PYRAZOLOPYRIMIDINONE cGMP PDE5 INHIBITORS FOR THE TREATMENT OF SEXUAL DYSFUNCTION

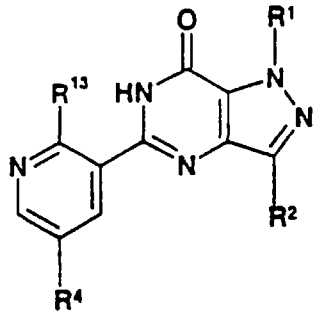
This invention relates to a series of pyrazolo[4,3-d]pyrimidin-7-ones, which inhibit cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs). More notably, the compounds of the invention are potent and selective inhibitors of type 5 cyclic guanosine 3',5'-monophosphate phosphodiesterase (cGMP PDE5) and have utility therefore in a variety of therapeutic areas.

In particular, the compounds are of value in the treatment of male erectile dysfunction (MED) and female sexual dysfunction (FSD) but, clearly, will be useful also for treating other medical conditions for which a potent and selective cGMP PDE5 inhibitor is indicated. Such conditions include premature labour, dysmenorrhoea, benign prostatic hyperplasia (BPH), bladder outlet obstruction, incontinence, stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency, e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

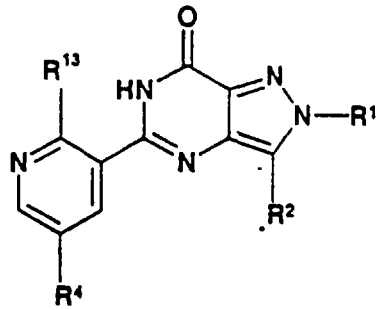
Other conditions which may be mentioned include pre-eclampsia, Kawasaki's syndrome, nitrate tolerance, multiple sclerosis, peripheral diabetic neuropathy, stroke, Alzheimer's disease, acute respiratory failure, psoriasis, skin necrosis, cancer, metastasis, baldness, nutcracker oesophagus, anal fissure and hypoxic vasoconstriction.

Particularly preferred conditions include MED and FSD.

Thus the invention provides compounds of formulae (IA) and (IB):



(IA)



(IB)

or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of either entity,

wherein R^1 is C_1 to C_3 alkyl optionally substituted with phenyl, Het or a N-linked heterocyclic group selected from piperidinyl and morpholinyl; wherein said phenyl group is optionally substituted by one or more substituents selected from C_1 to C_4 alkoxy; halo; CN; CF_3, OCF_3 or C_1 to C_4 alkyl wherein said C_1 to C_4 alkyl group is optionally substituted by C_1 to C_4 haloalkyl or C_1 to C_4 haloalkoxy either of which is substituted by one or more halo atoms;

R^2 is C_1 to C_6 alkyl;

R^{13} is OR^3 or NR^5R^6;

R^3 is C_1 to C_6 alkyl optionally substituted with one or two substituents selected from C_3 to C_5 cycloalkyl, OH, C_1 to C_4 alkoxy, benzyloxy, NR^5R^6, phenyl, furanyl and pyridinyl; C_3 to C_6 cycloalkyl; 1-(C_1 to C_4 alkyl)piperidinyl; tetrahydrofuranyl or tetrahydropyranyl; and wherein the C_1 to C_6 alkyl and C_1 to C_4 alkoxy groups may optionally be terminated by a haloalkyl group such as CF_3 ;

R^4 is $SO_2NR^7R^8$;

R^5 and R^6 are each independently selected from H and C_1 to C_4 alkyl optionally substituted with C_3 to C_5 cycloalkyl or C_1 to C_4 alkoxy, or, together with the nitrogen atom to which they are attached, form an azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl group;

R^7 and R^8, together with the nitrogen atom to which they are attached, form a 4-R^{10}-piperazinyl group optionally substituted with one or two C_1 to C_4 alkyl groups and optionally in the form of its 4-N-oxide;

R^{10} is H; C_1 to C_4 alkyl optionally substituted with one or two substituents selected from OH, NR^5R^6, $CONR^5R^6$, phenyl optionally substituted with C_1 to C_4 alkoxy, benzodioxolyl and benzodioxanyl; C_3 to C_6 alkenyl; pyridinyl or pyrimidinyl;

and Het is a C-linked 6-membered heterocyclic group containing one or two nitrogen atoms, optionally in the form of its mono-N-oxide, or a C-linked 5-membered heterocyclic group containing two or three nitrogen atoms, wherein either of said heterocyclic groups is optionally substituted with C_1 to C_4 alkyl, C_1 to C_4 alkoxy or NHR^{15} wherein R^{15} is H, C_1 to C_4 alkyl or C_1 to C_4 alkanoyl.

In the above definition, unless otherwise indicated, alkyl, alkoxy and alkenyl groups having three or more carbon atoms, and alkanoyl groups having four or more carbon atoms, may be straight chain or branched chain. The term halo atom includes, Cl, Br, F, and I. Haloalkyl and haloalkoxy are preferably CF_3 and O CF_3 respectively.

The compounds of formulae (IA) and (IB) may contain one or more chiral centres and therefore can exist as stereoisomers, i.e. as enantiomers or diastereoisomers, as well as mixtures thereof. The invention includes both the individual stereoisomers of the compounds of formulae (IA) and (IB) and any mixture thereof. Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation or chromatography (including HPLC) of a diastereoisomeric mixture of a compound of formula (IA) or (IB) or a suitable salt or derivative thereof. An individual enantiomer of a compound of formula (IA) or (IB) may be prepared from a corresponding optically pure intermediate or by resolution, either by HPLC of the racemate

using a suitable chiral support or, where appropriate, by fractional crystallisation of the diastereoisomeric salts formed by reaction of the racemate with a suitable optically active acid or base.

The compounds of formulae (IA) and (IB) may also exist in tautomeric forms and the invention includes both mixtures thereof and the individual tautomers.

Also included in the invention are radiolabelled derivatives of compounds of formulae (IA) and (IB) which are suitable for biological studies.

The pharmaceutically or veterinarily acceptable salts of the compounds of formulae (IA) and (IB) which contain a basic centre are, for example, non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acid, with carboxylic acids or with organo-sulphonic acids. Compounds of formulae (IA) and (IB) can also provide pharmaceutically or veterinarily acceptable metal salts, in particular non-toxic alkali metal salts, with bases. Examples include the sodium and potassium salts.

A preferred group of compounds of formulae (IA) and (IB) is that wherein R^1 is C_1 to C_2 alkyl optionally substituted with Het; 2-(morpholin-4-yl)ethyl or benzyl; R^2 is C_2 to C_4 alkyl; R^{13} is OR^3 or NR^5R^6; R^3 is C_1 to C_4 alkyl optionally substituted with one or two substituents selected from cyclopropyl, cyclobutyl, OH, methoxy, ethoxy, benzyloxy, NR^5R^6, phenyl, furan-3-yl, pyridin-2-yl and pyridin-3-yl; cyclobutyl; 1-methylpiperidin-4-yl; tetrahydrofuran-3-yl or tetrahydropyran-4-yl; R^5 and R^6 are each independently selected from H and C_1 to C_2 alkyl optionally substituted with cyclopropyl or methoxy, or, together with the nitrogen atom to which they are attached, form a azetidinyl, pyrrolidinyl or morpholinyl group; R^7 and R^8, together with the nitrogen atom to which they are attached, form a 4-R^{10}-piperazinyl group optionally substituted with one or two methyl groups and optionally in the form of its 4-N-oxide; R^{10} is H, C_1 to C_3 alkyl optionally substituted with one or two substituents

selected from OH, NR^5R^6, $CONR^5R^6$, phenyl optionally substituted with methoxy, benzodioxol-5-yl and benzodioxan-2-yl; allyl; pyridin-2-yl; pyridin-4-yl or pyrimidin-2-yl; and Het is selected from pyridin-2-yl; 1-oxidopyridin-2-yl; 6-methylpyridin-2-yl; 6-methoxypyridin-2-yl; pyridazin-3-yl; pyrimidin-2-yl and 1-methylimidazol-2-yl.

A more preferred group of compounds of formulae (IA) and (IB) is that wherein R^1 is C_1 to C_2 alkyl optionally substituted with Het; 2-(morpholin-4-yl)ethyl or benzyl; R^2 is C_2 to C_4 alkyl; R^{13} is OR^3; R^3 is C_1 to C_4 alkyl optionally monosubstituted with cyclopropyl, cyclobutyl, OH, methoxy, ethoxy, phenyl, furan-3-yl or pyridin-2-yl; cyclobutyl; tetrahydrofuran-3-yl or tetrahydropyran-4-yl; R^7 and R^8, together with the nitrogen atom to which they are attached, form a 4-R^{10}-piperazinyl group optionally in the form of its 4-N-oxide; R^{10} is C_1 to C_3 alkyl optionally monosubstituted with OH; and Het is selected from pyridin-2-yl; 1-oxidopyridin-2-yl; 6-methylpyridin-2-yl; 6-methoxypyridin-2-yl; pyridazin-3-yl; pyrimidin-2-yl and 1-methylimidazol-2-yl.

Particularly preferred individual compounds of the invention include
3-ethyl-5-[2-(2-methoxyethoxy)-5-(4-methylpiperazin-1-ylsulphonyl)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
3-ethyl-5-[5-(4-ethyl-4-oxidopiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-(2-methoxyethoxy)-5-(4-methylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
(+)-3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1(R)-methylethoxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1(R)-methylethoxy)pyridin-3-yl]-2-(6-methylpyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(6-methoxypyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-i-butoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-2,3-diethyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and

5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[1-(pyridin-2-yl)ethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

According to a further aspect of the present invention there are provided compounds of the formula (IA) and (IB) as defined hereinbefore but wherein R^1 is not unsubstituted C_1 alkyl; the optional substituent on the C_1 alkyl group of R^1 is not a substituted phenyl group or a N-linked heterocyclic group; the optional substituent on the C_2 or C_3 alkyl group of R^1 is not phenyl or Het; or wherein R^{13} is not NR^5R^6; or wherein the alkyl group of R^3 is not C_5 or C_6; or wherein the optional substituent on R^3 is not C_3 to C_5 cycloalkyl; or wherein neither the alkyl or the optional alkoxy substituents on R^3 are terminated by a haloalkyl group; or wherein the C_1 to C_4 alkyl groups of R^5 and R^6 are not substituted by C_3 to C_5 cycloalkyl or C_1 to C_4 alkoxy; or wherein the C_1 to C_4 alkyl groups of R^5 and R^6 do not, together with the nitrogen group to which they are attached form an azetidinyl group; or wherein Het is not a C_1 to C_4 alkoxy or an HNR^{15} group.

In a further aspect, the present invention provides processes for the preparation of compounds of formulae (IA) and (IB), their pharmaceutically and veterinarily acceptable salts, and pharmaceutically and veterinarily acceptable solvates of either entity, as illustrated below.

It will be appreciated by persons skilled in the art that, within certain of the processes described, the order of the synthetic steps employed may be varied and will depend inter alia on factors such as the nature of other functional groups present in a particular substrate, the availability of key intermediates and the protecting group strategy (if any) to be adopted. Clearly,

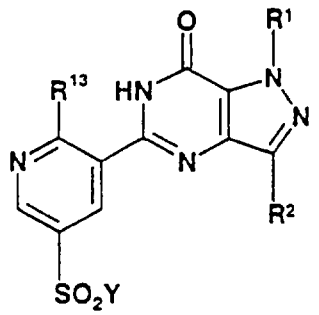
such factors will also influence the choice of reagent for use in the said synthetic steps.

Illustrative of a protecting group strategy is the route to the 2^1-(2-hydroxyethoxy) analogue (Example 33), the precursor to which (Example 32) contains benzyl as the alcohol-protecting group.

