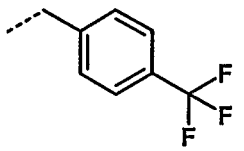
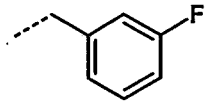
R^2 = H except for Example 40, where R^2 = CH_3.

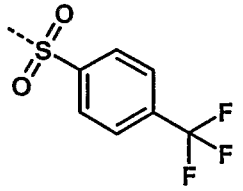
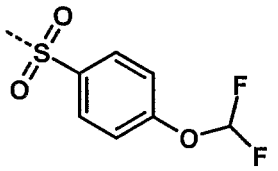
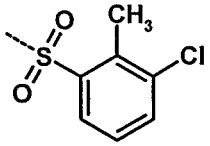
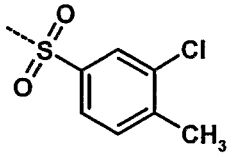
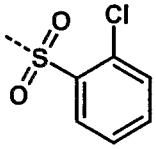
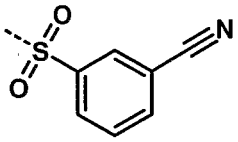
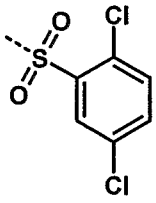
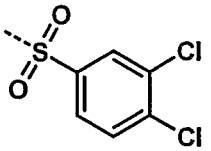
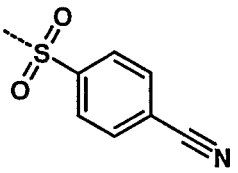
R^3 = CH_3 except for Example 81, where R^3 = H and except for Example 87 and 153, where R^3 = CH_2CH_3.R^4 = H except for Example 62 and Example 89, where R^4 = Cl.

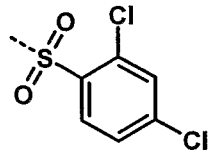
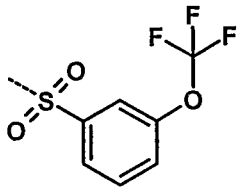
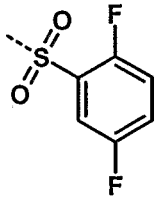
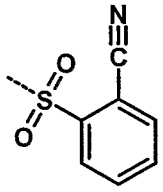
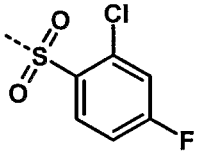
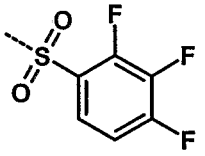
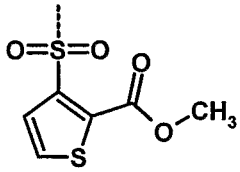
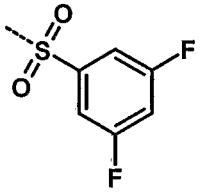
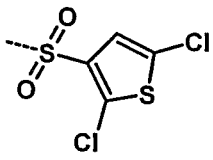
R^X = H except for Example 99 and 100, where R^6 = Cl

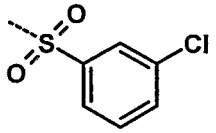
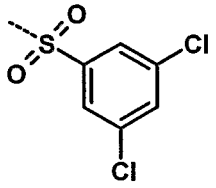
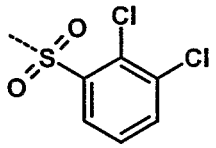
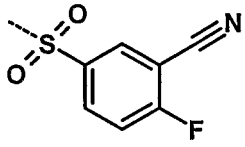
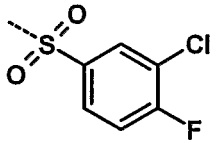
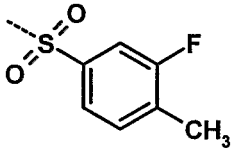
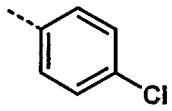
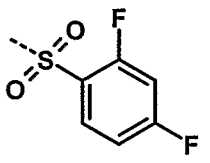
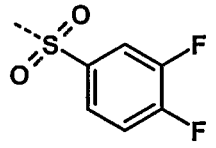
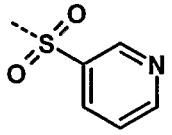
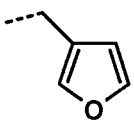
Example	X—W—$(R^5)_n$	MH^+
1		331
2		365
3		376
4		281
5		381
6		345
7		349
8		373
9		409
10		399

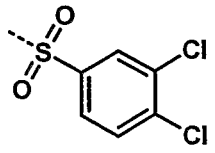
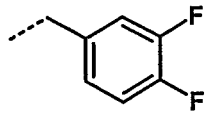
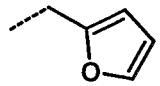
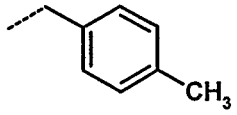
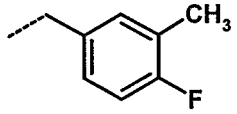
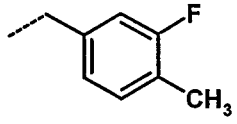
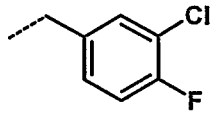
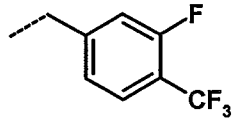
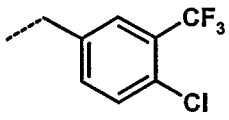
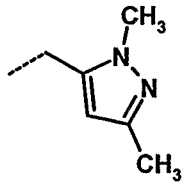
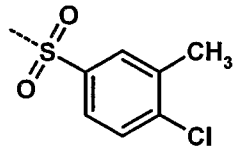
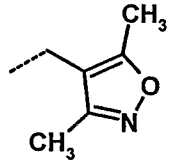
Example	X—W—$(R^5)_n$	MH^+
11		409
12		361
13		407
14		349
15		349
16		399
17		361
18		349
19		295
20		282

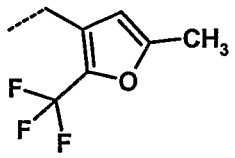
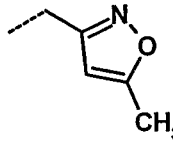
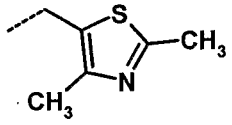
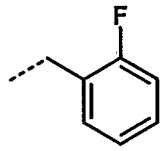
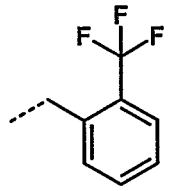
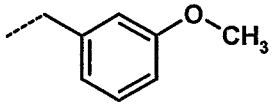
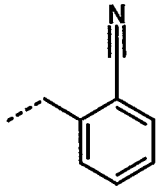
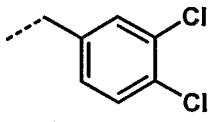
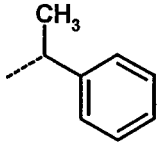
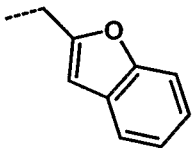
Example	X—W—$(R^5)_n$	MH^+
21		282
22		282
23		315
24		306
25		315
26		306
27		295
28		349
29		299
30		315
31		349
32		299

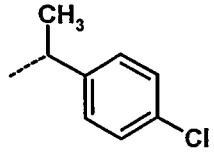
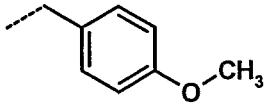
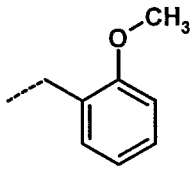
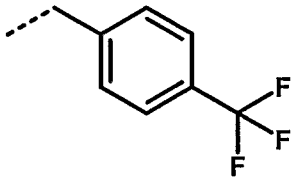
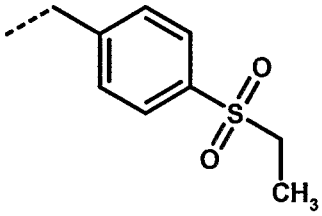
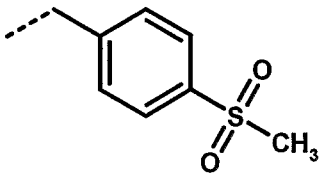
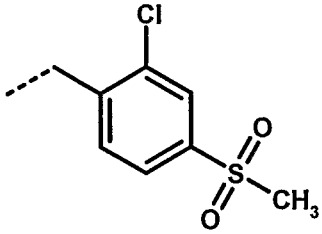
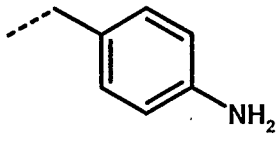
Example	X—W—$(R^5)_n$	MH^+
33		399
34		397
35		379
36		379
37		365
38		356
39		399
40		413
41		$[M-H]^-$ 354

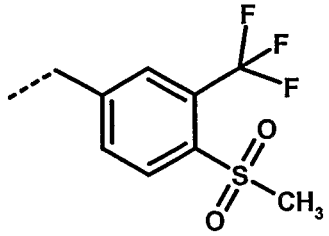
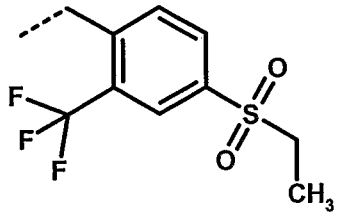
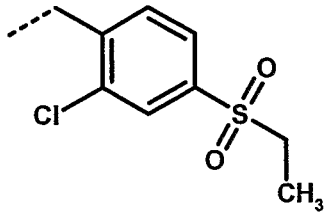
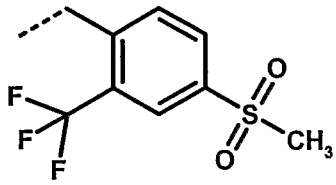
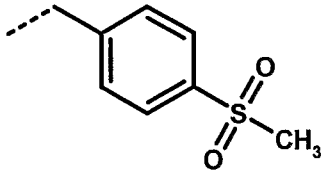
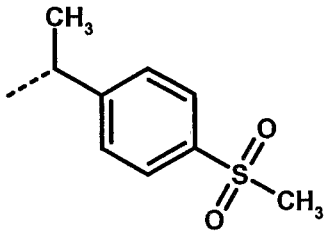
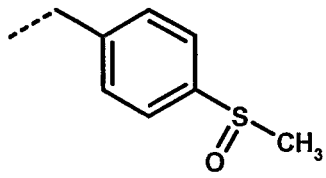
Example	X—W—$(R^5)_n$	MH^+
42		399
43		$[M-H]^-$ 413
44		$[M-H]^-$ 365
45		$[M-H]^-$ 354
46		383
47		$[M-H]^-$ 383
48		395
49		367
50		405

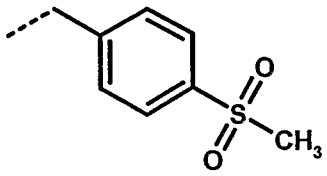
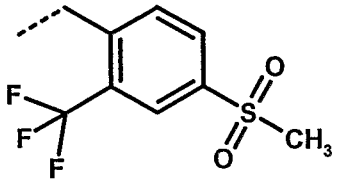
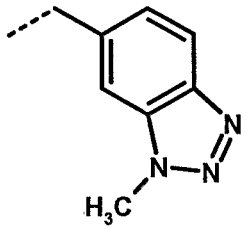
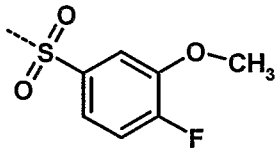
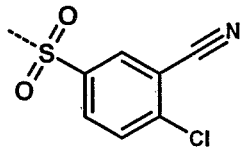
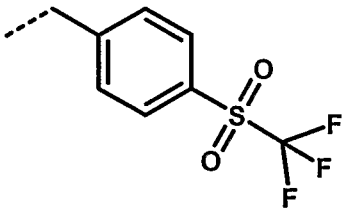
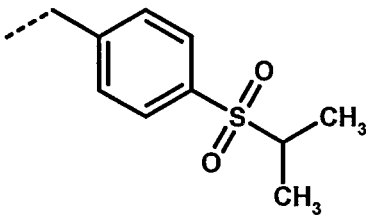
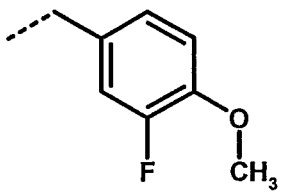
Example	X—W—$(R^5)_n$	MH^+
51		365
52		399
53		399
54		374
55		383
56		363
57		301
58		367
59		367
60		332
61		271

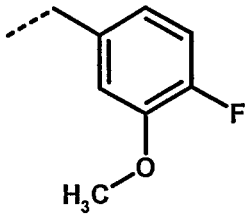
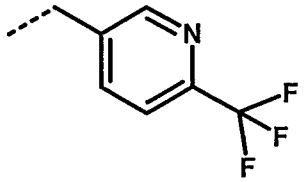
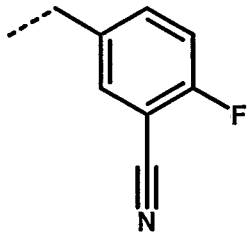
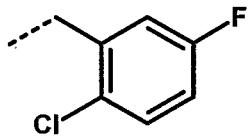
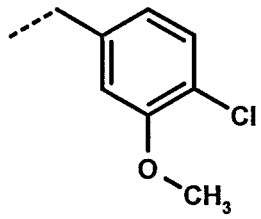
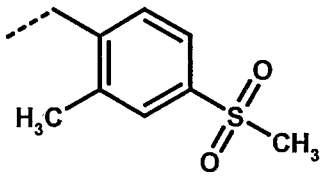
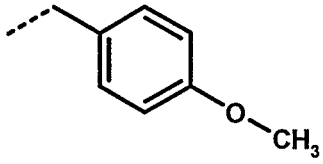
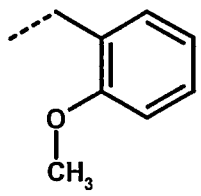
Example	X—W—$(R^5)_n$	MH^+
62		433
63		317
64		271
65		295
66		313
67		312
68		333
69		367
70		383
71		299
72		379/381
73		300

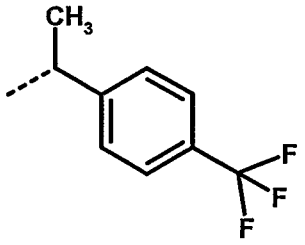
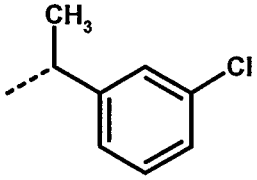
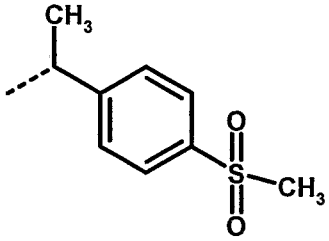
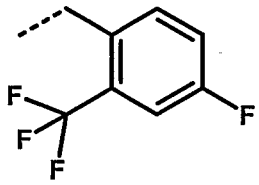
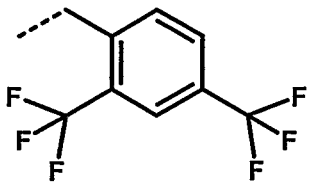
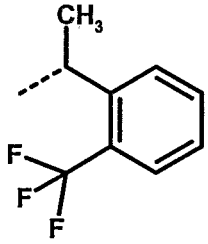
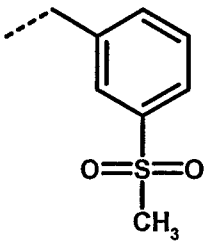
Example	X—W—$(R^5)_n$	MH^+
74		353
75		286
76		316
77		299
78		349
79		311
80		306
81		335
82		295
83		321

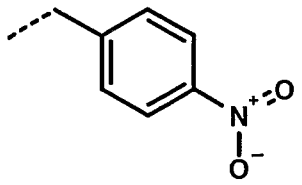
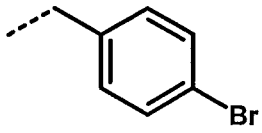
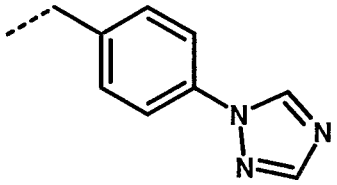
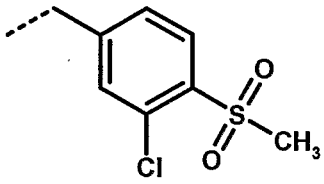
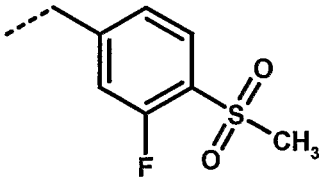
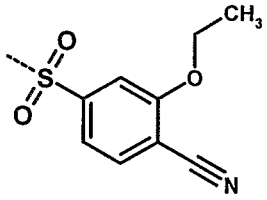
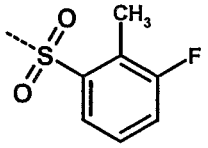
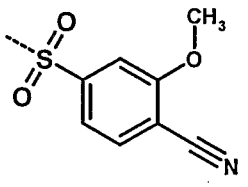
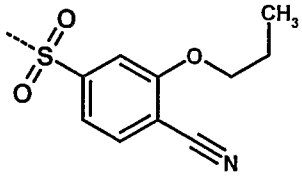
Example	X—W—$(R^5)_n$	MH^+
84		329
85		311
86		311
87		363
88		373
89		393
90		393
91		296

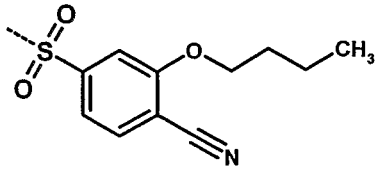
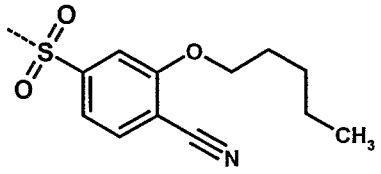
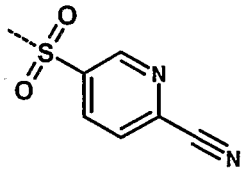
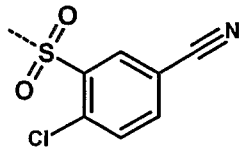
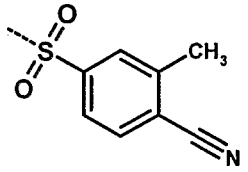
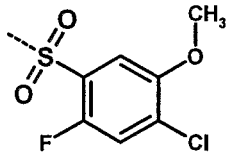
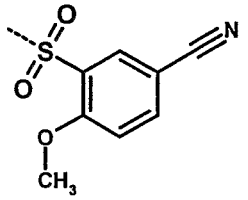
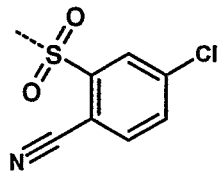
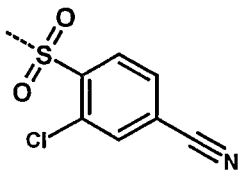
Example	X—W—$(R^5)_n$	MH^+
92		427
93		441
94		407
95		427
96		359
97	 Enantiomer 1	373/373
98		343

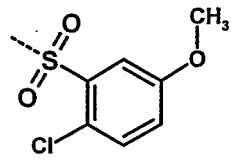
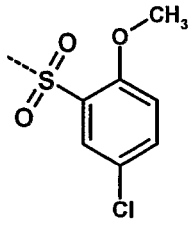
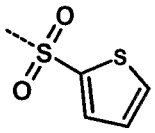
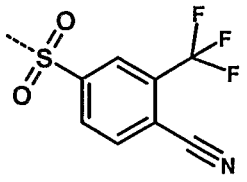
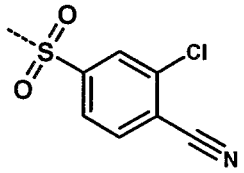
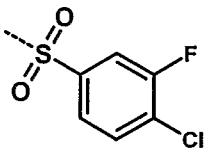
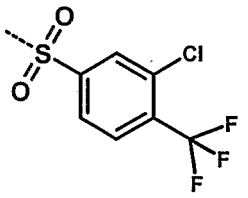
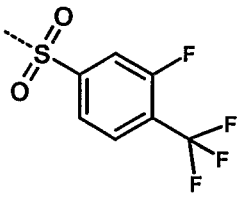
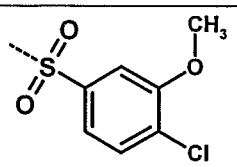
Example	X—W—$(R^5)_n$	MH^+
99		393
100		461
101		336
102		379
103		390
104		413
105		387
106		329

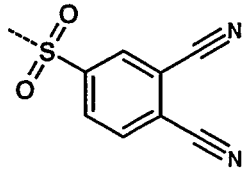
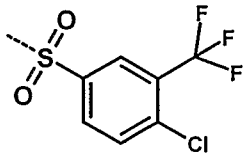
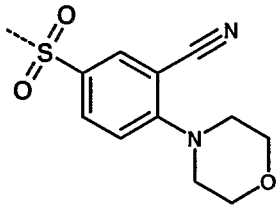
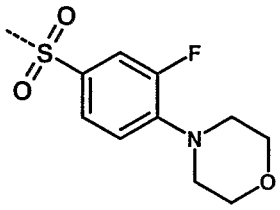
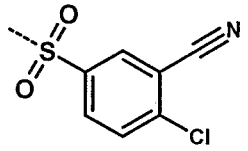
Example	X—W—$(R^5)_n$	MH^+
107		329
108		350
109		324
110		333
111		345
112		373
113		311
114		311

Example	X—W—$(R^5)_n$	MH^+
115		363
116		329
117		373
118		367
119		417
120		363
121		359

Example	X—W—$(R^5)_n$	MH^+
122		326
123		359
124		348
125		393
126		377
127		400
128		363
129		386
130		414

Example	X—W—$(R^5)_n$	MH^+
131		428
132		442
133		357
134		390
135		370
136		413
137		386
138		390
139		390

Example	X—W—$(R^5)_n$	MH^+
140		395
141		395
142		337
143		424
144		390
145		383
146		433
147		417
148		395

Example	X—W—$(R^5)_n$	MH^+
149		381
150		433
151		441
152		434
153		404

Preparation of Specific Examples – General Experimental Conditions

NMR are recorded at 400 MHz in $CDCl_3$, unless otherwise noted. LCMS are recorded on an Agilent 1100 LC system with a Waters Xterra MS C18 4.6 x 100 5 µM column, eluting with 5-95% 10 mM aqueous ammonium bicarbonate in acetonitrile over 10 minutes, with negative ion electrospray ionization or 5-95% water + 0.1% TFA in acetonitrile with positive ion electrospray ionization. MH^+ and $[M-H]^-$ refer to monoisotopic molecular weights.

The Emrys™ Optimiser microwave instrument (PersonalChemistry AB) is used in the standard configuration as delivered.

Example 4

(1-Benzyl-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid

4a) BEMP (182 µL, 0.63 mmol) is added to a stirring solution of (2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester prepared as described in U.S. Patent No. 3,320,268 (80 mg, 0.39 mmol) in DMF (2.4 mL). After 30 minutes, benzyl bromide (75 µL, 0.63 mmol) is added and the reaction stirred for 3 days, before partitioning between water and 1:1 EtOAc/ether. The organic layer is washed with brine then reduced *in vacuo*. The residue is purified by flash column chromatography (3:1 iso-hexane/EtOAc elution) to furnish (1-benzyl-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester; MH^+ = 295.

4b) 1M Aqueous NaOH (364 µL, 0.364 mmol) is added to a stirring solution of (1-benzyl-2-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester (65 mg, 0.22 mmol) in 5:1 THF/MeOH (2.4 mL). After 5.5 hours, the reaction is evaporated, and partitioned between water and EtOAc. The aqueous layer is acidified to pH 3, and the resulting precipitate collected by filtration to furnish 1-benzyl-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid; MH^+ = 281.

Examples 18, 19, 23-32, 63, 65-70, 77-80, 82 and 85-86

These examples, namely, [1-(3,4-Dichloro-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [2-Methyl-1-(2-methyl-benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(4-Chloro-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(3-Cyano-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(3-Chloro-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(4-Cyano-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [2-Methyl-1-(3-methyl-benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [2-Methyl-1-(3-trifluoromethyl-benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(4-Fluoro-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(2-Chloro-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [2-Methyl-1-(4-trifluoromethyl-benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(3-Fluoro-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(3,4-Difluoro-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [2-Methyl-1-(4-methyl-benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(4-Fluoro-3-methyl-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(3-Fluoro-4-methyl-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(3-Chloro-4-fluoro-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(3-Fluoro-4-trifluoromethyl-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(4-Chloro-3-trifluoromethyl-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(2-Fluoro-

benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [2-Methyl-1-(2-trifluoromethyl-benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(3-Methoxy-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(2-Cyano-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [2-Methyl-1-(1-phenyl-ethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(4-Methoxy-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; and [1-(2-Methoxy-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid, are prepared by the same process as that described for Example 4, using the appropriate benzyl halide.

Example 6

[2-Methyl-1-(toluene-4-sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid

A solution of BEMP (90 µL, 0.31 mmol) in DMF (400 µL) is added to a solution of (2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester (40 mg, 0.20 mmol) in DMF (400 µL). After 40-50 minutes, a solution of 4-methyl-benzenesulfonyl chloride (60 mg, 0.31 mmol) in DMF (400 µL) is added. After a further 30 minutes, 1M aqueous NaOH (800 µL) is added, and the reaction is shaken mechanically for 105 minutes, then 1M aqueous HCl (800 µL) is added. The reaction is partitioned between water and CH_2Cl_2. The organic phase is loaded directly onto a pre-packed Isolute™ silica column and eluted with EtOAc to give crude product which is triturated with water to afford [2-methyl-1-(toluene-4-sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; MH^+ = 345.

Examples 3, 5, 7-15, 17, 34, 35 and 37-39

These examples, namely, 2-Methyl-1-(4-nitro-benzenesulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid; [2-Methyl-1-(naphthalene-2-sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid; [1-(4-Fluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid; [1-(4-Isopropyl-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid; [1-(3-Bromo-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid, [2-Methyl-1-(3-trifluoromethyl-benzenesulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid; [1-(4-Methane-sulfonyl-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid; [1-(3-Methoxy-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid; [1-(Biphenyl-4-sulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid; [1-(3-Fluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid; [1-(2-Fluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid; [1-(4-Methoxy-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid; [1-(4-Difluoromethoxy-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(3-Chloro-2-methyl-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(2-Chloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(3-Cyano-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; and 1-(2,5-Dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid, are prepared using the same process as that described for Example 6, using the appropriate benzenesulfonyl halide.

Example 16

[1-(3,4-Dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid

16a) To an ice-cooled stirring suspension of NaH (60% dispersion in mineral oil; 63 mg, 1.6 mmol) in THF (3 mL) is added a solution of (2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester (200 mg, 1 mmol) in 3:1 THF/DMF (4 mL). After 45 minutes, a solution of 3,4-dichloro-benzenesulfonyl chloride (214 µL, 1.4 mmol) in THF (3 mL) is added. After 10 minutes, the reaction mixture is added to ice/water and extracted with EtOAc. The organic layer is washed with brine and evaporated. The crude product is purified by flash chromatography (3:1 iso-hexane/EtOAc elution), to afford [1-(3,4-dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid methyl ester; MH^+ = 413.

16b) 1M Aqueous NaOH (1.5 mL) is added to a solution of [1-(3,4-dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid methyl ester (218 mg, 0.53 mmol) in 1:1 THF/MeOH (6 mL). After 18 hours, the reaction is evaporated and the residue dissolved in water. The aqueous solution is acidified to pH 1, and the resulting

precipitate is collected by filtration to afford [1-(3,4-dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; MH^+ = 399.

Examples 1 and 2

These examples, namely, (1-Benzenesulfonyl-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acetic acid; and [1-(4-Chloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid, are prepared by the same process as that described for Example 16, using the appropriate benzenesulfonyl halide.

Example 20

(2-Methyl-1-pyridin-3-ylmethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid

20a) NaH (60% dispersion in mineral oil; 17 mg, 0.43 mmol) is added to a stirring, ice-cooled solution of 3-(bromomethyl)pyridine hydrobromide (109 mg, 0.43 mmol) in DMF (1.2 mL). After 20 minutes, a solution of (2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester (80 mg, 0.39 mmol) and BEMP (125 µL, 0.43 mmol) in 1.2 mL DMF is added dropwise. After 1 hour and 40 minutes, reaction is added to 25 mL water and extracted with EtOAc. The EtOAc layer is washed with water then brine, dried ($MgSO_4$) and evaporated.

The crude product is purified using flash chromatography (EtOAc elution) to give (2-methyl-1-pyridin-3-ylmethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester; MH^+ = 296.

20b) 1M Aqueous NaOH (0.5 mL) is added to a stirring solution of (2-methyl-1-pyridin-3-ylmethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester (35 mg, 0.12 mmol) in 1:1 THF/MeOH (2 mL). After 2 hours, the reaction is evaporated and the residue dissolved in water. The aqueous solution is acidified to pH 3-4, and the resulting precipitate collected by filtration to furnish (2-methyl-1-pyridin-3-ylmethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid; MH^+ = 282.

Examples 21 and 22

These examples, namely, (2-Methyl-1-pyridin-2-ylmethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid; and (2-Methyl-1-pyridin-4-ylmethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid, are prepared by the same process as that described for Example 20, using the appropriate (bromomethyl)pyridine hydrobromide.

Example 36

1-(3-Chloro-4-methyl-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid

36a) To a solution of (2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester (0.06 g, 0.294 mmol) in DMF (0.5 mL) is added a solution of BEMP (0.136 mL, 0.47 mmol) in DMF (0.5 mL). After 1 hour, a solution of 3-chloro-4-methyl-benzenesulfonyl chloride (0.105 g, 0.47 mmol) in DMF (0.5 mL) is added. The reaction mixture is stirred at room temperature overnight, then concentrated under reduced pressure to a minimum volume. The residue is loaded on a pre-packed Isolute™ silica column and eluted using a gradient eluent from 100% iso-hexane to 30% ethyl acetate in iso-hexane to afford [1-(3-chloro-4-methyl-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid methyl ester; MH^+ = 393.