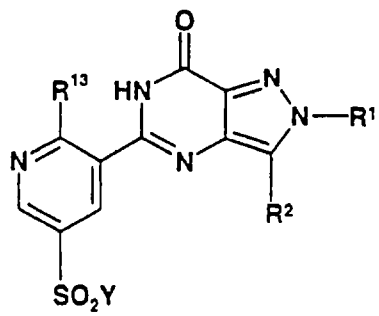
It will also be appreciated that various standard substituent or functional group interconversions and transformations within certain compounds of formulae (IA) and (IB) will provide other compounds of formulae (IA) and (IB). Examples include alkoxide exchange at the 2-position of the 5-(pyridin-3-yl) substituent (see conversions of Example 1 to Examples 4B, 9, 11, 13, 23, 24, 32 and 64, Example 2 to Example 14, Example 20 to Example 21, Example 26 to Examples 29, 65, 66, 67 and 68, Example 35 to Example 36, Example 38 to Examples 39 and 40, and Example 45 to Example 46), amine exchange at the 2-position of the 5-(pyridin-3-yl) substituent (see conversions of Example 78 to Examples 148 and 154) and piperazine and/or pyridine N-oxidation (see conversions of Example 1 to Example 70, Example 28 to Example 71, and Example 4 to Examples 72 and 73).

The following processes are illustrative of the general synthetic procedures which may be adopted in order to obtain the compounds of the invention.

1. A compound of formula (IA) or (IB) may be prepared from a compound of formula (IIA) or (IIB) respectively:



(IIA)



(IIB)

wherein Y is halo, preferably chloro, and R^1, R^2 and R^{13} are as previously defined for formulae (IA) and (IB), by reaction with a compound of formula (III):

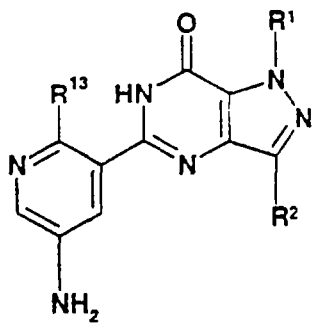
$$R^7R^8NH \qquad (III)$$

wherein R^7 and R^8 are as previously defined for formulae (IA) and (IB).

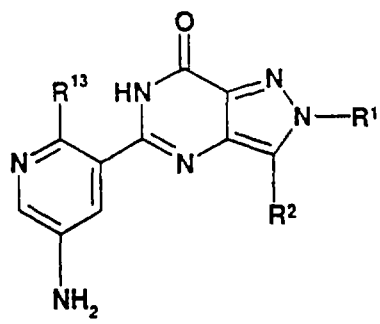
The reaction is generally conducted at from about 0°C to about room temperature, preferably in the presence of an appropriate solvent such as a C_1 to C_3 alkanol or dichloromethane, using an excess of (III) or other suitable base such as triethylamine to scavenge the acid by-product (HY).

Conveniently, this reaction lends itself to "high-speed analogue synthesis" (HSAS), as illustrated by Examples 203 to 212 in which a particular compound of formula (IIB) is coupled with a range of readily accessible amines of formula (III).

A compound of formula (IIA) or (IIB) may be prepared from a compound of formula (IVA) or (IVB) respectively:



(IVA)

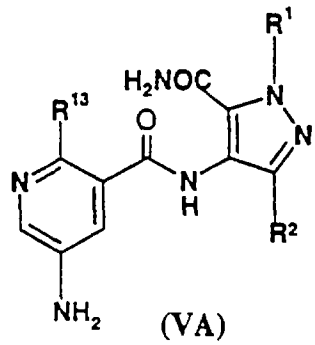


(IVB)

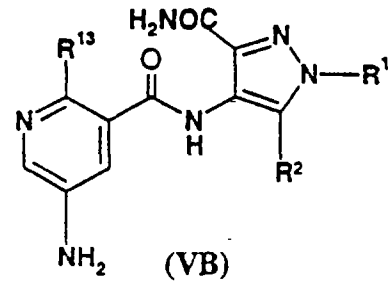
wherein R^1, R^2 and R^{13} are as previously defined for formulae (IIA) and (IIB), by the application of known methods for converting amino to a SO_2Y group wherein Y is also as previously defined for formulae (IIA) and (IIB). For example, when Y is chloro, by the action of about a two-fold excess of sodium

nitrite in a mixture of concentrated hydrochloric acid and glacial acetic acid at from about -25°C to about 0°C, followed by treatment with excess liquid sulphur dioxide and a solution of about a three-fold excess of cupric chloride in aqueous acetic acid at from about -15°C to about room temperature. When R^{13} contains a primary or secondary amino group, protection of the said amino group with an acid stable group such as acetyl or benzyl will generally be advantageous.

A compound of formula (IVA) or (IVB) may be prepared by cyclisation of a compound of formula (VA) or (VB) respectively:



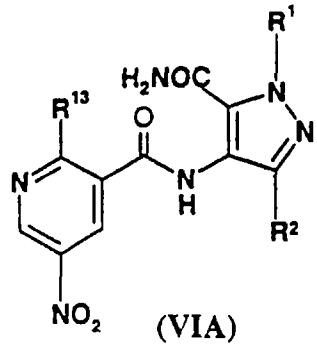
(VA)



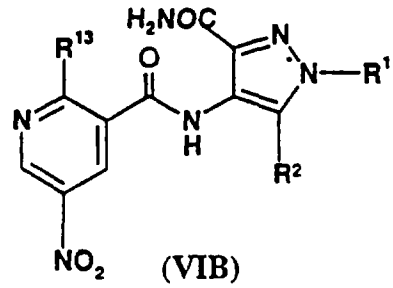
(VB)

wherein R^1, R^2 and R^{13} are as previously defined for formulae (IVA) and (IVB). Preferably, the cyclisation is base-mediated, using an alkali metal salt of a sterically hindered alcohol or amine. For example, the required cyclisation may be effected using about a 1.5 to 5, preferably a 3- to 5-fold excess of potassium t-butoxide or potassium bis(trimethylsilyl)amide, optionally in the presence of molecular sieves, in a suitable solvent at the reflux temperature of the reaction mixture, or, optionally in a sealed vessel at about 100°C. When R^{13} is OR^3 and an alcohol is selected as solvent, the appropriate alcohol of formula R^3OH should be employed in order to obviate potential problems associated with alkoxide exchange at the 2-position of the pyridine ring.

A compound of formula (VA) or (VB) may be prepared by reduction of a compound of formula (VIA) or (VIB) respectively:



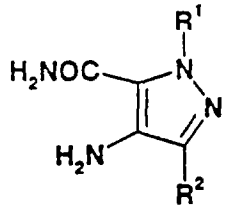
(VIA)



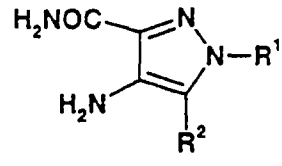
(VIB)

wherein R^1, R^2 and R^{13} are as previously defined for formulae (VA) and (VB), by conventional catalytic or catalytic transfer hydrogenation procedures. Typically, the hydrogenation is achieved using a Raney nickel catalyst or a palladium catalyst such as 10% Pd on charcoal, in a suitable solvent such as ethanol at a hydrogen pressure of from about 345 kPa (50 psi) to about 414 kPa (60 psi) at from about room temperature to about 60°C, preferably from about 40°C to about 50°C.

A compound of formula (VIA) or (VIB) may be prepared by reaction of a compound of formula (VIIA) or (VIIB) respectively:

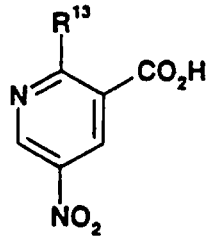


(VIIA)



(VIIB)

wherein R^1 and R^2 are as previously defined for formulae (VIA) and (VIB), with a compound of formula (VIII):



(VIII)

wherein R^{13} is also as previously defined for formulae (VIA) and (VIB). Again, as for (IVA) and (IVB), a conventional amine protecting group strategy is preferred for (VIII) when R^{13} contains a primary or secondary amino group.

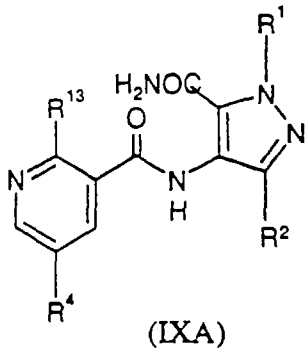
The coupling reaction may be achieved using conventional amide bond-forming techniques, e.g. via the acyl chloride derivative of (VIII) in the presence of up to about a five-fold excess of a tertiary amine such as triethylamine or pyridine to act as scavenger for the acid by-product (HY), optionally in the presence of a catalyst such as 4-dimethylaminopyridine, in a suitable solvent such as dichloromethane, at from about 0°C to about room temperature. For convenience pyridine may also be used as the solvent.

In particular, any one of a host of amino acid coupling variations may be used. For example, the acid of formula (VIII) or a suitable salt (e.g. sodium salt) thereof may be activated using a carbodiimide such as 1,3-dicyclohexylcarbodiimide or 1-ethyl-3-(3-dimethylaminoprop-1-yl)carbodiimide optionally in the presence of 1-hydroxybenzotriazole hydrate and/or a catalyst such as 4-dimethylaminopyridine, or by using a halotrisaminophosphonium salt such as bromotris(pyrrolidino)phosphonium hexafluorophosphate or by using a suitable pyridinium salt such as 2-chloro-1-methylpyridinium iodide. Either type of coupling is conducted in a suitable solvent such as dichloromethane or tetrahydrofuran, optionally in the presence of a tertiary amine such as N-methylmorpholine or N-ethyldiisopropylamine (for example when either the compound of formula (VIIA) or (VIIB), or the activating reagent, is presented in the form of an acid addition salt), at from about 0°C to about room temperature. Preferably, from 1 to 2 molecular equivalents of the activating reagent and from 1 to 3 molecular equivalents of any tertiary amine present are employed.

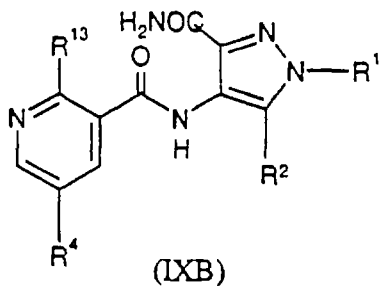
In a further variation, the carboxylic acid function of (VIII) may first of all be activated using up to about a 5% excess of a reagent such as N,N'-carbonyldiimidazole in a suitable solvent, e.g. ethyl acetate or butan-2-one, at from about room temperature to about 80°C, followed by reaction of the intermediate imidazolide with either (VIIA) or (VIIB) at from about 20°C to about 90°C.

2. An alternative, generally applicable, synthetic route to compounds of formulae (IA) and (IB) involves the incorporation of the R^4 substituent at an earlier stage of the synthesis.

Thus a compound of formula (IA) or (IB) may be prepared by cyclisation of a compound of formula (IXA) or (IXB) respectively:



(IXA)



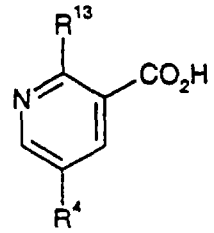
(IXB)

wherein R^1, R^2, R^{13} and R^4 are as previously defined for formulae (IA) and (IB), by analogy with the previously described cyclisation of the compounds of formulae (VA) and (VB).

Alternative reaction conditions are to conduct the reaction with about 1.2 to 4-molecular equivalents of sterically hindered base in a sealed vessel at from about 100°C to about 120°C or, rather than an alcohol of formula R^3OH, to use a sterically hindered alcohol, e.g. 3-methylpentan-3-ol, as solvent with about 1.5

to 4.5 molecular equivalents of sterically hindered base, such as potassium t-butoxide or KHMDS, and optionally in a sealed vessel at from about 120°C to about 150°C.