36b) 1M Aqueous NaOH (0.25 mL) is added to a stirring solution of [1-(3-chloro-4-methyl-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid methyl ester (80 mg, 0.20 mmol) in 1:1 dioxane / water (2 mL). After 2.5 hours, the reaction mixture is acidified to pH 1 with 1M HCl which leads to the formation of a precipitate. The solid is isolated by filtration, washed with water and dried to afford [1-(3-chloro- 4-methyl-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; MH^+ = 379.

Examples 33 and 46

These examples, namely, [2-Methyl-1-(4-trifluoromethyl-benzenesulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; and 1-(2-Chloro-4-fluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid, are prepared by the same process as that described for Example 36, using the appropriate benzenesulfonyl halide.

Example 40

2-[1-(3,4-Dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-propionic acid

40a) To a stirring solution of diisopropylamine (34 µL, 0.24 mmol) in THF (1 mL), at -78°C, is added a 2.5M solution of *n*-BuLi in hexanes (105 µL, 0.26 mmol). After 20 minutes, a solution of [1-(3,4-dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid methyl ester (Method B; 100 mg, 0.24 mmol) and MeI (15.2 µL, 0.24 mmol) in THF (1mL) is added. The reaction is continued for 30 minutes, then allowed to warm to room temperature. The reaction mixture is evaporated to dryness and purified by flash chromatography (4:1 iso-hexane/EtOAc elution), to afford 2-[1-(3,4-dichloro-

benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-propionic acid methyl ester; MH^+ = 427.

40b) 1M Aqueous NaOH (0.25 mL) is added to a stirring solution of 2-[1-(3,4-dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-propionic acid methyl ester (17 mg, 0.04 mmol) in 1:1 THF/MeOH (1 mL). After 4 hours, the reaction is evaporated and the residue dissolved in water. The aqueous solution is acidified to pH 1, and resulting solid is collected by filtration. The crude product is purified by flash chromatography (10:1 EtOAc/MeOH), followed by trituration with iso-hexane, to afford 2-[1-(3,4-dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-propionic acid; MH^+ = 413.

Example 54

[1-(3-Cyano-4-fluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid

54a) To a solution of (2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester (0.5 g, 2.45 mmol) in DMF (3 mL) is added BEMP (1.13 mL, 3.92 mmol). After 1 hour, a solution of 3-cyano-4-fluoro-benzenesulfonyl chloride (0.86 g, 3.92 mmol) in DMF (3 mL) is added. The reaction mixture is stirred at room temperature overnight, then concentrated under reduced pressure to a minimum volume. The residue is loaded onto a pre-packed Isolute™ silica column and eluted using a gradient eluent from 100% iso-hexane to 50% EtOAc in iso-hexane to afford [1-(3-cyano-4-fluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid methyl ester; MH^+ = 388.

54b) 1M BBr_3 in CH_2Cl_2 (7.66 mL, 7.66 mmol) is added to a solution of [1-(3-cyano-4-fluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid methyl ester (0.495 g, 1.27 mmol) in CH_2Cl_2 (2 mL). The reaction mixture is exposed to microwave irradiation at 60°C for 45 minutes. Water is added to the reaction mixture which is stirred for further 20 minutes. The organic layer is isolated using the Isolute™ phase separator cartridge and evaporated. The residue is loaded on a pre-packed Isolute™ silica column and eluted using a gradient eluent from 100% CH_2Cl_2 to 5% methanol in CH_2Cl_2 to afford the title compound; MH^+ = 374.

Examples 41-45, 47-53, 55, 56, 58 and 60

These examples, namely, [1-(4-Cyano-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(2,4-Dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [2-Methyl-1-(3-trifluoromethoxy-benzenesulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-

acetic acid; [1-(2,5-Difluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(2-Cyano-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [2-Methyl-1-(2,3,4-trifluoro-benzenesulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; 3-(3-Carboxymethyl-2-methyl-pyrrolo[2,3-*b*]pyridine-1-sulfonyl)-thiophene-2-carboxylic acid methyl ester; [1-(3,5-Difluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(2,5-Dichloro-thiophene-3-sulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(3-Chloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(3,5-Dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(2,3-Dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(3-Chloro-4-fluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(3-Fluoro-4-methyl-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(2,4-Difluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; and [2-Methyl-1-(pyridine-3-sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid, are made by the same process as that described for Example 54, using the appropriate benzenesulfonyl halide.

Example 57

1-(4-Chloro-phenyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid

57a) A mixture of (2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester (100 mg, 0.49 mmol), 1-chloro-4-iodo-benzene (117 mg, 0.49 mmol), CuI (5 mg, 0.03 mmol), cyclohexane-1,2-diamine (6 µL, 0.05 mmol), potassium phosphate (218 mg, 1.0 mmol) and 1,4-dioxane (0.5 mL) is heated at 160°C for 140 minutes. The reaction is cooled, diluted with EtOAc, filtered through silica and evaporated to dryness. The residue is purified by flash column chromatography (5:1 iso-hexane/EtOAc elution) to furnish [1-(4-chloro-phenyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid methyl ester; MH^+ = 315.

57b) 1M Aqueous NaOH (0.5 mL) is added to a stirring solution of [1-(4-chloro-phenyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid methyl ester (4 mg, 0.013 mmol) in 1:1 THF/MeOH (2 mL). After 18 hours, the reaction is evaporated and the residue dissolved in water. The aqueous solution is acidified to pH 1, and extracted with ethyl acetate. The organic layer is washed with water then brine, dried ($MgSO_4$) then evaporated, to give [1-(4-chloro-phenyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; MH^+ = 301.

Example 59

[1-(3,4-Difluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid

59a) To a solution of (2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester (0.8 g, 3.92 mmol) in DMF (3 mL) is added BEMP (1.81 mL, 6.27 mmol). After 1 hour, the reaction mixture is cooled to 0°C and a solution of 3,4-difluoro-benzenesulfonyl chloride (0.83 mL, 6.27 mmol) in DMF (3 mL) is added. The reaction mixture is allowed to warm to room temperature, stirred at room temperature overnight, then concentrated under reduced pressure to a minimum volume. The residue is loaded on a pre-packed Isolute™ silica column and eluted using a gradient eluent from 100% iso-hexane to 30% EtOAc in iso-hexane to afford [1-(3,4-difluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid methyl ester; MH^+ = 381.

59b) 1M Aqueous LiOH (0.52 mL) is added at 0°C to a stirring solution of [1-(3,4-difluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid methyl ester (200 mg, 0.526 mmol) in 1:1 dioxane / water (4 mL). The reaction mixture is stirred at 0°C for 15 minutes, then allowed to warm to room temperature. After 2.5 hours, the reaction mixture is neutralised to pH 7 with 1M HCl and the solvent is removed under reduced pressure. The residue is loaded on a pre-packed Isolute™ silica column and eluted using a gradient eluent from 100% CH_2Cl_2 to 5% methanol in CH_2Cl_2 to afford [1-(3,4-difluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; MH^+ = 367.

Example 72

[1-(4-Chloro-3-methyl-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid

This Example, is prepared by the same method as Example 59, using the appropriate benzenesulfonyl halide.

Example 61

(1-Furan-3-ylmethyl-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid

61a) BEMP (182 µL, 0.63 mmol) is added to a stirring solution of (2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester (80 mg, 0.39 mmol) in DMF (1.2 ml). After 30 minutes, a solution of toluene-4-sulfonic acid furan-3-ylmethyl ester in THF (1.4 ml, 0.45 mmol) is added. After 18 hours, the reaction is partitioned between water and ether. The organic layer is washed with brine then reduced *in vacuo*. The residue is purified by flash column chromatography (3:1 iso-hexane/EtOAc elution) to furnish (1-furan-3-ylmethyl-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester; MH^+ = 285.

61b) 1M Aqueous NaOH (0.25 mL) is added to a stirring solution of (1-furan-3-ylmethyl-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester (7.5 mg, 0.026 mmol) in 1:1 THF/MeOH (1 mL). After 18 hours, the reaction is evaporated and the residue dissolved in water. The aqueous solution is acidified to pH 3-4, and extracted with EtOAc. The organic layer is washed with water then brine, dried ($MgSO_4$), then evaporated to furnish (1-furan-3-ylmethyl-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid; MH^+ = 271.

Example 64

This example, namely, (1-furan-2-ylmethyl-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid is made by the same process as that described for Example 61, using the appropriate furan methyl ester.

Example 62

[4-Chloro-1-(3,4-dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid

62a) *m*-Chloroperoxybenzoic acid (1.35 g, 7.8 mmol) is added to a solution of (2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester (1 g, 4.9 mmol) in 1,2-dimethoxyethane (15 mL) and is stirred at ambient temperature for 1.5 hours. The reaction mixture is poured into water and basified to pH 9-10 with aqueous saturated potassium carbonate. The precipitate is filtered off and the filtrate is extracted with CH_2Cl_2 then dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The residue obtained is purified by column chromatography on silica gel using 10:1 CH_2Cl_2/MeOH as the eluent affording (2-methyl-7-oxy-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester; MH^+ = 221.

62b) To (2-methyl-7-oxy-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester (250 mg, 1.14 mmol) is added an excess of $POCl_3$ (20 mL) with cooling in an ice bath. The reaction mixture is heated at reflux for 5 hours. The $POCl_3$ is removed *in vacuo*. The residue is dissolved in CH_2Cl_2, washed with water, brine then dried (Na_2SO_4) and concentrated to dryness *in vacuo*. The crude product is purified by column chromatography on silica gel using 10:1 CH_2Cl_2/MeOH as the eluent, furnishing (4-chloro-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester; MH^+ = 239.

62c) To a solution of (4-chloro-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester (58 mg, 0.24 mmol) in DMF (1.2 mL) is added BEMP (113 µL, 0.39 mmol). The reaction mixture is stirred at ambient temperature for 40 minutes. 3,4-Dichloro-benzenesulfonyl chloride (60 µL, 0.39 mmol) is added and the reaction mixture is stirred for

10 minutes at ambient temperature. The reaction mixture is poured into ice cold water, extracted with EtOAc, washed with brine, dried (Na_2SO_4) and evaporated. The crude product is purified by column chromatography on silica gel using 1:8 EtOAc/iso-hexane as the eluent, furnishing [4-chloro-1-(3,4-dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-yl]-acetic acid methyl ester; MH^+ = 449.

62d) To a solution of [4-chloro-1-(3,4-dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-yl]-acetic acid methyl ester (40 mg, 0.09 mmol) in CH_2Cl_2 (1 mL), is added 1M BBr_3 in CH_2Cl_2 (536 µL, 0.54 mmol). The solution is subjected to microwave irradiation in a sealed reaction vessel with stirring at 60°C over 45 minutes. The reaction mixture is evaporated to dryness *in vacuo*. Water is added and the suspension sonicated then filtered, washed with water and dried *in vacuo*, furnishing [4-chloro-1-(3,4-dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-yl]-acetic acid; MH^+ = 433.

Example 71

[1-(2,5-Dimethyl-2*H*-pyrazol-3-ylmethyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid

71a) To a stirring solution of (2,5-dimethyl-2*H*-pyrazol-3-yl)-methanol (100 mg, 0.79 mmol) in diethyl ether (3 mL) is added PBr_3 (25 µL, 0.26 mmol). The reaction is stirred at room temperature for 18 hours, then water is added. The diethyl ether layer is separated and stored over solid NaOH and used in Step 71b without further characterization.

71b) BEMP (137 µL, 0.47 mmol) is added to a solution of (2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid methyl ester (60 mg, 0.29 mmol) in DMF (0.8 mL). After 35 minutes, the diethyl ether layer from Step 71a (1.8 mL) is added. After 3 days, the reaction is partitioned between water and 1:1 EtOAc/ether. The organic layer is washed with brine then evaporated. The residue is purified by flash column chromatography (49:1 EtOAc/MeOH elution) to furnish [1-(2,5-dimethyl-2*H*-pyrazol-3-ylmethyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid methyl ester; MH^+ = 313.

71c) 1M Aqueous NaOH (0.5 mL) is added to a stirring solution of [1-(2,5-dimethyl-2*H*-pyrazol-3-ylmethyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid methyl ester (29 mg, 0.09 mmol) in 1:1 THF/MeOH (2 mL). After 18 hours, the reaction is evaporated and the residue dissolved in water. The aqueous solution is acidified to pH 1, and the resulting precipitate collected by filtration to furnish [1-(2,5-dimethyl-2*H*-pyrazol-3-ylmethyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; MH^+ = 299.

Examples 73-76 and 83-84

These examples, namely, [1-(3,5-Dimethyl-isoxazol-4-ylmethyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [2-Methyl-1-(5-methyl-2-trifluoromethyl-furan-3-ylmethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [2-Methyl-1-(5-methyl-isoxazol-3-ylmethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; [1-(2,4-Dimethyl-thiazol-5-ylmethyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid; (1-Benzofuran-2-ylmethyl-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid; and {1-[1-(4-Chloro-phenyl)-ethyl]-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl}-acetic acid, are made by the same process as that described for Example 71, using the appropriate heterocyclic methanol.

Example 81

[1-(3,4-Dichloro-benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid

81a) 1*H*-Pyrrolo[2,3-*b*]pyridine (0.500 g, 4.2 mmol) is added to a stirred suspension of aluminium chloride (2.8 g, 21 mmol) in CH_2Cl_2 (100 mL) at 25°C. The suspension is stirred at 25°C for 1 hour. Methyl oxalyl chloride (1.93 mL, 21 mmol) is added dropwise to the reaction mixture and the resulting suspension is stirred at 25°C for 72 hours. The reaction mixture is cooled to 0°C in an ice bath. MeOH (20 mL) is added dropwise then the reaction mixture is evaporated to dryness *in vacuo*. The crude material is triturated with 10:1 EtOAc/MeOH and filtered. The solid collected is further triturated with water and dried *in vacuo* to afford oxo-(1*H*-pyrrolo[2,3-*b*]pyridine-3-yl)-acetic acid methyl ester; MH^+ = 335.

81b) A mixture of oxo-(1*H*-pyrrolo[2,3-*b*]pyridine-3-yl)-acetic acid methyl ester (0.300 g, 1.47 mmol) is refluxed in hydrazine monohydrate (10 mL) for 1 hour to give a solution. KOH pellets (0.300 g, 5.35 mmol) are added and reflux is continued for 1 hour. The reaction mixture is evaporated to dryness *in vacuo*. To the residue is added dry MeOH (10 mL) and the solution is cooled in an ice bath. Concentrated H_2SO_4 (0.5 mL) is carefully added and the reaction mixture is refluxed at 80°C for 1 hour. The reaction mixture is evaporated to dryness *in vacuo*, then partitioned between saturated $NaHCO_3$ aqueous and EtOAc. The EtOAc layer is separated and the aqueous phase is extracted with a further portion of EtOAc. The organics are combined, dried (Na_2SO_4) and evaporated *in vacuo*. The crude product is purified by flash chromatography with a pre-packed Isolute™ silica column, eluting with 1:8 EtOAc/iso-hexane-neat EtOAc gradient to afford (1*H*-pyrrolo[2,3-*b*]pyridine-3-yl)-acetic acid methyl ester; MH^+ = 191.

81c) To an ice cold solution of (1*H*-pyrrolo[2,3-*b*]pyridine-3-yl)-acetic acid methyl ester (50 mg, 0.26 mmol) in DMF (1 mL), is added BEMP (0.122 mL, 0.42 mmol). The reaction mixture is stirred at ambient temperature for 40 minutes, then 3,4-dichlorobenzyl

bromide (0.101 g, 0.42 mmol) is added and the reaction mixture is stirred for 16 hours at ambient temperature. The reaction mixture is poured into ice cold water (40 mL) and extracted with EtOAc, washed with brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude product is purified by column chromatography on silica gel using a pre-packed Isolute™ silica column (2 g) eluting with 1:20 EtOAc/iso-hexane, furnishing [1-(3,4-dichloro-benzyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-yl]-acetic acid methyl ester; MH^+ = 349.

81d) To a solution of [1-(3,4-dichloro-benzyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-yl]-acetic acid methyl ester (23 mg, 0.066 mmol) in MeOH (0.5 mL), is added 4N NaOH (0.25 mL). The reaction mixture is stirred at 25°C for 5 minutes. The reaction mixture is evaporated *in vacuo*, to remove MeOH then cooled in an ice bath and acidified with concentrated HCl. The resultant solid is collected by filtration and triturated in $CHCl_3$ to afford [1-(3,4-dichloro-benzyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-y]-acetic acid; MH^+ = 335.

Example 87

[2-Ethyl-1-(4-trifluoromethyl-benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

87a) 2-Ethyl-1H-pyrrolo[2,3-b]pyridine:

To a solution of 2-methyl-7-azaindole (1.32 g, 10 mmol) in dry diethyl ether (60 ml) at room temperature under an inert atmosphere is added *n*-BuLi (18.8 ml of a 1.6 M solution in hexanes, 30 mmol) followed by *t*-BuOK (2.24 g, 20 mmol). The reaction mixture is stirred at room temperature for 40 minutes and then cooled to -70 °C whereupon methyl iodide (1.25 ml, 20 mmol) is added dropwise. Stirring continues for a further 2 hours after which time, the reaction mixture is quenched with water (2 ml) and is allowed to slowly warm to room temperature. The cooled solution is poured onto water (200 ml), neutralized with 1N HCl and then extracted with diethyl ether (80 ml). The organic portion is washed with water (2 x 60 ml), dried (Na_2SO_4) and concentrated *in vacuo* to yield the titled compound as orange crystals. [MH + CH_3CN]+ = 188)

87b) (2-Ethyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-oxo-acetic acid methyl ester:

A suspension of aluminium chloride (1.87 g, 14 mmol) in DCM (100 ml) under an inert atmosphere at room temperature is treated with 2-ethyl-1H-pyrrolo[2,3-b]pyridine (0.415 g,

14 mmol). After stirring at room temperature for 1 hour, methyl oxalyl chloride (1.29 ml, 14 mmol) is added dropwise to the reaction mixture and stirring continued overnight. The reaction mixture is cooled in an ice bath and methanol is added dropwise. The mixture is then poured onto ice-water (200 ml) and stirred . The organic portion is separated, dried (Na_2SO_4) and concentrated *in vacuo*. The resulting crude is triturated with ice cold water (20 ml) and sonicated. The solid is filtered and dried under vacuum at 50 °C to yield the titled compound. (MH+ 233)

87c) (2-Ethyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester:

To a solution of triethylsilane (818 µl, 5.12 mmol) in TFA (1.6 ml) at -10 °C is added portion wise (2-ethyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-oxo-acetic acid methyl ester (0.34 g, 1.46 mmol). After stirring at room temperature overnight, the solvent is removed *in vacuo* and the resulting residue is neutralized with saturated sodium bicarbonate solution. The solution is extracted with DCM (3 x 20 ml) and the organic portions are combined, dried (Na_2SO_4) and concentrated *in vacuo*. The residue is loaded on a pre-packed Isolute™ silica column and eluted with DCM/MeOH (100:0 increasing to 98:2) to yield the titled compound as a yellow powder. (MH+ 219)

87d) [2-Ethyl-1-(4-trifluoromethyl-benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester:

To an ice-cooled stirring solution of (2-ethyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester (80 mg, 0.37 mmol) in DMF (1 ml) is added BEMP (171 µl, 0.59 mmol). The solution is stirred at room temperature for 40 minutes and then re-cooled. 4-(Trifluoromethyl)benzyl bromide ((91 µl, 0.59 mmol) is added and stirring continues while the reaction mixture gradually warmed up to room temperature overnight. The resulting mixture is poured into water (30 ml) and extracted with 1:1 EtOAc/ether. The organic layer is washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue is loaded on a pre-packed Isolute™ silica column and eluted with DCM to yield the titled compound as a pale yellow oil. (MH+ 377)

87e) [2-Ethyl-1-(4-trifluoromethyl-benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid:

0.5 M Aqueous NaOH (1.0 ml) is added to a solution of [2-ethyl-1-(4-trifluoromethyl-benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester (48 mg, 0.13 mmol) in 1:1 THF/MeOH (1 ml). After 3 hours the reaction is concentrated *in vacuo*, and the residue dissolved in water. The aqueous solution is cooled in an ice-bath and acidified to pH 2 using concentrated HCl. The resulting precipitate is filtered and dried under high vacuum at 50 °C to yield the titled compound as a white powder. (MH+ 363)

Example 88

[1-(4-Ethanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

88a) BEMP (182 µl, 0.64 mmol) is added to a stirring solution of (2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester (prepared as described in US Patent 3320268, 82 mg, 0.40 mmol) in DMF (2.6 ml). After 80 minutes, 1-bromomethyl-4-ethanesulfonyl-benzene (75 µl, 0.63 mmol) is added and the reaction stirred for 2 hours before partitioning between water and 1:1 EtOAc/diethyl ether. The organic layer is washed with brine then reduced *in vacuo*. The residue is purified by flash column chromatography (1:1 *iso*-hexane/EtOAc elution) to furnish [1-(4-ethanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester as a solid.

88b)1M Aqueous NaOH (1 ml) is added to a stirring solution of [1-(4-ethanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester (89 mg, 0.23 mmol) in 1:1 THF/MeOH (4 ml). After 1 hour the reaction is evaporated and the resulting oil is dissolved in water (8 ml) and acidified to pH 3. The resulting precipitate is collected by filtration and dried *in vacuo* to afford [1-(4-ethanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (MH+ 373)

Example 89

[4-Chloro-1-(4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

89 a) (2-Methyl-7-oxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester:

A stirred suspension of (2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester (5 g, 24.5 mmol) in 1,2-dimethoxyethane (100 ml) at room temperature under an inert atmosphere of Argon is treated portionwise with *m*-chloroperoxybenzoic acid (9.7 g, of a 77 %w/w solid, 39.2 mmol). The reaction temperature is maintained at room temperature using an ice-bath due to the exothermic nature of the acid addition. The reaction mixture is stirred at room temperature for 3 hours and then poured onto water (400 ml) and basified to pH 9-10 using saturated potassium carbonate solution. The aqueous is extracted with DCM (2x100 ml) and the organic portions are combined, dried (Na_2SO_4) and concentrated *in vacuo* to yield (2-methyl-7-oxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester. (MH+ 221)

89b) (4-Chloro-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester:

A suspension of (2-methyl-7-oxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester (360 mg, 1.63 mmol) in phosphorus oxychloride (5 ml) is stirred and heated using microwave radiation in a Personal Chemistry Emrys™ Optimizer microwave reactor at 160 °C for 5 minutes. After standing at room temperature overnight, the reaction mixture is poured carefully onto ice water and extracted with DCM (3 x 40ml). The organic portions are combined, washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The resulting dark brown residue is loaded on a pre-packed Isolute™ silica column and eluted with DCM:methanol (10:1) to yield the titled compound as a cream solid. (MH+ 239)

89c) [4-Chloro-1-(4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester:

To a cooled (0 °C) stirred solution of (4-chloro-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester (0.1 g, 0.42 mmol) in dry DMF (2.5 ml) is added sodium hydride (0.019 g of a 60 % dispersion in mineral oil, 0.47 mmol). After stirring at room temperature for 5 hours, the reaction mixture is re-cooled to 0 °C and treated with 4-methylsulfonylbenzyl bromide (0.105 g, 0.42 mmol). The resulting mixture is stirred and allowed to warm to room temperature overnight. The reaction mixture is diluted with water (3 ml) and extracted with ether (3 x 15 ml). The organic portions are combined, washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The resulting crude residue is loaded on a pre-

packed Isolute™ silica column and eluted with *iso*-hexane : ethyl acetate (1:8) to yield the titled compound as a white powder. (MH+ 407).

89d) 1M Aqueous NaOH (0.5 ml) is added to a stirring solution of [4-chloro-1-(4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester (38 mg, 0.093 mmol) in 1:1 THF/MeOH (1 ml). After stirring at room temperature for 4 hours, the reaction mixture is filtered to remove any undissolved material and is evaporated to dryness. The resulting oil is dissolved in water (1 ml) and acidified to pH 2. The resulting precipitate collected by filtration and dried *in vacuo* to afford [4-chloro-1-(4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid. (MH+ 393)

Example 90

[1-(2-Chloro-4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

90a) 2-Chloro-4-methanesulfonyl-benzaldehyde:

A suspension of 2-chloro-4-fluorobenzaldehyde (24.9 g, 0.16 mol) and dry sodium methanesulfinate (17.9 g, 0.175 mmol) in dry DMSO (60 ml) is stirred at 90 °C overnight. The reaction mixture is allowed to cool to room temperature and then poured onto ice-water (400 ml). The resulting precipitated is collected by filtration and dried under high vacuum to yield the titled compound as a yellow powder.

90b) (2-Chloro-4-methanesulfonyl-phenyl)-methanol

To a stirred dispersion of 2-chloro-4-methanesulfonyl-benzaldehyde (25 g, 0.11 mol) in absolute ethanol (120 ml) is added sodium borohydride (4.6 g, 0.12 mol) whilst cooling with an ice-bath to maintain room temperature. After stirring at room temperature for 3 hours, the reaction mixture is poured carefully onto ice-water (600 ml) and acidified to pH 1-2 with 1N HCl. The resulting suspension is extracted with ethyl acetate (400 ml) and the organic portions are combined, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting crude product is dried in a vacuum oven at 40 °C overnight to yield the titled product which is used crude in the next step.

90c) 1-Bromomethyl-2-chloro-4-methanesulfonyl-benzene

A cooled (0 °C), stirred suspension of (2-chloro-4-methanesulfonyl-phenyl)-methanol (19.1 g, 0.087 mol) in diethyl ether (250 ml) under an inert atmosphere, is treated with phosphorus tribromide (5.2 ml, 0.029 mol) and allowed to stir and warm to room temperature overnight. The resulting mixture is diluted with water (100 ml) and the organic portion is separated and dried over NaOH pellets for 5 minutes. The solvent is removed *in vacuo* and the resulting crude residue is loaded on a pre-packed Isolute™ silica column and eluted with *iso*-hexane/ethyl acetate (4:1) to yield the titled compound as a white powder.

90d) [1-(2-Chloro-4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester:

To an ice cooled (0 °C) stirred solution of (2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester ((2.25 g, 1.1 mmol) in dry DMF (15 ml) is added sodium hydride (0.484 g of a 60 % dispersion in mineral oil, 12.1 mmol). After stirring at room temperature for 3 hours, the reaction mixture is re-cooled to 0 °C and treated with 1-bromomethyl-2-chloro-4-methanesulfonyl-benzene (5.0 g, 17.6 mmol) and sodium iodide (2.64 g, 17.6 mmol). The resulting mixture is stirred and allowed to warm to room temperature overnight. The reaction mixture is poured onto water (300 ml) and extracted with 1:1 ethyl acetate/diethyl ether. The organic portions are washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* and the resulting crude is purified by chromatography on silica eluting with ethyl acetate/*iso*-hexane (1:4 increasing to 1:2) to yield the titled product. (MH+ 407)

90e) [1-(2-Chloro-4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

1M Aqueous NaOH (15 ml) is added to a stirring suspension of [1-(2-chloro-4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester (2.6 g, 6.39 mmol) in 1:1 THF/MeOH (40 ml). After stirring at 45 °C for 1 hour, the reaction mixture is filtered to remove any undissolved material and is evaporated to dryness. The resulting solid is dissolved in water (30 ml) and acidified to pH 2-3 using concentrated HCl. The resulting suspension is collected by filtration and dried *in vacuo* at 50 °C to yield a

solid which is purified by recrystallisation from IPA/water (1:3) to afford the titled product. (MH+ 393)

Example 91

[1-(4-Amino-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

91a) [2-Methyl-1-(4-nitro-benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester:

To a stirred solution of (2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester ((0.78 g, 3.8 mmol) in dry DMF (10 ml) is added dropwise, BEMP (1.21 ml, 4.2 mmol) over two minutes. After stirring at room temperature for 1 hour, the resulting solution is treated with 4-nitrobenzyl bromide (1.0 g, 4.6 mmol) in one portion and stirring continues overnight. The reaction is concentrated *in vacuo* with toluene and the resulting oil is purified by chromatography on silica eluting with *iso*-hexane/ethyl acetate (3:1) to yield [2-methyl-1-(4-nitro-benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester. (MH+ 340)

91b) [2-Methyl-1-(4-nitro-benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid:

1M Aqueous NaOH (1.18 ml) is added to a stirring suspension of [2-methyl-1-(4-nitro-benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester (0.2 g, 0.54 mmol) in 4:1 THF/MeOH (5 ml). The reaction mixture is allowed to stir at room temperature for 4 hours and then the solvent is removed in vacuo. The crude residue is dissolved in 1:1 THF/water and acidified to pH 3-4 using 6M HCl. After stirring for 30 minutes the resulting suspension is filtered and dried *in vacuo* at 110 °C to yield the titled product as a yellow solid. (MH+ 326)

91c) [1-(4-Amino-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid:

[2-Methyl-1-(4-nitro-benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid: is dissolved in 25:3 methanol/acetic acid under an inert atmosphere of Argon and then treated with palladium on carbon (10 %w/w). The resulting suspension is stirred under an atmosphere of

hydrogen for 4 hours and then filtered. The solvent is removed *in vacuo* to yield the titled product as a yellow solid. (MH+ 296)

Example 92

[1-(4-Methanesulfonyl-3-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

92a) 1-Bromomethyl-4-methanesulfonyl-3-trifluoromethyl-benzene:

The titled compound is prepared analogously to 1-bromomethyl-2-chloro-4-methanesulfonyl-benzene by replacing 2-chloro-4-fluorobenzaldehyde (step 90a) with 4-fluoro-3-trifluoromethylbenzaldehyde.