A compound of formula (IXA) or (IXB) may be prepared by reaction of a compound of formula (VIIA) or (VIIB) respectively, wherein R^1 and R^2 are as previously defined for formulae (IXA) and (IXB) with a compound of formula (X):



(X)

wherein R^{13} and R^4 are also as previously defined for formulae (IXA) and (IXB), by analogy with the reactions of (VIIA) or (VIIB) with the nicotinic acid derivatives of formula (VIII) already described. Compounds having the general formula (X) may be prepared directly from compounds having the general formula (VIII) by reduction and subsequent conversion to R^4 as detailed previously herein.

3. As mentioned earlier, certain compounds of formulae (IA) and (IB) can be interconverted by inducing alkoxide exchange or displacement at the 2-position of the 5-(pyridin-3-yl) substituent.

(i) When R^{13} is OR^3, this may be achieved, by treating the appropriate alcohol with an alkali metal salt of a sterically hindered alcohol or amine in order to generate the required alkoxide anion which then reacts with the substrate. Typically, in a two-step procedure, a mixture of from about 5 to about 8 molecular equivalents of potassium bis(trimethylsilyl)amide and the required alcohol as solvent is heated at from about 80°C to

about 100°C for about 0.5 to 1 hour, followed by addition of the compound of formula (IA) or (IB) and heating of the reaction mixture at from about 100°C to about 120°C. Alternatively, in a one-step procedure, the substrate may be treated directly, in the required alcohol as solvent, with from about 1.2 to about 6, preferably from about 4 to about 6 molecular equivalents of, for example, potassium bis(trimethylsilyl)amide or potassium t-butoxide at from about 80°C to about 130°C. A further variation employs the required alcohol as solvent, saturated with ammonia, at about 100°C in a sealed vessel.

(ii) When R^{13} is NR^5R^6, the substrate may be treated with an excess of R^5R^6NH, or a suitable acid addition salt thereof, in the presence of an excess of a sterically hindered amine in a suitable solvent. Typically, R^5R^6NH is used as the free base with about a 3-fold excess (over the substrate) of potassium bis(trimethylsilyl)amide (KHMDS) in dimethylformamide (DMF) as solvent at about 100°C. Alternatively, an excess of R^5R^6NH may be used as the solvent and the reaction conducted in the presence of about a 50% excess of copper(II) sulphate at up to the reflux temperature of the reaction medium. Where the desired amino substituent on the compound of the formula (IA) or (IB) is $-NR^5R^6$ and one of either R^5 or R^6 is H, then the exchange reaction may be carried out by refluxing with the appropriate amine, and copper(II)sulphate penta- or hepta-hydrate or KHDMS in DMF. Typically, to exchange the OR^3 group for alternative amines of the formula NHR^5R^6, such as compounds wherein R^5 or R^6 are selected from aliphatic or cyclic amines, optionally including oxygen, then the reaction is preferably carried out by treating with the appropriate amine and about 3 equivalents of potassium bis(trimethylsilyl)amide in DMF for about 18 hours at 100°C.

4. Clearly, for certain compounds of formulae (IA) and (IB) wherein R^{13} is OR^3, by exploiting the cyclisation and alkoxide exchange methodology described hereinbefore, it may be particularly advantageous to generate a compound of formula (IA) or (IB) from a compound of formula (IXA) or (IXB) respectively, wherein the 2-alkoxy group of the 5-(pyridin-3-yl) substituent in the former is different from that in the latter, directly in a "one-pot reaction".

When the alcohol which is to provide the new 2-alkoxy group is too scarce or expensive to be employed as the reaction solvent, then it will be expedient to use a suitable alternative such as 1,4-dioxan.

5. A further, generally applicable, synthetic route to compounds of formula (IA) and (IB) involves incorporation of the R^1 substituent in the final step of the synthesis.

Thus a compound of formula (IA) or (IB) may be prepared by alkylation of a compound of formula (IA) or (IB) wherein R^1 is hydrogen and R^2, R^{13} and R^4 are as previously defined for formulae (IA) and (IB), using one or more of a plethora of well-known methods, such as:

(i) reaction with a compound of formula R^1X, wherein R^1 is as previously defined for formulae (IA) and (IB), and X is a suitable leaving group, e.g. halo (preferably chloro, bromo or iodo), C_1-C_4 alkanesulphonyloxy, trifluoromethanesulphonyloxy or arylsulphonyloxy (such as benzenesulphonyloxy or p-toluenesulphonyloxy), in the presence of an appropriate base, optionally in the presence of sodium iodide or potassium iodide, at from about -70°C to about 100°C. Preferably the alkylation is conducted at from about room temperature to about 80°C. Suitable base-solvent combinations may be selected from

(a) sodium, potassium or caesium carbonate, sodium or potassium bicarbonate, or a tertiary amine such as triethylamine or pyridine, together with a C_1 to C_4 alkanol, 1,2-

dimethoxyethane, tetrahydrofuran, 1,4-dioxan, acetonitrile, pyridine, dimethylformamide or N,N-dimethylacetamide;

(a) sodium or potassium hydroxide, or a sodium or potassium C_1 to C_4 alkoxide, together with a C_1 to C_4 alkanol, water or mixtures thereof;

(b) lithium, sodium or potassium hydride, lithium, sodium or potassium bis(trimethylsilyl)amide, lithium diisopropylamide or butyllithium, together with toluene, ether, 1,2-dimethoxyethane, tetrahydrofuran or 1,4-dioxan; or

(d) under phase transfer catalysis conditions, a tetraalkylammonium halide or hydroxide, together with a mixture of an aqueous solution of sodium or potassium hydroxide and dichloromethane, 1,2-dichloroethane or chloroform;

(i) reaction with a compound of formula R^1OH, wherein R^1 is as previously defined for formulae (IA) and (IB), using classical Mitsunobu methodology. Typical reaction conditions involve treating the substrate with the alkanol in the presence of a triarylphosphine and a di(C_1 to C_4)alkyl azodicarboxylate, in a suitable solvent such as tetrahydrofuran or 1,4-dioxan, at from about -5°C to about room temperature.

Typically, about a 10% excess of sodium hydride is added to a solution of the substrate in a suitable solvent, e.g. anhydrous tetrahydrofuran, and the resulting anion treated with about a 10% excess of the required R^1X.

A compound of formula (IA) or (IB) wherein R^1 is hydrogen and R^2, R^{13} and R^4 are as previously defined for formulae (IA) and (IB) may be obtained from a compound of formula (IXA) or (IXB) respectively wherein R^1 is hydrogen and R^2, R^{13} and R^4 are as previously defined for formulae (IXA) and (IXB), under the same conditions as those used for the conversion of a compound of formula (IXA) or (IXB) to a compound of formula (IA) or (IB) respectively when R^1 is other than hydrogen, followed by acidification of the reaction mixture to a pH of about 6.

The amines of formula (III), the 4-aminopyrazole-5-carboxamides of formulae (VIIA) and (VIIB), the carboxylic acids of formulae (VIII) and (X), the nitriles of formula (XIII) and the esters of formula (XVI), when neither commercially available nor subsequently described, can be obtained either by analogy with the processes described in the Preparations section or by conventional synthetic procedures, in accordance with standard textbooks on organic chemistry or literature precedent, from readily accessible starting materials using appropriate reagents and reaction conditions.

Moreover, persons skilled in the art will be aware of variations of, and alternatives to, those processes described hereinafter in the Examples and Preparations sections which allow the compounds defined by formulae (IA) and (IB) to be obtained.

The pharmaceutically acceptable acid addition salts of the compounds of formulae (IA) and (IB) which contain a basic centre may also be prepared in a conventional manner. For example a solution of the free base is treated with the appropriate acid, either neat or in a suitable solvent, and the resulting salt isolated either by filtration of by evaporation under vacuum of the reaction solvent.

Pharmaceutically acceptable base addition salts can be obtained in an analogous manner by treating a solution of a compound of formula (IA) or (IB) with the appropriate base. Both types of salt may be formed or interconverted using ion-exchange resin techniques.

The biological activities of the compounds of the present invention were determined by the following test methods.

Phosphodiesterase (PDE) inhibitory activity

In vitro PDE inhibitory activities against cyclic guanosine 3',5'-monophosphate (cGMP) and cyclic adenosine 3',5'-monophosphate (cAMP) phosphodiesterases were determined by measurement of their IC_{50} values (the concentration of compound required for 50% inhibition of enzyme activity).

The required PDE enzymes were isolated from a variety of sources, including human corpus cavernosum, human and rabbit platelets, human cardiac ventricle, human skeletal muscle and bovine retina, essentially by the method of W.J. Thompson and M.M. Appleman (Biochem., 1971, 10, 311). In particular, the cGMP-specific PDE (PDE5) and the cGMP-inhibited cAMP PDE (PDE3) were obtained from human corpus cavernosum tissue, human platelets or rabbit platelets; the cGMP-stimulated PDE (PDE2) was obtained from human corpus cavernosum; the calcium/calmodulin (Ca/CAM)-dependent PDE (PDE1) from human cardiac ventricle; the cAMP-specific PDE (PDE4) from human skeletal muscle; and the photoreceptor PDE (PDE6) from bovine retina.

Assays were performed using a modification of the "batch" method of W.J. Thompson et al. (Biochem., 1979, 18, 5228). Results from these tests show that the compounds of the present invention are potent and selective inhibitors of cGMP-specific PDE5.

Functional activity

This was assessed in vitro by determining the capacity of a compound of the invention to enhance sodium nitroprusside-induced relaxation of pre-contracted rabbit corpus cavernosum tissue strips, as described by S.A. Ballard et al. (Brit. J. Pharmacol., 1996, 118 (suppl.), abstract 153P).

In vivo activity

Compounds were screened in anaesthetised dogs to determine their capacity, after i.v. administration, to enhance the pressure rises in the corpora cavernosa of the penis induced by intracavernosal injection of sodium nitroprusside, using a method based on that described by Trigo-Rocha et al. (Neurourol. and Urodyn., 1994, 13, 71).

In human therapy, the compounds of formulae (IA) and (IB), their pharmaceutically acceptable salts, and pharmaceutically acceptable solvates of either entity, can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. Preferably, they are administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or colouring agents. They can also be injected parenterally, for example intracavernosally, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example enough salts or monosaccharides to make the solution isotonic with blood. For buccal or sublingual administration they may be administered in the form of tablets or lozenges which can be formulated in a conventional manner. The compounds may also be administered intranasally or formulated for dermal application.

For oral, parenteral, buccal and sublingual administration to patients, the daily dosage level of the compounds of formulae (IA) and (IB) and their pharmaceutically acceptable salts and solvates may be from 10 to 500 mg (in single or divided doses). Thus, for example, tablets or capsules may contain from 5 to 250 mg of active compound for administration singly, or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case; there can, of course, be individual instances

where higher or lower dosage ranges are merited and such are within the scope of this invention. The skilled person will also appreciate that, in the treatment of certain conditions (including MED and FSD), compounds of the invention may be taken as a single dose on an "as required" basis (i.e. as needed or desired).

Generally, in humans, oral administration of the compounds of the invention is the preferred route, being the most convenient and, for example in MED, avoiding the well-known disadvantages associated with intracavernosal (i.c.) administration. A preferred oral dosing regimen in MED for a typical man is from 25 to 250 mg of compound when required. In circumstances where the recipient suffers from a swallowing disorder or from impairment of drug absorption after oral administration, the drug may be administered parenterally, sublingually or buccally.

For veterinary use, a compound of formula (IA) or (IB), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular animal.

Thus the invention provides a pharmaceutical composition comprising a compound of formula (IA) or (IB), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, together with a pharmaceutically acceptable diluent or carrier.

It further provides a veterinary formulation comprising a compound of formula (IA) or (IB), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, together with a veterinarily acceptable diluent or carrier.

The invention also provides a compound of formula (IA) or (IB), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, or a pharmaceutical composition containing any of the foregoing, for use as a human medicament.

In addition, it provides a compound of formula (IA) or (IB), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, or a veterinary formulation containing any of the foregoing, for use as an animal medicament.

In yet another aspect, the invention provides the use of a compound of formula (IA) or (IB), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, for the manufacture of a human medicament for the curative or prophylactic treatment of a medical condition for which a cGMP PDE5 inhibitor is indicated. There is further provided the use of a compound of formula (IA) or (IB) or a suitable salt or solvate thereof, in the manufacture of a medicament for the treatment of a medical condition in which inhibition of a cGMP PDE5 is desirable.

It also provides the use of a compound of formula (IA) or (IB), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, for the manufacture of an animal medicament for the curative or prophylactic treatment of a medical condition for which a cGMP PDE5 inhibitor is indicated.

Moreover, the invention provides the use of a compound of formula (IA) or (IB), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate containing either entity, for the manufacture of a human medicament for the curative or prophylactic treatment of male erectile dysfunction (MED), female sexual dysfunction (FSD), premature labour, dysmenorrhoea, benign prostatic hyperplasia (BPH), bladder outlet obstruction, incontinence, stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency, (e.g. post transluminal coronary angioplasty (post-PTCA)), chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility (e.g. irritable bowel syndrome (IBS)). Other conditions which may be mentioned include pre-eclampsia, Kawasaki's syndrome, nitrate tolerance, multiple sclerosis, peripheral diabetic neuropathy,

stroke, Alzheimer's disease, acute respiratory failure, psoriasis, skin necrosis, cancer, metastasis, baldness, nutcracker oesophagus, anal fissure and hypoxic vasoconstriction. Particularly preferred conditions include MED and FSD.

It also provides the use of a compound of formula (IA) or (IB), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate containing either entity, for the manufacture of an animal medicament for the curative or prophylactic treatment of male erectile dysfunction (MED), female sexual dysfunction (FSD), premature labour, dysmenorrhoea, benign prostatic hyperplasia (BPH), bladder outlet obstruction, incontinence, stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency (e.g. post-PTCA), chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility (e.g. IBS). Other conditions which may be mentioned include pre-eclampsia, Kawasaki's syndrome, nitrate tolerance, multiple sclerosis, peripheral diabetic neuropathy, stroke, Alzheimer's disease, acute respiratory failure, psoriasis, skin necrosis, cancer, metastasis, baldness, nutcracker oesophagus, anal fissure and hypoxic vasoconstriction. Particularly preferred conditions include MED and FSD.

Additionally, the invention provides a method of treating or preventing a medical condition for which a cGMP PDE5 inhibitor is indicated, in a mammal (including a human being), which comprises administering to said mammal a therapeutically effective amount of a compound of formula (IA) or (IB), or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of either entity, or a pharmaceutical composition or veterinary formulation containing any of the foregoing.

Still further, the invention provides a method of treating or preventing male erectile dysfunction (MED), female sexual dysfunction (FSD), premature labour, dysmenorrhoea, benign prostatic hyperplasia (BPH), bladder outlet obstruction, incontinence, stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced

blood vessel patency (e.g. post PTCA), chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility in a mammal (including a human being), which comprises administering to said mammal a therapeutically effective amount of a compound of formula (IA) or (IB), or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of either entity, or a pharmaceutical composition or veterinary formulation containing any of the foregoing.

The invention also includes any novel intermediates described herein, for example those of formulae (IIA), (IIB), (IVA), (IVB), (IXA), (IXB), (VA) and (VB).

The syntheses of the compounds of the invention and of the intermediates for use therein are illustrated by the following Examples and Preparations.

^{1}H Nuclear magnetic resonance (NMR) spectra were recorded using either a Varian Unity 300 or a Varian Inova 400 spectrometer and were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Mass spectra (m/z) were recorded using a Fisons Instruments Trio mass spectrometer in the thermospray ionisation mode.

Room temperature means 20 to 25°C.

EXAMPLE 1

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Alternative A

60% Sodium hydride dispersion in mineral oil (14.3mg, 0.36mmol) was added to a stirred suspension of the title compound of Preparation 44 (150mg, 0.325mmol) in anhydrous tetrahydrofuran (5ml) under nitrogen. After 1 hour, a solution of 2-(chloromethyl)pyridine (45.5mg, 0.36mmol) in tetrahydrofuran (1ml) was added and the reaction mixture heated at 40°C for 16 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residue partitioned between dichloromethane (15ml) and water (5ml). The organic phase was separated, combined with a dichloromethane extract (20ml) of the aqueous phase, dried ($MgSO_4$) and evaporated under reduced pressure. The residual yellow foam was purified by column chromatography on silica gel, using dichloromethane: methanol (97:3) as eluant, followed by HPLC using a 5μm Spherisorb silica column with water: acetonitrile: diethylamine (50:50:0.1) as eluant at a rate of 1ml/min, to give the title compound (30mg, 17%) as a white foam. δ ($CDCl_3$): 1.03 (3H,t), 1.30 (3H,t), 1.57 (3H,t), 2.40 (2H,q), 2.53 (4H,m), 3.05 (2H,q), 3.12 (4H,m), 4.75 (2H,q), 5.68 (2H,s), 7.10 (1H,d), 7.22 (1H,m), 7.64 (1H,m), 8.56 (1H,d), 8.64 (1H,s), 9.04 (1H,s), 10.65 (1H,s). LRMS: m/z 553 $(M+1)^+$.

Alternative B

A mixture of the title compound of Preparation 45B (17.4g, 30.5mmol) and potassium bis(trimethylsilyl)amide (7.28g, 36.5mmol) in ethanol (155ml) was heated at 120°C in a sealed vessel for 10 hours, allowed to cool and evaporated under reduced pressure. The residue was suspended in water (200ml), the suspension extracted with dichloromethane (2x300ml) and the

combined extracts dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel, using dichloromethane: methanol (97:3) as eluant, to give a pale yellow foam (11.2g, 66%) which was crystallised from diisopropyl ether-methanol to yield the title compound as a crystalline solid. Found: C, 55.58; H, 5.90; N, 19.58. $C_{26}H_{32}N_8O_4S$; 0.50 H_2O requires C, 55.60; H, 5.92; N, 19.95%.

EXAMPLE 2

5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

1-Methylpiperazine (0.2ml, 1.8mmol) was added dropwise to a stirred suspension of the title compound of Preparation 63 (450mg, 0.92mmol) in ethanol (40ml) and the reaction mixture stirred at room temperature for 18 hours, then evaporated under reduced pressure. The residue was partitioned between saturated aqueous sodium bicarbonate solution (30ml) and ethyl acetate (90ml), then the organic phase separated, washed with brine (2x20ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 96:4), followed by crystallisation from hexane-ethyl acetate to provide the title compound (340mg, 67%) as a white solid. Found: C, 55.90; H, 5.85; N, 20.04. $C_{26}H_{32}N_8O_4S$; 0.50 H_2O requires C, 55.60; H, 5.92; N, 19.95%. δ ($CDCl_3$): 0.94 (3H,t), 1.58 (3H,t), 1.74 (2H,m), 2.27 (3H,s), 2.40 (4H,m), 2.99 (2H,t), 3.14 (4H,m), 4.69 (2H,q), 5.68 (2H,s), 7.09 (1H,d), 7.23 (1H,m), 7.63 (1H,m), 8.58 (1H,d), 8.63 (1H,s), 9.03 (1H,s), 10.64 (1H,s). LRMS: m/z 552 $(M)^+$.

EXAMPLE 3

3-Ethyl-5-[2-(2-methoxyethoxy)-5-(4-methylpiperazin-1-ylsulphonyl)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Triethylamine (83µl, 0.59mmol) and 1-methylpiperazine (36mg, 0.356mmol) were added to a stirred, ice-cooled suspension of the title compound of Preparation 64 (150mg, 0.30mmol) in dichloromethane (10ml) and the reaction mixture stirred for 2 hours at room temperature. The resulting mixture was washed with water (5ml), dried ($MgSO_4$) and evaporated under reduced pressure to give a beige solid, which was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (98:2 to 95:5), followed by trituration with ether, to furnish the title compound (145mg, 85%) as a white solid. Found: C, 54.53; H, 5.69; N, 19.38. $C_{26}H_{32}N_8O_5S$ requires C, 54.92; H, 5.67; N, 19.71%. δ ($CDCl_3$): 1.30 (3H,t), 2.28 (3H,s), 2.50 (4H,m), 3.04 (2H,q), 3.14 (4H,m), 3.57 (3H,s), 3.86 (2H,t), 4.78 (2H,t), 5.68 (2H,s), 7.09 (1H,d), 7.22 (1H,m), 7.62 (1H,m), 8.58 (1H,d), 8.62 (1H,s), 8.97 (1H,s), 10.81 (1H,s). LRMS: m/z 569 $(M+1)^+$.

EXAMPLE 4

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Alternative A

Potassium *t*-butoxide (56mg, 0.50mmol) was added to a stirred solution of the title compound of Preparation 45A (200mg, 0.35mmol) in 2-methoxyethanol (10ml) and the reaction mixture stirred under reflux for 2 hours, then allowed to cool. Saturated aqueous ammonium chloride solution (1ml) was added, followed by water (5ml), and the mixture extracted with ethyl acetate (2x10ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure, then the residue purified by column chromatography on silica gel,

using an elution gradient of dichloromethane: methanol (100:0 to 95:5), to afford the title compound (11mg, 5%) as a solid. δ ($CDCl_3$): 1.03 (3H,t), 1.30 (3H,t), 2.41 (2H,q), 2.54 (4H,m), 3.04 (2H,q), 3.14 (4H,m), 3.56 (3H,s), 3.87 (2H,t), 4.78 (2H,t), 5.69 (2H,s), 7.10 (1H,d), 7.21 (1H,m), 7.61 (1H,m), 8.56 (1H,d), 8.62 (1H,s), 8.95 (1H,s), 10.82 (1H,s). LRMS: m/z 583 $(M+1)^+$.

Alternative B

A mixture of potassium bis(trimethylsilyl)amide (16.58g, 83mol) and 2-methoxyethanol (250ml) was stirred at 90°C for 30 minutes, then allowed to cool. The title compound of Example 1 (9.21g, 16.7mmol) was then added and the reaction mixture stirred at 110°C for 6 hours. The resulting mixture, when cool, was evaporated under reduced pressure, the residue dissolved in water (300ml) and the solution neutralised to pH 7 with 2M hydrochloric acid and then extracted with ethyl acetate (3x200ml). The combined extracts were washed with brine (3x200ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residual yellow solid was purified by column chromatography on silica gel, using dichloromethane: methanol (98:2) as eluant, followed by trituration with ether, crystallisation from ethyl acetate and recrystallisation from acetone, to afford a solvate (with acetone) of the title compound (7.7g, 79%) as colourless crystals, m.p. 171.5-173°C. Found: C, 55.59; H, 5.94; N, 18.78. $C_{27}H_{34}N_8O_5S$; 0.125 C_3H_6O requires C, 55.72; H, 5.94; N, 19.00%.

The product was suspended in water (200ml), sufficient 2M hydrochloric acid added to achieve dissolution and then the solution washed with ether (3x50ml) and neutralised with saturated aqueous sodium bicarbonate solution. The resulting precipitate was collected, washed with water and dried at 80°C to afford a hemihydrate of the title compound (5.99g, 61.6%) as a white solid, m.p.

139-140°C. Found: C, 54.74; H, 5.92; N, 18.86. $C_{27}H_{34}N_8O_5S$; 0.50 H_2O requires C, 54.81; H, 5.96; N, 18.94%.