92b) 1-(4-Methanesulfonyl-3-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester:

To a stirred solution of (2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester ((12.8 g, 62.8 mmol) in dry DMF (200 ml) under an inert atmosphere of Argon is added dropwise, BEMP (19.9 ml, 69.1 mmol) over five minutes. After stirring at room temperature for 1 hour, the resulting solution is added dropwise to a stirred solution of 1-bromomethyl-4-methanesulfonyl-3-trifluoromethyl-benzene (23.9 g, 75.4 mmol) and stirred for 18 hours. The reaction is concentrated *in vacuo* with toluene and the resulting oil is purified by chromatography on silica eluting with *iso*-hexane/acetone (15:1). The crude is further purified by dissolving in hot ethyl acetate and refluxing in the presence of charcoal for 5 minutes. The solution is filtered and the solvent is removed *in vacuo*. The resulting solid is re-crystallized from ethyl acetate/*iso*-hexane to yield the titled product as a white solid. (MH+ 441)

92c) [1-(4-Methanesulfonyl-3-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

1-(4-Methanesulfonyl-3-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester (14.1 g, 32 mmol) in THF (150 ml) is treated dropwise with 1M NaOH (64 ml) at room temperature and after heating to 50 °C, the suspension is treated with methanol (50 ml). The reaction mixture is stirred at 50 °C for 2 hours and then the solvent is removed in vacuo. The crude is triturated with ethyl acetate (200 ml) and the resulting solid is filtered and dissolved in water/dioxane (250 ml of a 2:1 mixture). The solution acidified to pH 3-4 using concentrated HCl and the resulting suspension is filtered, washed with water and then dried *in vacuo*. Further purification of the solid by recrystallisation from IPA/water (1:3) affords the titled product. (MH+ 427)

Example 93

[1-(4-Ethanesulfonyl-2-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

93a) 1-Bromomethyl-4-ethanesulfonyl-2-trifluoromethyl-benzene:

The titled compound is prepared analogously to 1-bromomethyl-2-chloro-4-methanesulfonyl-benzene by replacing 2-chloro-4-fluorobenzaldehyde (step 90a) with 4-fluoro-3-trifluoromethylbenzaldehyde and by replacing sodium methanesulfinate with sodium ethanesulfinate.

93b) [1-(4-Ethanesulfonyl-2-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester:

To a stirred solution of (2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester ((0.77 g, 3.78 mmol) in dry DMF (12 ml) under an inert atmosphere of Argon is added dropwise, BEMP (1.75 ml, 6.04 mmol). The mixture was allowed to stir at room temperature for 1 hour and then treated with 1-bromomethyl-4-ethanesulfonyl-2-trifluoromethyl-benzene (2 g, 6.04 mmol). Stirring continues for a further 2 hours after which time, the reaction mixture is partitioned between ethyl acetate/diethyl ether (80 ml of a 1:1 mixture) and water (100 ml). The organic portion is separated and washed with brine and concentrated *in vacuo*. Purification of the crude by chromatography on silica eluting with *iso*-hexane/ethyl acetate (3:1 increasing to 2:1) yields the titled product. (MH+ 455)

93c) [1-(4-Ethanesulfonyl-2-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

To a stirred solution of [1-(4-ethanesulfonyl-2-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester (0.6 g, 1.32 mmol) in methanol/THF (8 ml of a 1:1 mixture) is added 1M NaOH (3 ml). After stirring at room temperature for 1.5 hours, the solvent is removed *in vacuo* and the residue is dissolved in water (3 ml). The solution is acidified to pH1 using 6M HCl and the resulting suspension is filtered and dried to yield the titled product. (MH+ 441)

Example 94

[1-(2-Chloro-4-ethanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

94a) 1-Bromomethyl-2-chloro-4-ethanesulfonyl-benzene:

The titled compound is prepared analogously to 1-bromomethyl-2-chloro-4-methanesulfonyl-benzene by replacing sodium methanesulfinate with sodium ethanesulfinate.

94b) [1-(2-Chloro-4-ethanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester:

To an ice cooled (0 °C) stirred solution of (2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester ((2.68 g, 13.1 mmol) in dry DMF (95 ml) is added sodium hydride (577 mg of a 60 % dispersion in mineral oil, 14.41 mmol). After stirring at room temperature for 1.5 hours, the reaction mixture is re-cooled to 0 °C and treated with 1-bromomethyl-2-chloro-4-ethanesulfonyl-benzene (6.6 g, 22.2 mmol) and sodium iodide (3.3 g, 22.2 mmol). The resulting mixture is stirred and allowed to warm to room temperature overnight. The reaction mixture is poured onto water (600 ml) and extracted with 1:1 ethyl acetate/diethyl ether (4 x 300 ml). The organic portions are washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* and the resulting crude is purified by chromatography on silica

eluting with ethyl acetate/*iso*-hexane (1:8 increasing to 1:2) to yield the titled product. (MH+ 421)

94c) [1-(2-Chloro-4-ethanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

To a stirred solution of [1-(2-chloro-4-ethanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester: (3.32 g, 7.89 mmol) in methanol/THF (30 ml of a 1:1 mixture) is added 1M NaOH (15 ml). After stirring at room temperature overnight, the solvent is removed *in vacuo* and the residue is dissolved in water (20 ml). The solution is acidified to pH1 using 6M HCl and the resulting suspension is filtered and recrystallised from IPA/water to yield the titled product. (MH+ 407)

Example 95

[1-(4-Ethanesulfonyl-2-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

95a) 1-Bromomethyl-4-methanesulfonyl-2-trifluoromethyl-benzene:

The titled compound is prepared analogously to 1-bromomethyl-2-chloro-4-methanesulfonyl-benzene by replacing 2-chloro-4-fluorobenzaldehyde (step 90a) with 4-fluoro-2-trifluoromethylbenzaldehyde.

95b) [1-(4-Methanesulfonyl-2-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester:

To an ice-cooled solution of (2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester ((12.8 g, 62.8 mmol) in dry DMF (400 ml) under an inert atmosphere of Argon is added dropwise, BEMP (18.1 ml, 62.8 mmol) over two minutes. After stirring at 10 °C for 40 minutes, the resulting solution is treated dropwise with1-bromomethyl-4-methanesulfonyl-2-trifluoromethyl-benzene (23.8 g, 75.4 mmol) and allowed to warm to room temperature while stirring overnight. The reaction is concentrated *in vacuo* with

toluene azeotroping and the resulting oil is partitioned between water (400 ml) and DCM (500 ml) and extracted with DCM (500 ml). The organic portions are combined and washed with water (2 x 200 ml). The resulting suspension is filtered and concentrated *in vacuo* with toluene azeotroping. The crude is purified by chromatography on silica eluting with *iso*-hexane/acetone (16:4) to yield the titled product. (MH+ 441)

95c) [1-(4-Ethanesulfonyl-2-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

To a mixture comprising [1-(4-methanesulfonyl-2-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester: (11.8 g, 26.8 mmol) in water (100 ml) and THF (250 ml) is added dropwise NaOH (53.6 ml of a 1M aqueous solution) at room temperature and the two phase suspension is allowed to stir overnight. The solvent is removed *in vacuo* and the crude is triturated with diethyl ether, DCM and ethyl acetate. The resulting solid is dissolved in hot water (150 ml) and adjusted to pH 3-4 using 6M HCl. The suspension that forms is filtered and is further purified by dissolving in hot IPA (250 ml) and refluxing in the presence of charcoal for 5 minutes. The solution is filtered and the titled product is recrystallised from water/IPA as a white/pale green crystals. (MH+ 427)

Example 96

1-(4-Methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

96a) [1-(4-Methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester:

A solution of (2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester ((6.8 g, 33.5 mmol) in dry DMF (150 ml) under an inert atmosphere of Argon is treated with BEMP (10.5 ml, 36.5 mmol) dropwise, over two minutes. The solution is stirred at room temperature for 1 hour and then a solution of 4-methylsulphonyl benzyl bromide (10.0 g, 40.2 mmol) in DMF (60 ml) is added dropwise over 5 minutes. After stirring at room temperature overnight, the solvent is removed *in vacuo* and azeotroped with toluene (200 ml). The resulting crude is purified by chromatography on silica eluting with ethyl acetate/*iso*-hexane (20-100 % ethyl acetate) to yield the titled compound as a green oil. (MH+ 373)

96b) 1-(4-Methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

To a solution of [1-(4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester (6.54 g, 17.6 mmol) in THF (100 ml) is added dropwise, 1M NaOH (35.2 ml). The turbid solution is heated to 40 °C and methanol (10 ml) is added to afford a clear solution. After stirring at room temperature for a 4 hours, the solvent is removed *in vacuo* and the crude is triturated with ethyl acetate. The resulting solid is filtered and dissolved in water/THF (200 ml of a 3:1 mixture) and then acidified to pH 3. The solvent is removed *in vacuo* and the resulting solid is recrystallised from ethanol/water to yield the titled product. (MH+ 359)

Example 97

{1-[1-(4-Methanesulfonyl-phenyl)-ethyl]-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl}-acetic acid - Enantiomer 1 and 2

97a) {1-[1-(4-Methanesulfonyl-phenyl)-ethyl]-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl}-acetic acid methyl ester:

A solution of (2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester ((2.37 g, 11.12 mmol) in dry DMF (38 ml) at room temperature is treated with BEMP (4.39 ml, 15.19 mmol) dropwise. The reaction mixture is stirred at room temperature for 35 minutes and then 1-(1-bromo-ethyl)-4-methanesulfonyl-benzene (4.00 g, 15.18 mmol) and sodium iodide (12.29 g, 15.28 mmol) is added. After stirring at 60 °C for 1 hour, the reaction mixture is allowed to cool to room temperature and then diluted with ethyl acetate/ether (200 ml of a 1:1 mixture) and water (150 ml). The organic portion is washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* and the resulting crude is purified by chromatography on silica eluting with ethyl acetate/*iso*-hexane (2:3 increasing to 1:1 ethyl acetate) to yield the titled product as a racemic mixture. The enantiomers are resolved using a chiralcel OD column eluting with 30 % IPA in hexanes to afford enantiomer A (retention time =14.33 minutes) and enantiomer B (retention time = 17.68 minutes)

97b) {1-[1-(4-Methanesulfonyl-phenyl)-ethyl]-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl}-acetic acid - Enantiomer 1

A solution of {1-[1-(4-methanesulfonyl-phenyl)-ethyl]-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl}-acetic acid methyl ester (Enantiomer A) (22 mg, 0.05 mmol) in THF (0.5 ml) and methanol (0.5 ml) is treated with 2M lithium hydroxide (0.2 ml) and stirred at room temperature for 30 minutes. The solvent is removed *in vacuo* and the crude is dissolved in water (10 ml) and acidified to pH1 using concentrated HCl. The mixture is then extracted with ethyl acetate (2 x 10 ml) and the organic portions are washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to yield the titled product as a colourless glassy solid. (MH+ 373) The enantiomer of the titled compound (Enantiomer 2) is prepared analogously using the procedure described above by replacing Enantiomer A with Enantiomer B. (MH+ 373)

Example 98

[1-(4-Methanesulfinyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-

acetic acid:

98a) [1-(4-Methanesulfinyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-

acetic acid methyl ester:

A solution of (2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester ((0.512g, 2.51 mmol) in dry DMF (5.6 ml) at room temperature is treated with BEMP (1.17 ml, 4.01 mmol) dropwise. The reaction mixture is stirred at room temperature for 80 minutes and then treated with 1-bromomethyl-4-methanesulfinyl-benzene (0.934 g, 4.01 mmol). After stirring at room temperature for a further 2 hours, the reaction mixture is partitioned between ethyl acetate/ether (300 ml of a 1:1 mixture) and water (30 ml). The organic portion is separated and washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The resulting crude is purified by chromatography on silica eluting with DCM/methanol (10:1) to yield the titled product. (MH+ 357)

98b) [1-(4-Methanesulfinyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-

acetic acid:

To a stirred solution of [1-(4-methanesulfinyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester (0.340 g, 0.95 mmol) in THF/MeOH (8 ml of a 1:1 mixture) is added 1M NaOH (2 ml) and the reaction mixture is stirred for 2 hours. The solvent is removed *in vacuo* and the resulting oil is dissolved in water and acidified to pH2 using concentrated HCl. A precipitate forms which is filtered, washed with water and dried *in vacuo* to yield the titled product. (MH+ 343)

Example 99

[6-Chloro-1-(4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

99a) 2-Methyl-1H-pyrrolo[2,3-b]pyridine 7-oxide:

To a cooled (0 °C) solution of 2-methyl-7-azaindole (5 g, 37.8 mmol) in 1,2-dimethoxyethane (40 ml) is added m-chloroperoxybenzoic acid (10.4 g, of a 77 %w/w solid, 46.6 mmol). The reaction mixture is stirred at 0 °C for 30 minutes, at room temperature for 3 hours and then poured into water (400 ml). The solution is basified to pH 9-10 using saturated potassium carbonate solution. The aqueous is extracted with DCM (2x100 ml) and the organic portions are combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the resulting crude by chromatography on silica eluting firstly with neat ethyl acetate followed by DCM/MeOH (10:1) yields the titled compound as a yellow powder. (MH+ 297 appears as a dimer)

99b) 6-Chloro-2-methyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid methyl ester:

To a solution of 2-methyl-1H-pyrrolo[2,3-b]pyridine 7-oxide: (0.89 g, 6 mmol) in THF (20 ml) under an inert atmosphere of Argon is added HMDS (1.25 ml, 6 mmol) at room temperature. The solution is cooled (0 °C) and treated with methyl chloroformate (1.16 ml, 15 mmol). The reaction mixture is stirred at room temperature overnight and the solvent is then removed *in vacuo*. The residue is dissolved in ethyl acetate (30 ml) and washed with saturated sodium hydrogencarbonate solution. The aqueous is back-extracted with ethyl acetate (2 x 20 ml) and the organic portions are combined, dried ($MgSO_4$) and concentrated

in vacuo. Purification of the resulting crude by chromatography on silica eluting with ethyl acetate/*iso*-hexane (1:8) yields the titled product. (MH+ 225).

99c) 6-Chloro-2-methyl-1H-pyrrolo[2,3-b]pyridine:

6-Chloro-2-methyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid methyl ester (0.225 g, 1 mmol) is dissolved in methanol (30 ml) and 1M NaOH (10 ml) and stirred at room temperature overnight. The methanol is removed *in vacuo* and the resulting white suspension is extracted with chloroform (3 x 20 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield a white powder which is dried under high vacuum to yield the titled product. (MH+ 167).

99d) (6-Chloro-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-oxo-acetic acid methyl ester:

A stirred suspension of aluminium chloride (0.56 g, 4.2 mmol) in DCM (10 ml) at room temperature under an inert atmosphere of Argon is treated with a solution of 6-chloro-2-methyl-1H-pyrrolo[2,3-b]pyridine: (0.14 g, 0.84 mmol) and stirred for 1 hour. Methyl oxalyl chloride (0.386 ml, 4.2 mmol) is added and the resulting suspension is stirred at room temperature overnight. The reaction mixture is cooled (0 °C) and quenched dropwise with methanol (10 ml). The resulting solution is poured into ice-water (100 ml) and the organic layer is separated, dried (Na_2SO_4) and concentrated *in vacuo*. The resulting crude is triturated with ice-cold water, sonicated and then filtered to afford a solid which, after drying under high vacuum, yields the titled compound. (MH+ 253).