EXAMPLE 5

3-Ethyl-5-{2-(2-methoxyethoxy)-5-[4-(prop-1-yl)piperazin-1-ylsulphonyl]-pyridin-3-yl}-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a yellow foam (88%) from the title compound of Preparation 64 and 1-(prop-1-yl)piperazine dihydrobromide, using the procedure of Example 3. Found: C, 56.12; H, 6.06; N, 18.62. $C_{28}H_{36}N_8O_5S$ requires C, 56.36; H, 6.08; N, 18.78%. δ ($CDCl_3$): 0.86 (3H,t), 1.30 (3H,t), 1.43 (2H,m), 2.30 (2H,t), 2.53 (4H,m), 3.04 (2H,q), 3.12 (4H,m), 3.57 (3H,s), 3.88 (2H,t), 4.78 (2H,t), 5.68 (2H,s), 7.10 (1H,d), 7.23 (1H,m), 7.62 (1H,m), 8.58 (1H,d), 8.62 (1H,s), 8.97 (1H,s), 10.81 (1H,s). LRMS: m/z 597 $(M+1)^+$.

EXAMPLE 6

3-Ethyl-5-{2-(2-methoxyethoxy)-5-[4-(prop-2-yl)piperazin-1-ylsulphonyl]-pyridin-3-yl}-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimdin-7-one

Obtained as a white powder (78%) from the title compound of Preparation 64 and 1-(prop-2-yl)piperazine, using the procedure of Example 3. Found: C, 55.95; H, 6.06; N, 18.46. $C_{28}H_{36}N_8O_5S$ requires C, 56.36; H, 6.08; N, 18.78%. δ ($CDCl_3$): 1.00 (6H,2xd), 1.30 (3H,t), 2.61 (4H,m), 2.68 (1H,m), 3.02 (2H,q), 3.12 (4H,m), 3.57 (3H,s), 3.86 (2H,t), 4.79 (2H,t), 5.68 (2H,s), 7.10 (1H,d), 7.22 (1H,m), 7.62 (1H,m), 8.58 (1H,d), 8.62 (1H,s), 8.97 (1H,s), 10.71 (1H,s). LRMS: m/z 597 $(M+1)^+$.

EXAMPLE 7

5-{5-[4-(2-Aminoethyl)piperazin-1-ylsulphonyl]-2-(2-methoxyethoxy)pyridin-3-yl}-3-ethyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A solution of the title compound of Preparation 64 (100mg, 0.198mmol) in dichloromethane (10ml) was added dropwise over 1 hour to a stirred solution of 1-(2-aminoethyl)piperazine (102mg, 0.79mmol) in dichloromethane (10ml) and the reaction mixture stirred for a further 1 hour at room temperature. The resulting mixture was washed with water (10ml), dried ($MgSO_4$) and evaporated under reduced pressure to give a beige solid, which was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol:0.88 ammonia (90:10:0 to 90:10:1), to yield the title compound (104mg, 88%) as a white foam. δ ($CDCl_3$): 1.29 (3H,t), 2.43 (2H,t), 2.54 (4H,m), 2.74 (2H,t), 3.04 (2H,q), 3.12 (4H,m), 3.56 (3H,s), 3.88 (2H,t), 4.79 (2H,t), 5.68 (2H,s), 7.10 (1H,d), 7.22 (1H,m), 7.63 (1H,m), 8.56 (1H,d), 8.62 (1H,s), 8.99 (1H,s). LRMS: m/z 598 $(M+1)^+$.

EXAMPLE 8

5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Potassium *t*-butoxide (104mg, 0.97mmol) was added to a stirred suspension of the title compound of Preparation 53 (380mg, 0.618mmol) in 3-methylpentan-3-ol (30ml) and the reaction mixture heated under reflux for 1 hour, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residual yellow gum partitioned between dichloromethane (20ml) and saturated aqueous sodium bicarbonate solution (10ml). The phases were separated, the aqueous phase extracted with dichloromethane (2x10ml) and the combined extracts dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by

column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (98:2 to 95:5) to provide the title compound (75mg, 13%) as a white foam. δ ($CDCl_3$): 0.93 (3H,t), 1.04 (3H,t), 1.73 (2H,m), 2.41 (2H,q), 2.54 (4H,m), 2.97 (2H,t), 3.13 (4H,m), 3.56 (3H,s), 3.86 (2H,t), 4.78 (2H,t), 5.68 (2H,s), 7.08 (1H,d), 7.21 (1H,m), 7.61 (1H,m), 8.54 (1H,d), 8.62 (1H,s), 8.97 (1H,s), 10.80 (1H,s). LRMS: m/z 597 $(M+1)^+$.

EXAMPLE 9

5-[2-(2-Ethoxyethoxy)-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A stirred mixture of potassium bis(trimethylsilyl)amide (434mg, 2.2mmol) and 2-ethoxyethanol (2ml) was heated at 90°C for 30 minutes, then allowed to cool. A solution of the title compound of Example 1 (153mg, 0.27mmol) in 2-ethoxyethanol (2ml) was added and the reaction mixture stirred at 110°C for 18 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residual brown oil purified by column chromatography on silica gel, using dichloromethane: methanol (95:5) as eluant, to furnish the title compound (110mg, 68%) as a yellow foam. δ ($CDCl_3$): 1.04 (3H,t), 1.31 (6H,m), 2.41 (2H,q), 2.54 (4H,m), 3.04 (2H,q), 3.14 (4H,m), 3.72 (2H,q), 3.90 (2H,t), 4.78 (2H,t), 5.67 (2H,s), 7.10 (1H,d), 7.22 (1H,m), 7.63 (1H,m), 8.57 (1H,d), 8.62 (1H,s), 8.99 (1H,s), 10.78 (1H,s). LRMS: m/z 597 $(M+1)^+$.

EXAMPLE 10

5-[2-(2-Ethoxyethoxy)-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A mixture of potassium *t*-butoxide (110mg, 0.98mmol), the title compound of Preparation 54 (400mg, 0.63mmol) and 3-methylpentan-3-ol (5ml) was stirred at 150°C for 3 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residue partitioned between

water (5ml) and ethyl acetate (5ml). The phases were separated, the aqueous phase extracted with ethyl acetate (2x10ml) and the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol:0.88 aqueous ammonia (99:1:0.5 to 98:2:0.5), to afford the title compound (74mg, 12%) as a white foam. Found: C, 56.92; H, 6.33; N, 17.80. $C_{29}H_{36}N_8O_5S$ requires C, 57.21; H, 5.96; N, 18.41%. δ ($CDCl_3$): 0.94 (3H,t), 1.03 (3H,t), 1.30 (3H,t), 1.72 (2H,m), 2.41 (2H,q), 2.54 (4H,m), 3.14 (4H,m), 3.72 (2H,q), 3.90 (2H,t), 4.78 (2H,t), 5.67 (2H,s), 7.09 (1H,d), 7.22 (1H,m), 7.62 (1H,m), 8.57 (1H,d), 8.62 (1H,s), 8.98 (1H,s), 10.77 (1H,s).

EXAMPLE 11

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(3-methoxyprop-1-oxy)-pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A mixture of the title compound of Example 1 (200mg, 0.36mmol), potassium bis(trimethylsilyl)amide (361mg, 1.81mmol) and 3-methoxypropan-1-ol (1.5ml) was stirred at 90°C for 18 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (97:3 to 95:5), to give the title compound (81mg, 38%) as a foam. Found: C, 55.36; H, 6.11; N, 18.18. $C_{28}H_{36}N_8O_5S$; 0.50 H_2O requires C, 55.52; H, 6.16; N, 18.50%. δ ($CDCl_3$): 1.01 (3H,t), 1.29 (3H,t), 2.19 (2H,m), 2.40 (2H,q), 2.54 (4H,m), 3.02 (2H,q), 3.12 (4H,m), 3.39 (3H,s), 3.65 (2H,t), 4.76 (2H,t), 5.68 (2H,s), 7.09 (1H,d), 7.21 (1H,m), 7.62 (1H,m), 8.56 (1H,d), 8.62 (1H,s), 8.93 (1H,s), 10.84 (1H,s). LRMS: m/z 597 $(M+1)^+$.

EXAMPLE 12

5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(3-methoxyprop-1-oxy)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a foam (26%) from the title compound of Preparation 55, using the procedure of Example 10. Found: C, 56.86; H, 6.47; N, 17.78. $C_{29}H_{38}N_8O_5S$ requires C, 57.04; H, 6.27; N, 18.35%. δ ($CDCl_3$): 0.93 (3H,t), 1.02 (3H,t), 1.72 (2H,m), 2.20 (2H,m), 2.40 (2H,q), 2.54 (4H,m), 2.97 (2H,t), 3.12 (4H,m), 3.40 (3H,s), 3.65 (2H,t), 4.77 (2H,t), 5.67 (2H,s), 7.08 (1H,d), 7.21 (1H,m), 7.61 (1H,m), 8.58 (1H,d), 8.62 (1H,s), 8.94 (1H,s), 10.83 (1H,s). LRMS: m/z 611 $(M+1)^+$.

EXAMPLE 13

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(1-methoxyprop-2(S)-oxy)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a foam (33%) from the title compound of Example 1 and 1-methoxypropan-2(S)-ol (J.Chem.Soc., Perkin Trans. I, 1996, 1467), using the procedure of Example 9, but with ether:methanol:0.88 aqueous ammonia (97:3:1) as chromatographic eluant. Found: C, 55.91; H, 6.17; N, 18.10. $C_{28}H_{36}N_8O_5S$; 0.50 H_2O requires C, 55.52; H, 6.16; N, 18.50%. δ ($CDCl_3$): 1.04 (3H,t), 1.30 (3H,t), 1.52 (3H,d), 2.42 (2H,q), 2.56 (4H,m), 3.04 (2H,q), 3.14 (4H,m), 3.55 (3H,s), 3.66 (1H,dd), 3.74 (1H,dd), 5.60 (1H,m), 5.68 (2H,s), 7.08 (1H,d), 7.21 (1H,m), 7.62 (1H,m), 8.57 (1H,d), 8.61 (1H,s), 8.89 (1H,s), 10.85 (1H,s). LRMS: m/z 597 $(M+1)^+$.

EXAMPLE 14

5-[2-(2-Methoxyethoxy)-5-(4-methylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A mixture of potassium bis(trimethylsilyl)amide (460mg, 2.3mmol) and 2-methoxyethanol (40ml) was stirred at 90°C for 30 minutes, then allowed to cool. The title compound of Example 2 (270mg, 0.46mmol) was added and the reaction mixture stirred at 110°C for 5 hours, allowed to cool and evaporated under reduced pressure. The residue was suspended in water (20ml), the pH adjusted to 7 with hydrochloric acid and the resulting solution extracted with ethyl acetate (3x30ml). The combined extracts were washed with brine (3x20ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 96:4), followed by crystallisation from hexane-ethyl acetate, to yield the title compound (200mg, 75%) as a white solid. Found: C, 54.83; H, 5.83; N, 18.90. $C_{27}H_{34}N_8O_5S$; 0.50 H_2O requires C, 54.81; H, 5.96; N, 18.94%. δ ($CDCl_3$): 0.94 (3H,t), 1.74 (2H,m), 2.28 (3H,s), 2.50 (4H,m), 2.98 (2H,t), 3.15 (4H,m), 3.57 (3H,s), 3.87 (2H,t), 4.80 (2H,t), 5.68 (2H,s), 7.08 (1H,d), 7.22 (1H,m), 7.62 (1H,m), 8.57 (1H,d), 8.64 (1H,s), 8.96 (1H,s), 10.80 (1H,s). LRMS: m/z 583 $(M+1)^+$.

EXAMPLE 15

5-[2-(1,3-Dimethoxyprop-2-oxy)-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one

A mixture of the title compound of Preparation 72 (70mg, 0.10mmol), potassium *t*-butoxide (23mg, 0.20mmol) and 3-methylpentan-3-ol (3ml) was stirred under reflux for 4 hours, then allowed to cool and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using dichloromethane: methanol (98:2) as eluant, to provide the title

compound (6mg, 9%) as an off-white solid. δ ($CDCl_3$): 0.93 (3H,t), 1.03 (3H,t), 1.72 (2H,m), 2.42 (2H,q), 2.55 (4H,m), 2.98 (2H,t), 3.16 (4H,m), 3.50 (6H,s), 3.77 (2H,m), 3.86 (2H,m), 5.68 (3H,m), 7.08 (1H,d), 7.21 (1H,m), 7.62 (1H,m), 8.57 (1H,d), 8.61 (1H,s), 8.84 (1H,s), 10.87 (1H,s). LRMS: m/z 641 $(M+1)^+$.

EXAMPLE 16

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-1-(pyridin-2-yl)methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a white solid (50%) from the title compound of Preparation 65, using the procedure of Example 10. Found: C, 55.45; H, 5.91; N, 18.94. $C_{27}H_{34}N_8O_5S$ requires C, 55.66; H, 5.88; N, 19.23%. δ ($CDCl_3$): 1.02 (3H,t), 1.40 (3H,t), 2.42 (2H,q), 2.56 (4H,m), 3.00 (2H,q), 3.16 (4H,m), 3.55 (3H,s), 3.86 (2H,t), 4.78 (2H,t), 5.95 (2H,s), 7.01 (1H,d), 7.17 (1H,m), 7.60 (1H,m), 8.57 (1H,d), 8.62 (1H,s), 9.02 (1H,s), 11.04 (1H,s). LRMS: m/z 583 $(M+1)^+$.

EXAMPLE 17

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(tetrahydrofuran-3(S)-yloxy)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a solid (29%) from the title compound of Preparation 56, using the procedure of Example 10. Found: C, 55.85; H, 5.98; N, 17.86. $C_{28}H_{34}N_8O_5S$; 0.20 H_2O; 0.10 CH_2Cl_2 requires C, 55.24; H, 5.73; N, 18.41%. δ ($CDCl_3$): 1.02 (3H,t), 1.28 (3H,t), 2.40 (4H,m), 2.55 (4H,m), 3.02 (2H,q), 3.13 (4H,m), 4.00 (2H,m) 4.16 (2H,m), 5.68 (2H,s), 5.86 (1H,m), 7.10 (1H,d), 7.22 (1H,m), 7.63 (1H,m), 8.56 (1H,d), 8.63 (1H,s), 8.98 (1H,s), 10.42 (1H,s). LRMS: m/z 594 $(M)^+$. $[\alpha]_D^{25}$ -13.8° (c = 0.10, CH_3OH).

EXAMPLE 18

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(tetrahydrofuran-3(R)-yloxy)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a solid (24%) from the title compound of Preparation 75, using the procedure of Example 10. Found: C, 55.32; H, 5.82; N, 17.70. $C_{28}H_{34}N_8O_5S$; H_2O requires C, 54.88; H, 5.92; N, 18.29%. δ ($CDCl_3$): 1.02 (3H,t), 1.28 (3H,t), 2.40 (4H,m), 2.55 (4H,m), 3.02 (2H,q), 3.13 (4H,m), 4.00 (2H,m), 4.16 (2H,m), 5.68 (2H,s), 5.86 (1H,m), 7.10 (1H,d), 7.22 (1H,m), 7.63 (1H,m), 8.56 (1H,d), 8.63 (1H,s), 8.98 (1H,s), 10.42 (1H,s). LRMS: m/z 595 $(M+1)^+$. $[\alpha]_D^{25}$ + 14.0° (c = 0.14, CH_3OH).

EXAMPLE 19

5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(tetrahydropyran-4-yloxy)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a white solid (30%) from the title compound of Preparation

76, using the procedure of Example 10. δ ($CDCl_3$): 0.94 (3H,t), 1.03 (3H,t), 1.73 (2H,m), 2.01 (2H,m), 2.22 (2H,m), 2.40 (2H,q), 2.55 (4H,m), 2.98 (2H,t), 3.12 (4H,m), 3.66 (2H,m), 4.06 (2H,m), 5.60 (1H,m), 5.69 (2H,s), 7.10 (1H,d), 7.22 (1H,m), 7.63 (1H,m), 8.57 (1H,d), 8.61 (1H,s), 9.01 (1H,s), 10.55 (1H,s). LRMS: m/z 623 $(M+1)^+$.

EXAMPLE 20

3-Ethyl-5-[5-(4-methylpiperazin-1-ylsulphonyl)-2-n-propoxypyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Potassium t-butoxide (540mg, 4.8mmol) was added to a stirred solution of the title compound of Preparation 52 (683mg, 1.2mmol) in n-propanol (10ml) and the reaction mixture stirred under reflux for 18 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residual oil purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 95:5) to furnish the title compound (290mg, 44%) as a foam. Found: C, 56.32; H, 6.04; N, 19.36. $C_{26}H_{32}N_8O_4S$ requires C, 56.50; H, 5.83; N, 20.27%. δ ($CDCl_3$): 1.02 (3H,t), 1.30 (3H,t), 1.98 (2H,m), 2.38 (3H,s), 2.50 (4H,m), 3.04 (2H,q), 3.13 (4H,m), 4.64 (2H,t), 5.69 (2H,s), 7.10 (1H,d), 7.22 (1H,m), 7.30 (1H,m), 8.58 (1H,d), 8.63 (1H,s), 9.04 (1H,s), 10.66 (1H,s). LRMS: m/z 553 $(M+1)^+$.

EXAMPLE 21

3-Ethyl-5-[5-(4-methylpiperazin-1-ylsulphonyl)-2-(prop-2-oxy)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Potassium t-butoxide (290mg, 2.60mmol) was added to a stirred solution of the title compound of Example 20 (239mg, 0.43mmol) in propan-2-ol (7ml) under nitrogen and the reaction mixture heated under reflux for 48 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residue partitioned between water (20ml) and ethyl acetate (20ml).

The phases were separated, the aqueous phase extracted with ethyl acetate and the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 95:5), to afford the title compound (84mg,35%) as a foam. δ ($CDCl_3$): 1.28 (3H,t), 1.56 (6H,2xd), 2.28 (3H,s), 2.50 (4H,m), 3.04 (2H,q), 3.14 (4H,m), 5.68 (3H,m), 7.09 (1H,d), 7.22 (1H,m), 7.62 (1H,m), 8.57 (1H,d), 8.62 (1H,s), 9.02 (1H,s), 10.68 (1H,s). LRMS: m/z 553 $(M+1)^+$.

EXAMPLE 22

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(prop-2-oxy)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A mixture of the title compound of Preparation 45A (200mg, 0.35mmol), 60% sodium hydride dispersion in mineral oil (400mg, 10mmol) and propan-2-ol (20ml) was stirred under reflux for 18 hours, then allowed to cool. Saturated aqueous ammonium chloride solution (20ml) was added, the resulting mixture extracted with ethyl acetate (3x50ml), then the combined extracts washed with aqueous sodium bicarbonate solution (150ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 95:5), to give the title compound (11mg, 6%) as a foam. δ ($CDCl_3$): 1.04 (3H,t), 1.30 (3H,t), 1.56 (6H,2xd), 2.1 (2H,q), 2.55 (4H,m), 3.04 (2H,q), 3.13 (4H,m), 5.68 (3H,m), 7.10 (1H,d), 7.22 (1H,m), 7.62 (1H,m), 8.57 (1H,d), 8.62 (1H,s), 9.02 (1H,s), 10.68 (1H,s). LRMS: m/z 567 $(M+1)^+$.

EXAMPLE 23

5-[2-n-Butoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A mixture of the title compound of Example 1 (200mg, 0.36mmol), potassium bis(trimethylsilyl)amide (360mg, 1.81mmol) and n-butanol (5ml) was stirred at 100°C for 18 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residue partitioned between water (5ml) and dichloromethane (5ml). The phases were separated and the aqueous layer extracted with dichloromethane (2x10ml), then the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. The residual yellow solid was purified by column chromatography on silica gel, using dichloromethane: methanol (97.5:2.5) as eluant, to yield the title compound (145 mg, 69%) as a white solid. Found: C, 57.43; H, 6.29; N, 18.82. $C_{28}H_{36}N_8O_4S$, 0.20 H_2O requires C, 57.56; H, 6.28; N, 19.18%. δ ($CDCl_3$): 1.03 (6H,2xt), 1.30 (3H,t), 1.55 (2H,m), 1.94 (2H,m), 2.40 (2H,q), 2.55 (4H,m), 3.03 (2H,q), 3.13 (4H,m), 4.67 (2H,t), 5.68 (2H,s), 7.10 (1H,d), 7.22 (1H,m), 7.62 (1H,m), 8.56 (1H,d), 8.62 (1H,s), 9.01 (1H,s), 10.64 (1H,s). LRMS: m/z 581 $(M+1)^+$.

EXAMPLE 24

5-[2-i-Butoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a white solid (67%) from the title compound of Example 1 and i-butanol, using the procedure of Example 23. Found: C, 57.25; H, 6.24; N, 18.84. $C_{28}H_{36}N_8O_4S$; 0.20 H_2O requires C, 57.56; H, 6.28; N, 19.18%. δ ($CDCl_3$): 1.03 (3H,t), 1.12 (6H,d), 1.30 (3H,t), 2.30 (1H,m), 2.40 (2H,q), 2.55 (4H,m), 3.04 (2H,q), 3.13 (4H,m), 4.45 (2H,d), 5.68 (2H,s), 7.10 (1H,d), 7.22 (1H,m), 7.63 (1H,m), 8.58 (1H,d), 8.62 (1H,s), 9.02 (1H,s), 10.63 (1H,s). LRMS: m/z 581 $(M+1)^+$.

EXAMPLE 25

5-[2-Cyclobutoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A stirred mixture of the title compound of Preparation 45A (200mg, 0.35mmol), cyclobutanol (144mg, 2mmol), potassium t-butoxide (80mg, 0.70mmol) and 1,4-dioxan (5ml) was heated under reflux for 24 hours, then allowed to cool. The resulting mixture was poured into stirred aqueous sodium bicarbonate solution (20ml) and this mixture extracted with ethyl acetate (3x20ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure, then the residue purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 96:4), to provide the title compound (9 mg, 4%) as a solid. δ ($CDCl_3$): 1.03 (3H,t), 1.29 (3H,t), 1.78 (2H,m), 1.98 (2H,m), 2.35 (2H,m), 2.55 (6H,m), 3.04 (2H,q), 3.12 (4H,m), 5.48 (1H,m), 5.68 (2H,s), 7.10 (1H,d), 7.23 (1H,m), 7.63 (1H,m), 8.56 (1H,d), 8.60 (1H,s), 9.01 (1H,s), 10.67 (1H,s). LRMS: m/z 579 $(M+1)^+$.

EXAMPLE 26

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Potassium t-butoxide (2.38g, 21.2mmol) was added to a solution of the title compound of Preparation 77 (3.1g, 5.3mmol) in absolute ethanol (95ml) and the reaction mixture heated at 100°C in a sealed vessel for 40 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure, the residue dissolved in water (20ml) and the aqueous solution acidified to pH 5 with 2M hydrochloric acid. The aqueous suspension thus obtained was extracted with dichloromethane (3x30ml) and the combined extracts dried ($MgSO_4$) and evaporated under reduced pressure. The residual brown foam was purified by column chromatography on silica gel, using an elution gradient

of dichloromethane: methanol (99:1 to 97:3), to furnish the title compound (1.39 g, 46%) as a foam. δ ($CDCl_3$): 0.93 (3H,t), 1.02 (3H,t), 1.58 (3H,t), 1.74 (2H,m), 2.40 (2H,q), 2.54 (4H,m), 2.98 (2H,t), 3.13 (4H,m), 4.75 (2H,q), 5.68 (2H,s), 7.09 (1H,d), 7.23 (1H,m), 7.63 (1H,m), 8.58 (1H,d), 8.63 (1H,s), 9.02 (1H,s), 10.64 (1H,s).