99e) (6-Chloro-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester:

To a solution of triethylsilane (0.343 ml, 2.15 mmol) in TFA (2 ml) cooled to -10 °C is added portionwise (6-chloro-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-oxo-acetic acid methyl ester (0.155 g, 0.61 mmol). The reaction mixture is stirred at -10 °C for 1 hour and the solvent is removed *in vacuo*. The residue is washed with saturated sodium hydrogen carbonate solution and this aqueous portion is extracted with DCM (3 x 10 ml). The organics are combined, dried (Na_2SO_4) and concentrated *in vacuo* and the resulting crude is purified by chromatography on silica eluting with methanol/DCM (0-0.5 % methanol) to yield the titled product as an off-white powder. (MH+ 239).

99f) 6-Chloro-1-(4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester:

To a stirred, ice-cooled solution of (6-chloro-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester (0.045 g, 0.19 mmol) in DMF (1.5 ml) under an inert atmosphere of Argon is added sodium hydride (0.008 g of a 60 % dispersion in mineral oil, 0.21 mmol). After stirring at 0 °C for 30 minutes, the reaction mixture is stirred at room temperature for two hours and then re-cooled to 0 °C. 4-Methylsulphonylbenzyl bromide (0.076 g, 0.3 mmol) in DMF (1.5 ml) is added followed by sodium iodide (0.076 g, 0.30 mmol) and the resulting solution is stirred at room temperature overnight. The reaction mixture is poured onto water (20 ml) and extracted with 1:1 ethyl acetate/diethyl ether. The organic portions are washed with brine, dried ($MgSO_4$) and concentrated *in vacuo.* The resulting crude is purified by chromatography on silica eluting with ethyl acetate/*iso*-hexane (1:8 increasing to 1:4) to yield the titled product. (MH+ 407)

99g) [6-Chloro-1-(4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

1M Aqueous NaOH (0.25 ml) is added to a stirring suspension of (6-chloro-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester (0.018 g, 0.044 mmol) in 1:1 THF/MeOH (1 ml). After stirring at room temperature for 20 minutes the reaction mixture is evaporated to dryness. The resulting solid is dissolved in water (1 ml) and extracted with ethyl acetate to remove any residual 4-methylsulphonylbenzyl bromide. The aqueous phase is acidified to pH 2-3 using 2M HCl and extracted with ethyl acetate. The organic portion is concentrated *in vacuo* and the resulting crude is purified on silica eluting with DCM/MeOH (20:1) to yield the titled compound. (MH+ 393)

Example 100

[6-Chloro-1-(4-methanesulfonyl-2-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid:

100a) [6-Chloro-1-(4-methanesulfonyl-2-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester:

To a stirred, ice-cooled solution of (6-chloro-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester (Example 99e) (0.03 g, 0.13 mmol) in DMF (1.0 ml) under an inert atmosphere of Argon is added sodium hydride (0.006 g of a 60 % dispersion in mineral oil, 0.14 mmol). The reaction mixture is stirred at 0°C for 45 minutes and then treated with 1-bromomethyl-4-methanesulfonyl-2-trifluoromethyl-benzene (Example 95a) (0.067 g, 0.21 mmol) followed by sodium iodide (0.031 g, 0.21 mmol). Stirring is continued at 0 °C for 2 hours and then the reaction mixture is poured onto water (15 ml) and extracted with DCM (5 ml). The organic portion is separated and concentrated *in vacuo.* The resulting crude is purified by chromatography on silica eluting with ethyl acetate/*iso*-hexane (1:8 increasing to 1:4) to yield the product which was further purified by trituration with ethyl acetate/*iso*-hexane to afford the titled product. (MH+ 475).

100b) [6-Chloro-1-(4-methanesulfonyl-2-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid:

1M Aqueous NaOH (0.25 ml) is added to a stirring suspension of [6-chloro-1-(4-methanesulfonyl-2-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester: (0.01 g, 0.021 mmol) in 1:1 THF/MeOH (0.5 ml). The resulting suspension is sonicated and allowed to stir at room temperature overnight. The solvent is removed *in vacuo* and the crude solid is dissolved in water (0.5 ml) and acidified to pH 2-3 using1 N HCl. The suspension which forms is filtered, washed with water (0.5 ml) and dried under high vacuum to yield the titled compound. (MH+ 461)

Example 101

[2-Methyl-1-(3-methyl-3H-benzotriazol-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

101a) 5-Bromomethyl-1-methyl-1H-benzotriazole:

Phosphorus tribromide (0.230 ml, 2.45 mmol) is added to a stirred solution of (1-methyl-1H-1,2,3-benzotriazole-5-yl)methanol (0.4 g, 2.45 mmol) in diethyl ether (25 ml) under an inert atmosphere of Argon. After stirring overnight at room temperature, the reaction mixture is diluted with water (5 ml) and stirred vigorously for 10 minutes. The organic portion is

separated, washed with water (2 x 5 ml), brine (2 x 5 ml) and concentrated *in vacuo* to yield the titled product which is used crude in the next step. (MH+ 226).

101b) [2-Methyl-1-(3-methyl-3H-benzotriazol-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester:

To a solution of (2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester ((0.025 g, 0.122 mmol) in dry DMF (1 ml) under an inert atmosphere of Argon is added dropwise, BEMP (56.6 µl, 0.196 mmol). The mixture is agitated at room temperature for 1 hour before cooling to 0 °C with an ice-bath. A solution of 5-bromomethyl-1-methyl-1H-benzotriazole (0.044 g, 0.196 mmol) in DMF (1 ml) is added to the cooled solution and the resulting mixture is agitated at room temperature for 2 days. The solvent is removed *in vacuo* and purification of the crude by chromatography on silica eluting with *iso*-hexane/ethyl acetate (0 %- 20 % ethyl acetate) yields the titled product. (MH+ 350).

101c) [2-Methyl-1-(3-methyl-3H-benzotriazol-5-ylmethyl)-1H-pyrrolo[2,3-b]pyr

idin-3-yl]-acetic acid

1 M Lithium hydroxide (116 µl) is added to a cooled (0 °C) solution of [2-methyl-1-(3-methyl-3H-benzotriazol-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester (0.041 g, 0.116 mmol) in THF/water (4ml of a 1:1 mixture). After stirring at room temperature for 4 hours, the reaction mixture is diluted with DCM (3 ml) and stirred vigorously for 10 minutes. The resulting mixture is passed through a phase separation cartridge and the aqueous portion is acidified to pH 1-3 with 1M HCl. This portion is extracted with DCM (2 x 3 ml) and the organic extracts are combined and concentrated *in vacuo* to yield the titled compound as a white solid. (MH+ 336)

Example 102

[1-(4-Fluoro-3-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

102a) 4-Fluoro-3-methoxy-benzenesulfonyl chloride:

4-Fluoro-3-methoxyaniline (0.5 g, 3.55 mmol) in suspension in glacial acetic acid (15ml) is treated with a concentrated HCl (5 ml). The resulting solution is then cooled approximately to 0 °C and treated dropwise with a solution of sodium nitrite (0.245 g, 3.55 mmol) in water (2 ml). After 10 minutes the reaction mixture is added to a stirred solution of SO_2/AcOH/$CuCl_2$/H_2O (40 ml) (the preparation of the reagent is described below). The reaction mixture is allowed to warm to room temperature and is stirred overnight. The reaction mixture is then poured into water (250 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic layers are washed with water (2 x 100 ml) followed by brine (100 ml) and dried over $MgSO_4$. After filtration the solvent is removed *in vacuo* to give the titled product which is used crude in the next step.

Preparation of the reagent SO_2/AcOH/$CuCl_2$/H_2O:

According to the reported procedure (E. E. Gilbert, Synthesis 1969, 1-10, p6), glacial acetic acid (100 ml), vigorously stirred at room temperature, is treated by bubbling SO_2 gas. Once a saturated solution is achieved (approximately 10 g per 100 ml), the solution is treated with copper (II) chloride (4 g) in water (5 ml). The resulting mixture is allowed to settle to give a green solution.

102b) [1-(4-Fluoro-3-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester:

To a stirred, ice-cooled (0 °C)solution of sodium hydride (0.026 g of a 60 % dispersion in mineral oil, 0.686 mmol) in THF (3 ml) under an inert atmosphere of Argon is added dropwise (2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester ((0.1 g, 0.49 mmol) in dry THF (3 ml). The reaction mixture is stirred at 0 °C for 1 hour and then treated with 4-fluoro-3-methoxy-benzenesulfonyl chloride (0.154 g, 0.686 mmol) in dry THF (3 ml). Stirring continued at 0 °C for 30 minutes and then the reaction mixture is poured onto water (100 ml) and extracted with ethyl acetate (3 x 50 ml). The organic portions are separated and washed with water (2 x 50 ml), brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting crude is purified by chromatography on silica eluting with *iso*-hexane/ethyl acetate (0 % - 20 % ethyl acetate) yields the titled product. (MH+ 392).

102c) [1-(4-Fluoro-3-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

1 M Lithium hydroxide (119 µl) is added dropwise to a cooled (0 °C) solution of [1-(4-fluoro-3-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester (0.044 g, 0.119 mmol) in THF/water (4ml of a 1:1 mixture). After stirring at room temperature for 4 hours, the reaction mixture is diluted with DCM. The resulting mixture is passed through a phase separation cartridge and the aqueous portion is acidified to pH 1-3 with 1M HCl. This portion is extracted with DCM and the organic extracts are combined and concentrated *in vacuo* to yield the titled compound as a pale yellow solid. (MH+ 379)

Example 103

[1-(4-Chloro-3-cyano-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

103a) 4-Chloro-3-cyano-benzenesulfonyl chloride:

A suspension of 2-chloro-5-aminobenzonitrile (0.405 g, 2.66 mmol) in glacial acetic acid (20 ml) is treated with concentrated HCl (5 ml). The solution is cooled to below 5 °C and treated dropwise with sodium nitrite (0.183 g, 2.66 mmol) in water (2 ml). After 20 minutes the reaction mixture is added to a stirred solution of SO_2/AcOH/$CuCl_2$/H_2O (40 ml) (the preparation of the reagent is described herein). The reaction mixture is allowed to warm to room temperature and is stirred overnight. The reaction mixture is then poured into water (150 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic layers are washed with water (2 x 100 ml) followed by brine (100 ml) and dried over MgSO4. After filtration the solvent is removed *in vacuo* to give the titled product which is used crude in the next step.

103b) 1-(4-Chloro-3-cyano-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester:

To a stirred, ice-cooled (0 °C) suspension of sodium hydride (15.8 mg of a 60 % dispersion in mineral oil, 0.411 mmol) in dry THF (2 ml) under an inert atmosphere of Argon is added dropwise (2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester ((0.06 g, 0.294 mmol) in THF/DMF (4 ml of a 3:1 mixture). The reaction mixture is stirred at 0 °C for 45 minutes and then treated with 4-chloro-3-cyano-benzenesulfonyl chloride (97.1 mg, 0.411 mmol) in dry THF (3 ml). Stirring continued at 0 °C for 15 minutes and then the reaction mixture is poured onto water (30 ml) and extracted with ethyl acetate (100 ml). The organic portion is separated and washed brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo.* The resulting crude is purified by chromatography on silica eluting with *iso*-hexane/ethyl acetate (0 %- 20 % ethyl acetate) to yield the titled product. (MH+ 404)

103c) [1-(4-Chloro-3-cyano-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

1M Lithium hydroxide (76 µl) is added dropwise to a cooled (0 °C) solution of 1-(4-chloro-3-cyano-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester (0.026 g, 0.064 mmol) in THF/water (4ml of a 1:1 mixture). After stirring at 0 °C for 10 minutes, the reaction mixture is allowed to warm to room temperature overnight and then diluted with DCM (3 ml). The resulting mixture is passed through a phase separation cartridge and the aqueous portion is acidified to pH 1-3 with 1M HCl. This portion is extracted with DCM (2 x 3 ml) and the organic extracts are combined, passed through a phase separation cartridge, and concentrated *in vacuo* to yield the titled compound as an off-white solid. (MH+ 390)

Examples 104-105

These examples, namely

[2-Methyl-1-(4-trifluoromethanesulfonyl-benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 104) and

{2-Methyl-1-[4-(propane-2-sulfonyl)-benzyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-acetic acid (Example 105) are prepared analogously to Example 90 using the appropriate benzyl halide. The preparation of these benzyl halides is described herein.

Examples 106-111

These examples, namely

[1-(3-Fluoro-4-methoxy-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 106),

[1-(4-Fluoro-3-methoxy-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 107),

[2-Methyl-1-(6-trifluoromethyl-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 108),

[1-(3-Cyano-4-fluoro-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 109),

[1-(2-Chloro-5-fluoro-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 110) and

[1-(4-Chloro-3-methoxy-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 111),

are prepared analogously to Example 96 using the appropriate benzyl halide. The benzyl halides that are used to prepare these Examples are either commercially available or are prepared by methods described herein.

Examples 112-126

These examples, namely

[1-(4-Methanesulfonyl-2-methyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 112),

[1-(4-Methoxy-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 113),

[1-(2-Methoxy-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 114),

{2-Methyl-1-[1-(4-trifluoromethyl-phenyl)-ethyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-acetic acid (Example 115),

{1-[1-(3-Chloro-phenyl)-ethyl]-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl}-acetic acid (Example 116),

{1-[1-(4-Methanesulfonyl-phenyl)-ethyl]-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl}-acetic acid (Example 117),

1-(4-Fluoro-2-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 118),

[1-(2,4-Bis-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 119),

{2-Methyl-1-[1-(2-trifluoromethyl-phenyl)-ethyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-acetic acid (Example 120),

[1-(3-Methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 121),

[2-Methyl-1-(4-nitro-benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 122),

[1-(4-Bromo-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 123),

[2-Methyl-1-(4-[1,2,4]triazol-1-yl-benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 124),

[1-(3-Chloro-4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 125) and

[1-(3-Fluoro-4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 126)

are prepared analogously to Example 91 using the appropriate benzyl halide. The benzyl halides that are used to prepare these Examples are either commercially available or are prepared by methods described herein.

4-Bromomethyl-2-fluoro-1-methanesulfonyl-benzene:

a) 3-Fluoro-4-methanesulfonyl-benzaldehyde:

Methane sulfinic acid sodium salt (20.1 g, 200 mmol) is added to a stirred solution of 3,4-difluorobenzaldehyde (22.5 g, 158 mmol) in dry DMSO (200 ml) at 75 °C . After 2 hours the reaction is poured onto ice-water (200 ml). The precipitate is filtered, washed with water and dissolved in chloroform (400 ml). The organic extract is washed with water (2 x 200 ml), dried over MgSO4 and the solvent is removed *in vacuo* to give the titled compound as a white solid.

b) (3-Fluoro-4-methanesulfonyl-phenyl)-methanol:

To an ice-cooled suspension of 3-fluoro-4-methanesulfonyl-benzaldehyde (1.3 g, 6.44 mmol) in ethanol (5 ml) under an inert atmosphere of Argon is added sodium borohydride (0.275 g, 7.27 mmol) portionwise over 2-3 minutes. After stirring for 4 hours, the reaction mixture is poured carefully onto ice-cold water and acidified to pH 1 using 1M HCl. The product is extracted into ethyl acetate (80 ml) and this organic portion is washed with brine, dried over MgSO4 and the solvent is removed *in vacuo* to give an oil which solidifies on drying to yield the titled compound.

c) 4-Bromomethyl-2-fluoro-1-methanesulfonyl-benzene:

To a stirred suspension of (3-fluoro-4-methanesulfonyl-phenyl)-methanol (0.269 g, 1.31 mmol) in diethyl ether (5 ml) under an inert atmosphere of Argon is added dropwise phosphorus tribromide (46 µl, 0.434 mmol). After stirring at room temperature overnight, the reaction mixture is diluted with water (2 ml) and the diethyl ether layer separated. This organic portion is placed over NaOH pellets and after 20 minutes, is used as a reagent in solution in diethyl ether.

<u>1-Bromomethyl-4-methanesulfonyl-2-methyl-benzene:</u>

The titled compound is prepared analogously to 4-bromomethyl-2-fluoro-1-methanesulfonyl-benzene by replacing 3,4-difluorobenzaldehyde with 4-fluoro-2-methyl-benzaldehyde.

1-Bromomethyl-4-trifluoromethanesulfonyl-benzene:

The titled compound is prepared analogously to 4-bromomethyl-2-fluoro-1-methanesulfonyl-benzene by replacing 3-fluoro-4-methanesulfonyl-benzaldehyde with 4-trifluoromethanesulfonyl-benzaldehyde.

4-Bromomethyl-2-chloro-1-methanesulfonyl-benzene:

The titled compound is prepared analogously to 4-bromomethyl-2-fluoro-1-methanesulfonyl-benzene by replacing 3,4-difluorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde.

1-Bromomethyl-4-(propane-2-sulfonyl)-benzene:

The titled compound is prepared analogously to 4-bromomethyl-2-fluoro-1-methanesulfonyl-benzene by replacing 3,4-difluorobenzaldehyde with 4-fluorobenzaldehyde and by replacing methane sulfinic acid sodium salt with 2-propane sulfinic acid sodium salt.

Examples 127

[1-(4-Cyano-3-ethoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

127a) 2-Ethoxy-4-nitro-benzonitrile:

To a solution of 2-hydroxy-4-nitrobenzonitrile (0.5 g, 3.04 mmol) in DMF (5 ml) is added potassium carbonate (0.631 g, 4.56 mmol) followed by bromoethane (0.238 ml, 3.19 mmol) and the reaction mixture is stirred at room temperature for 5 days. The solvent is removed *in vacuo* and the crude is partitioned between ethyl acetate (100 ml) and water (100 ml). The organic layer is separated, washed with water (2 x 100 ml), saturated sodium hydrogen carbonate solution (100 ml) and concentrated *in vacuo* to afford the titled compound as a pale yellow solid which is used crude in the next step.

127b) 4-Amino-2-ethoxy-benzonitrile:

To a suspension of 2-ethoxy-4-nitro-benzonitrile (0.49 g, 2.54 mmol) in ethanol (50 ml) is added tin (II) chloride dihydrate (2.87 g, 12.7 mmol) and the suspension is stirred at 70 °C for 2 hours and at room temperature overnight. The reaction mixture is poured onto ice-water and the pH of the solution is adjusted to pH 7-8 by addition of sodium hydrogen carbonate solution (5 % solution in water). The aqueous emulsion is filtered under vacuum and the product is extracted with ethyl acetate (2 x 150 ml). The organic portions are combined, washed with brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield the titled product as a pale yellow solid which is used in the next step without further purification.

127c) 4-Cyano-3-ethoxy-benzenesulfonyl chloride:

The titled compound is prepared analogously to 4-fluoro-3-methoxy-benzenesulfonyl chloride (Intermediate 102a) by replacing 4-fluoro-3-methoxyaniline with 4-amino-2-ethoxy-benzonitrile.

127d) [1-(4-Cyano-3-ethoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester:

To a stirred, ice-cooled (0 °C) suspension of sodium hydride (26.3 mg of a 60 % dispersion in mineral oil, 0.686 mmol) in dry THF (10 ml) under an inert atmosphere of Argon is added dropwise (2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester ((0.1 g, 0.49 mmol) in THF/DMF (4 ml of a 3:1 mixture). The reaction mixture is stirred at 0 °C for 1 hour and then treated with 4-cyano-3-ethoxy-benzenesulfonyl chloride (168 mg, 0.686 mmol) in

dry THF (1 ml). Stirring continued at 0 °C for 10 minutes and at room temperature for 10 minutes and then the reaction mixture is poured onto water (50 ml). The mixture is extracted with ethyl acetate (2 x 50 ml) and the organic portions are combined, washed brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting crude is purified by chromatography on silica eluting with *iso*-hexane/ethyl acetate (0 %- 20 % ethyl acetate) to yield the titled product. (MH+ 414).

127 e) [1-(4-Cyano-3-ethoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

1M Lithium hydroxide (57 µl) is added dropwise to a cooled (0 °C) solution of [1-(4-cyano-3-ethoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester (0.024 g, 0.057 mmol) in THF/water (4ml of a 1:1 mixture). After stirring at 0 °C for 10 minutes, the reaction mixture is stirred at room temperature for 2.5 hours and then diluted with DCM (4 ml). The resulting mixture is passed through a phase separation cartridge and the aqueous portion is acidified to pH 4 with 1M HCl. This portion is extracted with DCM (2 x 4 ml) and the organic extracts are combined, passed through a phase separation cartridge, and concentrated *in vacuo*. The resulting solid is dissolved in ethyl acetate (2 ml) and triturated with *iso*-hexane (7 ml) to yield the titled compound as a white solid. (MH+ 400)

Examples 128 - 150

These examples, namely

[1-(3-Fluoro-2-methyl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 128),

[1-(4-Cyano-3-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 129),

[1-(4-Cyano-3-propoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 130),

[1-(3-Butoxy-4-cyano-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 131),

[1-(4-Cyano-3-pentyloxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 132),

[1-(6-Cyano-pyridine-3-sulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 133),

[1-(2-Chloro-5-cyano-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 134),

[1-(4-Cyano-3-methyl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 135),

[1-(4-Chloro-2-fluoro-5-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 136),

[1-(5-Cyano-2-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 137),

[1-(5-Chloro-2-cyano-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 138),

[1-(2-Chloro-4-cyano-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 139),

[1-(2-Chloro-5-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 140),

[1-(5-Chloro-2-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 141),

[2-Methyl-1-(thiophene-2-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 142),

[1-(4-Cyano-3-trifluoromethyl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 143),

[1-(3-Chloro-4-cyano-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 144),

[1-(4-Chloro-3-fluoro-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 145),

[1-(3-Chloro-4-trifluoromethyl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 146),

[1-(3-Fluoro-4-trifluoromethyl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 147),

[1-(4-Chloro-3-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 148),

[1-(3,4-Dicyano-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 149) and

[1-(4-Chloro-3-trifluoromethyl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 150) are prepared analogously to Example 127 using the appropriate sulphonyl chloride. The sulphonyl chlorides that are used to prepare these Examples are either commercially available or are prepared by methods described herein.

4-Cyano-3-methoxy-benzenesulfonyl chloride:

The titled compound was prepared analogously to 4-cyano-3-ethoxy-benzenesulfonyl chloride (Intermediate 127c) by replacing 2-ethoxy-4-nitro-benzonitrile with 2-methoxy-4-nitro-benzonitrile.

4-Cyano-3-propoxy-benzenesulfonyl chloride:

The titled compound was prepared analogously to 4-cyano-3-ethoxy-benzenesulfonyl chloride (Intermediate 127c) by replacing bromoethane with 1-bromopropane.

3-Butoxy-4-cyano-benzenesulfonyl chloride:

The titled compound was prepared analogously to 4-cyano-3-ethoxy-benzenesulfonyl chloride (Intermediate 127c) by replacing bromoethane with 1-bromobutane.

4-Cyano-3-pentyloxy-benzenesulfonyl chloride

The titled compound was prepared analogously to 4-cyano-3-ethoxy-benzenesulfonyl chloride (Intermediate 127c) by replacing bromoethane with 1-bromopentane.

6-Cyano-pyridine-3-sulfonyl chloride:

The titled compound is prepared analogously to 4-fluoro-3-methoxy-benzenesulfonyl chloride (Intermediate 102a) by replacing 4-fluoro-3-methoxyaniline with 5-amino-pyridine-2-carbonitrile.

2-Chloro-5-cyano-benzenesulfonyl chloride:

The titled compound is prepared analogously to 4-fluoro-3-methoxy-benzenesulfonyl chloride (Intermediate 102a) by replacing 4-fluoro-3-methoxyaniline with 3-amino-4-chloro-benzonitrile.

4-Cyano-3-methyl-benzenesulfonyl chloride:

The titled compound was prepared analogously to 4-cyano-3-ethoxy-benzenesulfonyl chloride (Intermediate 127c) by replacing 2-ethoxy-4-nitro-benzonitrile with 2-methyl-4-nitro-benzonitrile.

4-Chloro-2-fluoro-5-methoxy-benzenesulfonyl chloride:

The titled compound was prepared analogously to 4-cyano-3-ethoxy-benzenesulfonyl chloride (Intermediate 127c) by replacing 2-ethoxy-4-nitro-benzonitrile with 1-chloro-5-fluoro-2-methoxy-4-nitro-benzene.

5-Cyano-2-methoxy-benzenesulfonyl chloride:

The titled compound was prepared analogously to 4-cyano-3-ethoxy-benzenesulfonyl chloride (Intermediate 127c) by replacing 2-ethoxy-4-nitro-benzonitrile with 4-methoxy-3-nitro-benzonitrile.

5-Chloro-2-cyano-benzenesulfonyl chloride:

The titled compound is prepared analogously 4-fluoro-3-methoxy-benzenesulfonyl chloride (Intermediate 102a) by replacing 4-fluoro-3-methoxyaniline with 2-amino-4-chloro-benzonitrile.

2-Chloro-5-methoxy-benzenesulfonyl chloride:

The titled compound is prepared analogously to 4-fluoro-3-methoxy-benzenesulfonyl chloride (Intermediate 102a) by replacing 4-fluoro-3-methoxyaniline with 2-chloro-5-methoxy-phenylamine.

4-Cyano-3-trifluoromethyl-benzenesulfonyl chloride:

The titled compound is prepared analogously to 4-fluoro-3-methoxy-benzenesulfonyl chloride (Intermediate 102a) by replacing 4-fluoro-3-methoxyaniline with 4-amino-2-trifluoromethyl-benzonitrile.

3-Chloro-4-cyano-benzenesulfonyl chloride:

The titled compound is prepared analogously to 4-fluoro-3-methoxy-benzenesulfonyl chloride (Intermediate 102a) by replacing 4-fluoro-3-methoxyaniline with 4-amino-2-chloro-benzonitrile.

4-Chloro-3-fluoro-benzenesulfonyl chloride:

The titled compound is prepared analogously to 4-fluoro-3-methoxy-benzenesulfonyl chloride (Intermediate 102a) by replacing 4-fluoro-3-methoxyaniline with 4-chloro-3-fluoro-phenylamine.

3-Chloro-4-trifluoromethyl-benzenesulfonyl chloride:

The titled compound is prepared analogously to 4-fluoro-3-methoxy-benzenesulfonyl chloride (Intermediate 102a) by replacing 4-fluoro-3-methoxyaniline with 3-chloro-4-trifluoromethyl-phenylamine.

3-Fluoro-4-trifluoromethyl-benzenesulfonyl chloride:

The titled compound is prepared analogously to 4-fluoro-3-methoxy-benzenesulfonyl chloride (Intermediate 102a) by replacing 4-fluoro-3-methoxyaniline with 3-fluoro-4-trifluoromethyl-phenylamine.

4-Chloro-3-methoxy-benzenesulfonyl chloride:

The titled compound is prepared analogously to 4-fluoro-3-methoxy-benzenesulfonyl chloride (Intermediate 102a) by replacing 4-fluoro-3-methoxyaniline with 4-chloro-3-methoxy-phenylamine.

4-Chloro-3-trifluoromethyl-benzenesulfonyl chloride:

The titled compound is prepared analogously to 4-fluoro-3-methoxy-benzenesulfonyl chloride (Intermediate 102a) by replacing 4-fluoro-3-methoxyaniline with 4-chloro-3-trifluoromethyl-phenylamine.

3,4-Dicyano-benzenesulfonyl chloride:

The titled compound is prepared analogously to 4-fluoro-3-methoxy-benzenesulfonyl chloride (Intermediate 102a) by replacing 4-fluoro-3-methoxyaniline with 4-amino-phthalonitrile.

Example 151

[1-(3-Cyano-4-morpholin-4-yl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-

b]pyridin-3-yl]-acetic acid

151a) [1-(3-Cyano-4-morpholin-4-yl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester:

To a solution of [1-(3-cyano-4-fluoro-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester (Example 54a) (60.7 mg, 0.157 mmol) in acetonitrile (3 ml) is added potassium carbonate (43.3 mg, 0.314 mmol) followed by morpholine (27.6 µl, 0.314 mmol). The reaction mixture is stirred at room temperature for 2 hours and then filtered and concentrated *in vacuo* to yield the titled compound as an orange oil which is used crude in the next step. (MH+ 455).