EXAMPLE 27

5-{5-[4-(3-Dimethylaminoprop-1-yl)piperazin-1-ylsulphonyl]-2-ethoxypyridin-3-yl}-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one trihydrochloride

A solution of freshly distilled 1-(3-dimethylaminoprop-1-yl)piperazine (J.Chem.Soc. (C), 1971, 132; 160mg, 0.93mmol) in ethanol (2ml) was added to a stirred solution of the title compound of Preparation 63 (230mg, 0.467mmol) in ethanol (10ml) and the reaction mixture stirred at room temperature for 18 hours, then evaporated under reduced pressure. The residue was suspended in aqueous sodium bicarbonate solution (30ml), the suspension extracted with ethyl acetate (3x30ml) and the combined extracts washed with brine (2x30ml), dried (Na_2SO_4), and evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 90:10), then the product dissolved in the minimum volume of ethyl acetate. Saturated ethereal hydrogen chloride solution was added and the resulting white precipitate collected, triturated with ether and dried under suction to afford the title compound (140mg, 37%) as a white solid. Found: C, 44.45; H, 6.34; N, 15.38. $C_{30}H_{41}N_9O_4S$; 3HCl; $4H_2O$ requires C, 44.75; H, 6.51; N, 15.66%. δ ($DMSOd_6$): 0.86 (3H,t), 1.34 (3H,t), 1.64 (2H,m), 2.12 (2H,m), 2.72 (6H,2xs), 2.95 (2H,t), 3.00 (2H,m), 3.12 (2H,t), 3.18 (2H,m), 3.56 (2H,m), 3.84 (2H,m), 4.50 (2H,q), 5.75 (2H,s), 7.27 (1H,d), 7.42 (1H,m), 7.90 (1H,m), 8.28 (1H,s), 8.57 (1H,d), 8.73 (1H,s), 10.63 (1H,s), 11.47 (1H,s), 11.96 (1H,s). LRMS: m/z 624 $(M+1)^+$.

EXAMPLE 28

5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-n-propoxypyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a colourless solid (40%) from the title compound of Preparation 80, using the procedure of Example 20. Found: C, 57.16; H, 6.15; N, 18.85. $C_{28}H_{36}N_8O_4S$; 0.50 H_2O requires C, 57.03; H, 6.32; N, 19.00%. δ ($CDCl_3$): 0.94 (3H,t), 1.02 (3H,t), 1.13 (3H,t), 1.74 (2H,m), 1.98 (2H,m), 2.40 (2H,q), 2.54 (4H,m), 2.98 (2H,t), 3.12 (4H,m), 4.62 (2H,t), 5.66 (2H,s), 7.09 (1H,d), 7.21 (1H,m), 7.62 (1H,m), 8.57 (1H,d), 8.62 (1H,s), 9.02 (1H,s), 10.63 (1H,s). LRMS: m/z 582 $(M+2)^+$.

EXAMPLE 29

5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(prop-2-oxy)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a solid (48%) from the title compound of Example 26 and propan-2-ol, using the procedure of Example 21. δ ($CDCl_3$): 0.94 (3H,t), 1.03 (3H,t), 1.57 (6H,d), 1.74 (2H,m), 2.41 (2H,q), 2.56 (4H,m), 2.98 (2H,t), 3.12 (4H,m), 5.68 (3H,m), 7.08 (1H,d), 7.22 (1H,m), 7.63 (1H,m), 8.57 (1H,d), 8.63 (1H,s), 9.02 (1H,s), 10.67 (1H,s). LRMS: m/z 581 $(M+1)^+$.

EXAMPLE 30

5-[2-Ethoxy-5-[4-(2-hydroxyethyl)piperazin-1-ylsulphonyl]pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a white solid (49%) from the title compound of Preparation 63 and 1-(2-hydroxyethyl)piperazine, using the procedure of Example 2. Found: C, 55.48; H, 5.93; N, 18.85. $C_{27}H_{34}N_8O_5S$; 0.10 $C_4H_8O_2$ requires C, 55.64; H, 5.93; N, 18.94%. δ ($CDCl_3$): 0.95 (3H,t), 1.59 (3H,t), 1.75 (2H,m), 2.28 (1H,s), 2.58 (2H,m), 2.65 (4H,m), 3.00 (2H,t), 3.16 (4H,m), 3.60 (2H,t), 4.76 (2H,q), 5.68 (2H,s), 7.10 (1H,d), 7.22 (1H,m), 7.62 (1H,m), 8.58 (1H,d), 8.64 (1H,s), 9.04 (1H,s), 10.66 (1H,s). LRMS: m/z 583 $(M+1)^+$.

EXAMPLE 31

5-[2-Ethoxy-5-[4-(3-hydroxyprop-1-yl)piperazin-1-ylsulphonyl]pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a white solid (52%) from the title compound of Preparation 63 and 1-(3-hydroxyprop-1-yl)piperazine, using the procedure of Example 2. Found: C, 56.27; H, 6.13; N, 18.38. $C_{28}H_{36}N_8O_5S$ requires C, 56.36; H, 6.08; N, 18.78%. δ ($CDCl_3$): 0.94 (3H,t), 1.60 (3H,t), 1.72 (4H,m), 2.63 (6H,m), 2.98 (2H,t), 3.12 (4H,m), 3.72 (2H,t), 4.15 (1H,s), 4.77 (2H,q), 5.69 (2H,s), 7.08 (1H,d), 7.23 (1H,m), 7.63 (1H,m), 8.58 (1H,d), 8.61 (1H,s), 9.01 (1H,s), 10.67 (1H,s). LRMS: m/z 596 $(M)^+$.

EXAMPLE 32

5-[2-(2-Benzyloxyethoxy)-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a yellow oil (57%) from the title compound of Example 1 and 2-benzyloxyethanol, using the procedure of Example 11. δ ($CDCl_3$): 1.02 (3H,t), 1.32 (3H,t), 2.40 (2H,q), 2.54 (4H,m), 3.04 (2H,q), 3.13 (4H,m), 3.94 (2H,t), 4.76 (2H,s), 4.80 (2H,t), 5.69 (2H,s), 7.11 (1H,d), 7.20-7.37 (4H,m), 7.41 (2H,m), 7.64 (1H,m), 8.60 (2H,m), 8.98 (1H,s), 10.80 (1H,s). LRMS: m/z 659 $(M+1)^+$.

EXAMPLE 33

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-hydroxyethoxy)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Ammonium formate (62mg, 0.99mmol) was added to a mixture of the title compound of Example 32 (130mg, 0.197mmol), 10% palladium on charcoal (15mg) and acetone (9ml) and the reaction mixture stirred under reflux for 14 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 90:10), to

give the title compound (18mg, 16%) as a solid. δ (CD_3OD): 1.06 (3H,t), 1.28 (3H,t), 2.44 (2H,q), 2.58 (4H,m), 3.06 (2H,q), 3.14 (4H,m), 3.97 (2H,t), 4.68 (2H,t), 5.75 (2H,s), 7.20 (1H,d), 7.36 (1H,m), 7.80 (1H,m), 8.54 (2H,m), 8.68 (1H,s). LRMS: m/z 569 $(M+1)^+$.

EXAMPLE 34

5-[2-(2-Benzyloxyethoxy)-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A stirred mixture of the title compound of Preparation 84 (500mg, 0.72mmol), potassium bis(trimethylsilyl)amide (347mg, 3.09mmol) and 3-methylpentan-3-ol (8ml) was heated under reflux for 36 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residue partitioned between water (10ml) and dichloromethane (10ml). The phases were separated, the aqueous phase extracted with dichloromethane (2x10ml) and the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by two column chromatography operations on silica gel, using firstly dichloromethane: methanol:0.88 aqueous ammonia (90:10:1) and then a gradient of ethyl acetate: methanol (100:0 to 80:20) as eluants, to yield the title compound as an oil. δ ($CDCl_3$): 0.92 (3H,t), 1.02 (3H,t), 1.73 (2H,m), 2.40 (2H,q), 2.54 (4H,m), 2.99 (2H,t), 3.10 (4H,m), 3.84 (2H,t), 4.58 (2H,s), 4.78 (2H,t), 5.68 (2H,s), 7.09 (1H,d), 7.18-7.42 (6H,m), 7.62 (1H,m), 8.55 (1H,d), 8.61 (1H,s), 8.97 (1H,s), 10.81 (1H,s). LRMS: m/z 673 $(M+1)^+$.

EXAMPLE 35

2-Benzyl-5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a white foam (27%) from the title compound of Preparation 87, using the procedure of Example 10. δ ($CDCl_3$): 0.90 (3H,t), 1.03 (3H,t), 1.28 (3H,t), 2.40 (2H,q), 2.54 (4H,m), 2.94 (2H,q), 3.12 (4H,m), 4.75 (2H,q), 5.58 (2H,s), 7.22 (2H,m), 7.31 (3H,m), 8.62 (1H,s), 9.01 (1H,s), 10.65 (1H,s). LRMS: m/z 552 $(M+1)^+$.

EXAMPLE 36

2-Benzyl-3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a cream foam (80%) from the title compound of Example 35 and 2-methoxyethanol, using the procedure of Example 9. Found: C, 57.05; H, 6.19; N, 16.15. $C_{28}H_{35}N_7O_5S$; 0.10 CH_2Cl_2 requires C, 57.19; H, 6.01; N, 16.61%. δ ($CDCl_3$): 1.02 (3H,t), 1.27 (3H,t), 2.40 (2H,q), 2.55 (4H,m), 2.94 (2H,q), 3.13 (4H,m), 3.57 (3H,s), 3.86 (2H,t), 4.78 (2H,t), 5.56 (2H,s), 7.22 (2H,m), 7.32 (3H,m), 8.61 (1H,s), 8.96 (1H,s), 10.80 (1H,s).

EXAMPLE 37

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-(1-methylimidazol-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a foam (33%) from the title compound of Preparation 90, using the procedure of Example 10. δ ($CDCl_3$): 1.05 (3H,t), 1.34 (3H,t), 2.41 (2H,q), 2.54 (4H,m), 3.13 (4H,m), 3.19 (2H,q), 3.57 (3H,s), 3.79 (3H,s), 3.86 (2H,t), 4.78 (2H,t), 5.65 (2H,s), 6.84 (1H,s), 7.00 (1H,s), 8.62 (1H,s), 8.94 (1H,s), 10.83 (1H,s). LRMS: m/z 586 $(M+1)^+$.

EXAMPLE 38

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-2-(1-methylimidazol-2-yl)methyl-3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A mixture of the title compounds of Preparation 28 (232mg, 0.58mmol) and Preparation 92 (152mg, 0.58mmol), triethylamine (403µl, 2.9mmol) and dichloromethane (8ml) was stirred at room temperature for 18 hours. Brine (20ml) was added and the resulting mixture extracted with dichloromethane (2x20ml), then the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure.

A stirred solution of this intermediate and potassium bis(trimethylsilyl)amide (305mg, 1.53mmol) in ethanol (10ml) was heated at 100°C for 14 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using dichloromethane: methanol (95:5) as eluant, to provide the title compound (163mg, 49%) as a yellow oil. δ ($CDCl_3$): 0.96 (3H,t), 1.01 (3H,t), 1.57 (3H,t), 1.72 (2H,m), 2.40 (2H,q), 2.55 (4H,m), 3.13 (6H,m), 3.77 (3H,s), 4.75 (2H,q), 5.67 (2H,s), 6.85 (1H,s), 7.00 (1H,s), 8.63 (1H,s), 9.00 (1H,s), 10.65 (1H,s). LRMS: m/z 570 $(M+1)^+$.

EXAMPLE 39

5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-(1-methylimidazol-2-yl)methyl-3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a solid (61%) from the title compound of Example 38 and 2-methoxyethanol, using the procedure of Example 9. δ ($CDCl_3$): 0.97 (3H,t), 1.02 (3H,t), 1.74 (2H,m), 2.41 (2H,q), 2.55 (4H,m), 3.14 (6H,m), 3.57 (3H,s), 3.76 (3H,s), 3.86 (2H,t), 4.78 (2H,t), 5.66 (2H,s), 6.86 (1H,s), 7.00 (1H,s), 8.62 (1H,s), 8.94 (1H,s), 10.82 (1H,s). LRMS: m/z 600 $(M+1)^+$.