151b) [1-(3-Cyano-4-morpholin-4-yl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

The titled compound is prepared analogously to [1-(4-fluoro-3-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 102) by replacing [1-(4-fluoro-3-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester with [1-(3-cyano-4-morpholin-4-yl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester. (MH+ 441)

Example 152

[1-(3-Fluoro-4-morpholin-4-yl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

The titled compound is prepared analogously to [1-(3-cyano-4-morpholin-4-yl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester (Intermediate 151b) by replacing [1-(3-cyano-4-fluoro-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid methyl ester with [1-(3,4-difluoro-benzenesulfonyl)-2-

methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 59) and by heating using microwave radiation in a Personal Chemistry Emrys™ Optimizer microwave reactor at 60-80 °C for 4 hours. (MH+ 434)

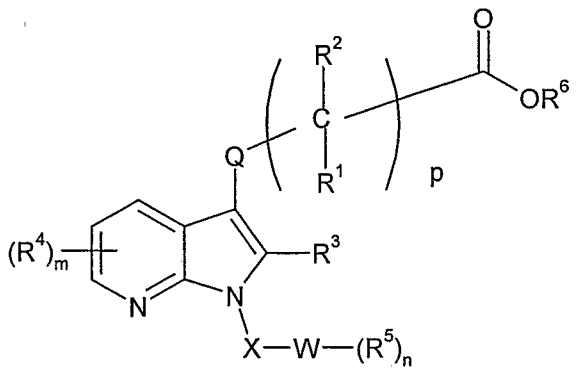
Example 153

[1-(4-Chloro-3-cyano-benzenesulfonyl)-2-ethyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid

The titled compound is prepared analogously to [1-(4-chloro-3-cyano-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid (Example 103) by replacing (2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester with (2-ethyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetic acid methyl ester (Intermediate 87c). (MH+ 404)

CLAIMS

1. a compound of formula (I)



(I)

in free or salt form,

wherein

Q is a bond or a C_1-C_{10}-alkylene group optionally substituted by halogen;

R^1 and R^2 are, independently, H, halogen or C_1-C_8-alkyl, or

R^1 and R^2, together with the carbon atom to which they are attached, form a divalent C_3-C_8-cycloaliphatic group;

R^3 is H, C_1-C_8-alkyl, a C_3-C_{15}-carbocyclic group, C_1-C_8-haloalkyl, alkoxy C_1-C_8 alkyl, C_1-C_8-hydroxyalkyl;

R^4 and R^5 are, independently, halogen, C_1-C_8-alkyl, C_1-C_8-haloalkyl, a C_3-C_{15}-carbocyclic group, nitro, cyano, C_1-C_8-alkylsulfonyl, C_1-C_8-alkylsulfinyl, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkoxy, C_1-C_8-haloalkoxy, carboxy, carboxy-C_1-C_8-alkyl, amino, C_1-C_8-alkylamino, di(C_1-C_8-alkyl)amino, SO_2NH_2, (C_1-C_8-alkylamino)sulfonyl, di(C_1-C_8-alkyl)aminosulfonyl, aminocarbonyl, C_1-C_8-alkylaminocarbonyl, di(C_1-C_8-alkyl)aminocarbonyl or a 4- to 10-membered heterocyclic group having one or more heteroatoms selected from the group consisting of oxygen, nitrogen and sulphur;

R^6 is H or C_1-C_8-alkyl;

W is a C_6-C_{15}-aromatic carbocyclic group or a 4- to 10-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur;

X is -SO_2-, -CH_2-, -CON(C_1-C_8-alkyl)-, -CH(C_1-C_8-alkyl)- or a bond;

m and n are each, independently, an integer from 0-3; and

p is 1.

2. A compound of formula (I) according to claim 1, in free or salt form

wherein

Q is a bond or a C_1-C_{10}-alkylene group optionally substituted by halogen;

R^1 and R^2 are, independently, H, halogen or C_1-C_8-alkyl, or

R^1 and R^2, together with the carbon atom to which they are attached, form a divalent C_3-C_8-cycloaliphatic group;

R^3 is H, C_1-C_8-alkyl, a C_3-C_{15}-carbocyclic group, C_1-C_8-haloalkyl, alkoxy C_1-C_8 alkyl, C_1-C_8-hydroxyalkyl;

R^4 and R^5 are, independently, halogen, C_1-C_8-alkyl, C_1-C_8-haloalkyl, a C_3-C_{15}-carbocyclic group, nitro, cyano, C_1-C_8-alkylsulfonyl, C_1-C_8-alkylsulfinyl, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkoxy, C_1-C_8-haloalkoxy, carboxy, carboxy-C_1-C_8-alkyl, amino, C_1-C_8-alkylamino, di(C_1-C_8-alkyl)amino, SO_2NH_2, (C_1-C_8-alkylamino)sulfonyl, di(C_1-C_8-alkyl)aminosulfonyl, aminocarbonyl, C_1-C_8-alkylaminocarbonyl, di(C_1-C_8-alkyl)aminocarbonyl or a 4- to 10-membered heterocyclic group having one or more heteroatoms selected from the group consisting of oxygen, nitrogen and sulphur;

R^6 is H or C_1-C_8-alkyl;

W is a C_6-C_{15}-aromatic carbocyclic group or a 4- to 10-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur;

X is -SO_2-, -CH_2-, -CON(C_1-C_8-alkyl)-, -CH(C_1-C_8-alkyl)- or a bond;

m and n are each, independently, an integer from 0-3; and

p is 1.

3. A compound of formula (I) according to Claim 2, in free or salt form,

wherein

Q is a bond;

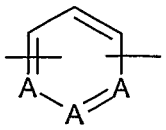
R^1 and R^2 are, independently, H or C_1-C_8-alkyl;

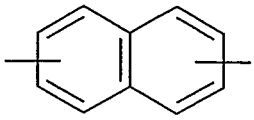
R^3 is C_1-C_8-alkyl;

R^4 and R^5 are, independently, halogen, C_1-C_8-alkyl, C_1-C_8-haloalkyl, a C_3-C_{15}-carbocyclic group, nitro, cyano, C_1-C_8-alkylsulfonyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkoxy or C_1-C_8-haloalkoxy;

R^6 is H or C_1-C_8-alkyl;

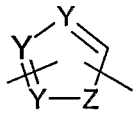
W is a group of formula (W_{a1}) or (W_{a2})



(W_{a1}) or  **(W_{a2})**,

wherein A is, independently, C or N, or

W is a group of formula (W_b);



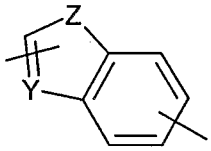
(W_b),

wherein

Y is, independently, C or N; and

Z is N, O or S, or

W is a group of formula (W_c)



(W_c),

wherein

Y is, independently, C or N; and

Z is O or S;

X is $-SO_2-$, $-CH_2-$, $-CH(C_1$-C_8-alkyl$)-$, $-CON(C_1$-C_8-alkyl$)-$ or a bond;

m and n are each, independently, an integer from 0-3; and

p is 1.

4. A compound of formula (I) according to Claim 3, in free or salt form,

Q is a bond;

R^1 and R^2 are, independently, H or C_1-C_4-alkyl;

R^3 is C_1-C_4-alkyl;

R^4 and R^5 are, independently, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, C_3-C_{10}-carbocyclic group, C_1-C_4-alkoxycarbonyl, C_1-C_4-alkylsulfonyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy;

R^6 is H or C_1-C_4-alkyl;

W is a group of formula (W_{a1}) or (W_{a2}) as defined in Claim 2, or

W is a group of formula (W_b) as defined in Claim 2;

X is $-SO_2-$, $-CH_2-$ or $-CH(C_1-C_4\text{-alkyl})-$;

m and n are each, independently, an integer from 0-3; and

p is 1.

5. A compound according to Claim 1 selected from:

(1-Benzyl-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid;

[1-(3,4-Dichloro-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(2-methyl-benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(4-Chloro-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(3-Cyano-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(3-Chloro-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(4-Cyano-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(3-methyl-benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(3-trifluoromethyl-benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(4-Fluoro-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(2-Chloro-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(4-trifluoromethyl-benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(3-Fluoro-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(3,4-Difluoro-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(4-methyl-benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(4-Fluoro-3-methyl-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(3-Fluoro-4-methyl-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(3-Chloro-4-fluoro-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(3-Fluoro-4-trifluoromethyl-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(4-Chloro-3-trifluoromethyl-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(2-Fluoro-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(2-trifluoromethyl-benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(3-Methoxy-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(2-Cyano-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(1-phenyl-ethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(4-Methoxy-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(2-Methoxy-benzyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid,

[2-Methyl-1-(toluene-4-sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

2-Methyl-1-(4-nitro-benzenesulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid;

[2-Methyl-1-(naphthalene-2-sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid;

[1-(4-Fluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid;

[1-(4-Isopropyl-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid;

[1-(3-Bromo-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid,

[2-Methyl-1-(3-trifluoromethyl-benzenesulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid;

[1-(4-Methane-sulfonyl-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid;

[1-(3-Methoxy-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid;

[1-(Biphenyl-4-sulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid;

[1-(3-Fluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid;

[1-(2-Fluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid;

[1-(4-Methoxy-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetic acid;

[1-(4-Difluoromethoxy-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(3-Chloro-2-methyl-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(2-Chloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(3-Cyano-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

1-(2,5-Dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(3,4-Dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

(1-Benzenesulfonyl-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acetic acid;

[1-(4-Chloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

(2-Methyl-1-pyridin-3-ylmethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid;

(2-Methyl-1-pyridin-2-ylmethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid;

(2-Methyl-1-pyridin-4-ylmethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid;

1-(3-Chloro-4-methyl-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(4-trifluoromethyl-benzenesulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

1-(2-Chloro-4-fluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

2-[1-(3,4-Dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-propionic acid;

[1-(3-Cyano-4-fluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(4-Cyano-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(2,4-Dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(3-trifluoromethoxy-benzenesulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(2,5-Difluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(2-Cyano-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(2,3,4-trifluoro-benzenesulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

3-(3-Carboxymethyl-2-methyl-pyrrolo[2,3-*b*]pyridine-1-sulfonyl)-thiophene-2-carboxylic acid methyl ester;

[1-(3,5-Difluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(2,5-Dichloro-thiophene-3-sulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(3-Chloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(3,5-Dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(2,3-Dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(3-Chloro-4-fluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(3-Fluoro-4-methyl-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(2,4-Difluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(pyridine-3-sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

1-(4-Chloro-phenyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(3,4-Difluoro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(4-Chloro-3-methyl-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

(1-Furan-3-ylmethyl-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid;

(1-furan-2-ylmethyl-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid;

[4-Chloro-1-(3,4-dichloro-benzenesulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(2,5-Dimethyl-2*H*-pyrazol-3-ylmethyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(3,5-Dimethyl-isoxazol-4-ylmethyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(5-methyl-2-trifluoromethyl-furan-3-ylmethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(5-methyl-isoxazol-3-ylmethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[1-(2,4-Dimethyl-thiazol-5-ylmethyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

(1-Benzofuran-2-ylmethyl-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-acetic acid;

{1-[1-(4-Chloro-phenyl)-ethyl]-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl}-acetic acid;

[1-(3,4-Dichloro-benzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-acetic acid;

[2-Ethyl-1-(4-trifluoromethyl-benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Ethanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[4-Chloro-1-(4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(2-Chloro-4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Amino-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Methanesulfonyl-3-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Ethanesulfonyl-2-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(2-Chloro-4-ethanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Ethanesulfonyl-2-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

1-(4-Methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

{1-[1-(4-Methanesulfonyl-phenyl)-ethyl]-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl}-acetic acid - Enantiomer 1 and 2;

[1-(4-Methanesulfinyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-

acetic acid;

[6-Chloro-1-(4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[6-Chloro-1-(4-methanesulfonyl-2-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(3-methyl-3H-benzotriazol-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Fluoro-3-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Chloro-3-cyano-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(4-trifluoromethanesulfonyl-benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

{2-Methyl-1-[4-(propane-2-sulfonyl)-benzyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-acetic acid;

[1-(3-Fluoro-4-methoxy-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Fluoro-3-methoxy-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(6-trifluoromethyl-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(3-Cyano-4-fluoro-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(2-Chloro-5-fluoro-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Chloro-3-methoxy-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Methanesulfonyl-2-methyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Methoxy-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(2-Methoxy-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

{2-Methyl-1-[1-(4-trifluoromethyl-phenyl)-ethyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-acetic acid;

{1-[1-(3-Chloro-phenyl)-ethyl]-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl}-acetic acid;

{1-[1-(4-Methanesulfonyl-phenyl)-ethyl]-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl}-acetic acid;

1-(4-Fluoro-2-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(2,4-Bis-trifluoromethyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

{2-Methyl-1-[1-(2-trifluoromethyl-phenyl)-ethyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}-acetic acid;

[1-(3-Methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(4-nitro-benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Bromo-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(4-[1,2,4]triazol-1-yl-benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(3-Chloro-4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(3-Fluoro-4-methanesulfonyl-benzyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Cyano-3-ethoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(3-Fluoro-2-methyl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Cyano-3-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Cyano-3-propoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(3-Butoxy-4-cyano-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Cyano-3-pentyloxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(6-Cyano-pyridine-3-sulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(2-Chloro-5-cyano-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Cyano-3-methyl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Chloro-2-fluoro-5-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(5-Cyano-2-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(5-Chloro-2-cyano-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(2-Chloro-4-cyano-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(2-Chloro-5-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(5-Chloro-2-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[2-Methyl-1-(thiophene-2-sulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Cyano-3-trifluoromethyl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(3-Chloro-4-cyano-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Chloro-3-fluoro-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(3-Chloro-4-trifluoromethyl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(3-Fluoro-4-trifluoromethyl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Chloro-3-methoxy-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(3,4-Dicyano-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(4-Chloro-3-trifluoromethyl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

[1-(3-Cyano-4-morpholin-4-yl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-

b]pyridin-3-yl]-acetic acid;

[1-(3-Fluoro-4-morpholin-4-yl-benzenesulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid; and

[1-(4-Chloro-3-cyano-benzenesulfonyl)-2-ethyl-1H-pyrrolo[2,3-b]pyridin-3-yl]-acetic acid;

6. A compound according to any one of Claims 1 to 5 for use as a pharmaceutical.

7. Pharmaceutical compositions comprising a compound according to any one of Claims 1 to 5.

8. The use of a compound according to any one of Claims 1 to 5 in the manufacture of a medicament for treatment of a disease mediated by the CRTh2 receptor.

9. The use of a compound according to any one of Claims 1 to 5 in the manufacture of a medicament for treatment of an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease.

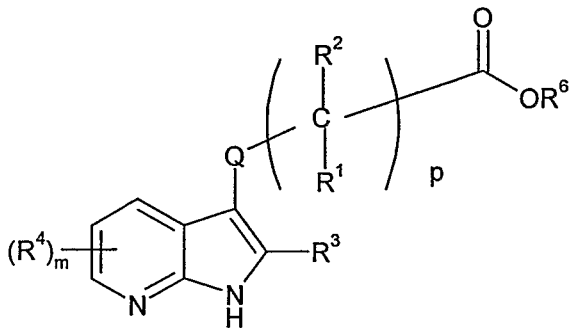
10. A process for the preparation of compounds of formula (I) as defined in Claim 1, in free or salt form, which comprises the steps of:

(i) (A) for the preparation of compounds of formula I where R^6 is H, cleaving the ester group -$COOR^6$ in a compound of formula (I),
wherein

R^6 is C_1-C_8-alkyl; and

Q, R^1, R^2, R^3, R^4, R^5, W, X, m, n and p are as hereinbefore defined; or

(B) for the preparation of compounds of formula (I), wherein R^6 is C_1-C_8-alkyl, reacting a compound of formula (II)

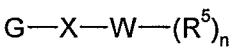


(II)

wherein

R^6 is C_1-C_8-alkyl; and

Q, R^1, R^2, R^3, R^4, m, n and p are as hereinbefore defined with a compound of formula (III)



(III)

wherein

G is a leaving moiety; and

R^5, W, X and n are as hereinbefore defined; or

(C) for the preparation of compounds of formula (I),

wherein

R^6 is C_1-C_8-alkyl;

R^1 is H or C_1-C_8-alkyl;

R^2 is C_1-C_8-alkyl; and

p is 1, reacting a compound of formula (I),

where

R^1 is H or C_1-C_8-alkyl; and

R^2 is H, with a compound of formula R^A G,

where

R^A is C_1-C_8-alkyl; and

G is as hereinbefore defined; and

(ii) recovering the resultant compound of formula I in free or salt form.