EXAMPLE 40

5-[2-n-Butoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-2-(1-methylimidazol-2-yl)methyl-3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a cream coloured foam (76%) from the title compound of Example 38 and n-butanol, using the procedure of Example 9. Found: C, 54.83; H, 6.74; N, 20.08. $C_{28}H_{39}N_9O_4S$; H_2O requires C, 54.62; H, 6.71; N, 20.47%. δ ($CDCl_3$): 0.93 (3H,t), 1.00 (6H,m), 1.54 (2H,m), 1.77 (2H,m), 1.92 (2H,m), 2.40 (2H,q), 2.53 (4H,m), 3.12 (6H,m), 3.76 (3H,s), 4.66 (2H,t,), 5.67 (2H,s), 6.85 (1H,s), 6.98 (1H,s), 8.62 (1H,s), 8.97 (1H,s), 10.64 (1H,s). LRMS: m/z 599 $(M+2)^+$.

EXAMPLE 41

5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(prop-2-oxy)pyridin-3-yl]-3-n-propyl-2-(pyridazin-3-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A mixture of the title compound of Preparation 98 (230mg, 0.38mmol), potassium t-butoxide (258mg, 2.3mmol) and propan-2-ol (10ml) was heated in a sealed vessel at 100°C for 24 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure, then the residue purified by two column chromatography operations on silica gel, using firstly an elution gradient of dichloromethane: methanol (100:0 to 95:5) and then an elution gradient of ethyl acetate: methanol (90:10 to 80:20), to furnish the title compound (42mg, 19%) as an orange gum. δ ($CDCl_3$): 0.93 (3H,t), 1.01 (3H,t), 1.55 (6H,d), 1.75 (2H,m), 2.40 (2H,q), 2.54 (4H,m), 3.02 (2H,t), 3.12 (4H,m), 5.67 (1H,m), 5.88 (2H,s), 7.47 (2H,m), 8.60 (1H,s), 8.98 (1H,s), 9.16 (1H,d), 10.70 (1H,s). LRMS: m/z 582 $(M+1)^+$.

EXAMPLE 42

5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-3-n-propyl-2-(pyrimidin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a yellow foam (14%) from the title compound of Preparation 102b, using the procedure of Example 10. δ ($CDCl_3$): 0.99 (3H,t), 1.03 (3H,t), 1.81 (2H,m), 2.42 (2H,q), 2.55 (4H,m), 2.97 (2H,t), 3.14 (4H,m), 3.54 (3H,s), 3.86 (2H,t), 4.78 (2H,t), 5.80 (2H,s), 7.22 (1H,m), 8.62 (1H,s), 8.70 (2H,d), 8.99 (1H,s), 10.72 (1H,s). LRMS: m/z 597 $(M)^+$.

EXAMPLE 43a

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-n-propyl-1-(pyrimidin-2-yl)methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

and

EXAMPLE 43b

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-n-propyl-2-(pyrimidin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A stirred mixture of the title compounds of Preparation 103a and Preparation 103b (390mg, 0.66mmol), potassium t-butoxide (224mg, 2.0mmol), 4Å molecular sieves and ethanol (10ml) was heated in a sealed vessel for 18 hours at 100°C , then allowed to cool and filtered. The filtrate was evaporated under reduced pressure and the residual brown oil suspended in dichloromethane (25ml). This mixture was washed with water (5ml), dried ($MgSO_4$) and evaporated under reduced pressure, then the residue purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (99:1 to 95:5) to give an orange foam. This product was further purified by HPLC using a C_{18} Magellan column and

methanol: water:diethylamine (50:50:0.1) as eluant, at a rate of 20ml/min, to afford the first title compound (1-isomer; 20mg) as a white solid. δ ($CDCl_3$): 1.04 (6H,m), 1.58 (3H,t), 1.88 (2H,m), 2.42 (2H,q), 2.57 (4H,m), 2.98 (2H,t), 3.14 (4H,m), 4.75 (2H,q), 6.07 (2H,s), 7.18 (1H,m), 8.64 (3H,m), 9.10 (1H,s), 10.75 (1H,s). LRMS: m/z 568 $(M+1)^+$;

followed by the second title compound (2-isomer; 20mg) as a white solid. δ ($CDCl_3$): 1.02 (6H,m), 1.58 (3H,t), 1.82 (2H,m), 2.42 (2H,q), 2.55 (4H,m), 2.98 (2H,t), 3.15 (4H,m), 4.74 (2H,q), 5.80 (2H,s), 7.23 (1H,m), 8.63 (1H,s), 8.70 (2H,m), 9.03 (1H,s), 10.56 (1H,s). LRMS: m/z 568 $(M+1)^+$.

EXAMPLE 44

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-n-propyl-1-(pyridin-2-yl)methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A stirred mixture of the title compound of Preparation 105 (304mg, 0.52mmol), potassium t-butoxide (175mg, 1.56mmol) and ethanol (10ml) was heated in a sealed vessel at 100°C for 18 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residual brown oil partitioned between dichloromethane (15ml) and water (5ml). The phases were separated, then the organic phase dried ($MgSO_4$) and evaporated under reduced pressure to give a brown foam, which was purified by column chromatography on silica gel, using dichloromethane: methanol (97:3) as eluant, to provide the title compound (230mg, 78%) as a white foam. Found: C, 56.93; H, 6.03; N, 19.42. $C_{27}H_{34}N_8O_4S$ requires C, 57.22; H, 6.04; N, 19.77%. δ ($CDCl_3$) 1.01 (3H,t), 1.59 (6H,m), 1.86 (2H,m), 2.42 (2H,q), 2.57 (4H,m), 2.97 (2H,t), 3.16 (4H,m), 4.74 (2H,q), 5.94 (2H,s), 7.02 (1H,d), 7.18 (1H,m), 7.60 (1H,m), 8.57 (1H,d), 8.63 (1H,s), 9.10 (1H,s), 10.85 (1H,s). LRMS: m/z 567 $(M+1)^+$.

EXAMPLE 45

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-1-(1-methylimidazol-2-yl)methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a pale yellow solid (60%) from the title compound of Preparation 107, using the procedure of Example 44. δ ($CDCl_3$): 1.02 (3H,t), 1.38 (3H,t), 1.59 (3H,t), 2.41 (2H,q), 2.56 (4H,m), 2.97 (2H,q), 3.15 (4H,m), 3.78 (3H,s), 4.75 (2H,q), 5.89 (2H,s), 6.85 (1H,s), 7.00 (1H,s), 8.64 (1H,s), 9.07 (1H,s), 10.87 (1H,s). LRMS: m/z 556 $(M+1)^+$.

EXAMPLE 46

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-1-(1-methylimidazol-2-yl)methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A stirred mixture of the title compound of Example 45 (150mg, 0.27mmol), potassium t-butoxide (126mg, 1.1mmol) and 2-methoxyethanol (6ml) was heated under reflux for 48 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using dichloromethane:methanol:0.88 aqueous ammonia (90:10:1) as eluant. The product was triturated with diisopropyl ether, the mixture filtered and the filtrate evaporated under reduced pressure to yield the title compound (43mg, 27%) as a foam. δ ($CDCl_3$): 1.10 (3H,t), 1.36 (3H,t), 2.52 (2H,q), 2.65 (4H,m), 2.96 (2H,q), 3.22 (4H,m), 3.56 (3H,s), 3.75 (3H,s), 3.86 (2H,t), 4.78 (2H,t), 5.92 (2H,s), 6.85 (1H,s), 7.01 (1H,s), 8.63 (1H,s), 8.99 (1H,s), 11.10 (1H,s). LRMS: m/z 585 $(M)^+$.

EXAMPLE 47

5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-1-(1-methylimidazol-2-yl)methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a solid (11%) from the title compound of Preparation 109, using the procedure of Example 10. Found: C, 52.43; H, 6.11; N, 20.12.

$C_{27}H_{37}N_9O_5S$; H_2O requires C, 52.50; H, 6.36; N, 20.41%. δ ($CDCl_3$): 0.98 (3H,t), 1.03 (3H,t), 1.81 (2H,m), 2.41 (2H,q), 2.55 (4H,m), 2.90 (2H,t), 3.15 (4H,m), 3.58 (3H,s), 3.75 (3H,s), 3.86 (2H,t), 4.78 (2H,t), 5.92 (2H,s), 6.85 (1H,s), 7.00 (1H,s), 8.63 (1H,s), 9.00 (1H,s), 11.07 (1H,s). LRMS: m/z 600 $(M+1)^+$.

EXAMPLE 48

5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-3-n-propyl-1-(pyrimidin-2-yl)methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a yellow foam (5%) from the title compound of Preparation 102a, using the procedure of Example 10. δ ($CDCl_3$): 1.02 (6H,m), 1.86 (2H,m), 2.42 (2H,q), 2.56 (4H,m), 2.97 (2H,t), 3.17 (4H,m), 3.54 (3H,s), 3.83 (2H,t), 4.77 (2H,t), 6.09 (2H,s), 7.16 (1H,m), 8.65 (3H,m), 9.03 (1H,s), 11.00 (1H,s). LRMS: m/z 598 $(M+1)^+$.

EXAMPLE 49

5-{2-Ethoxy-5-[4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-ylsulphonyl]pyridin-3-yl}-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A mixture of the title compound of Preparation 63 (350mg, 0.715mmol), 1-(pyrrolidin-1-ylcarbonylmethyl)piperazine (150mg, 0.715mmol) and ethanol (40ml) was stirred at room temperature for 18 hours, then evaporated under reduced pressure. The residue was suspended in aqueous sodium bicarbonate solution (30ml) and the suspension extracted with ethyl acetate (3x30ml). The combined extracts were washed with brine (3x20ml), dried (Na_2SO_4) and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 96:4) to give an oil, which was triturated with ether to furnish the title compound (240mg, 52%) as a colourless foam.

Found: C, 56.79; H, 6.30; N, 18.49. $C_{31}H_{39}N_9O_5S$; 0.50 H_2O; 0.25 $C_4H_{10}O$ requires C, 56.75; H, 6.32; N, 18.61%. δ ($CDCl_3$): 0.94 (3H,t), 1.60 (3H,t), 1.66-1.86 (4H,m), 1.92 (2H,m), 2.68 (4H,m), 2.98 (2H,t), 3.14 (2H,s), 3.18 (4H,m), 3.32-3.46 (4H,m), 4.75 (2H,q), 5.70 (2H,s), 7.18 (1H,d), 7.22 (1H,m), 7.62 (1H,m), 8.58 (1H,d), 8.63 (1H,s), 9.00 (1H,s), 10.66 (1H,s). LRMS: m/z 650 $(M+1)^+$.

EXAMPLE 50

5-[2-Ethoxy-5-(4-allyl-2(S),5(R)-dimethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

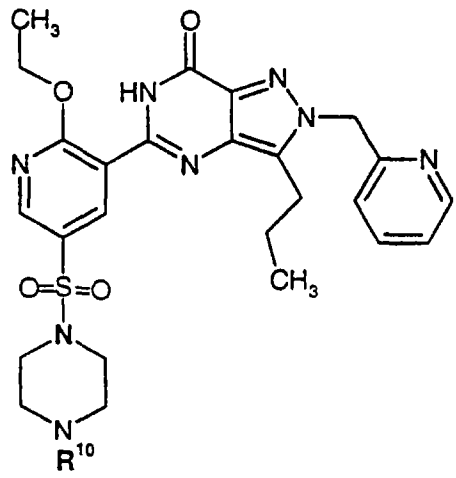
A solution of (-)-1-allyl-2(R),5(S)-dimethylpiperazine (WO 93/15062; 502mg, 3.2mmol) in ethanol (4ml) was added dropwise to a stirred suspension of the title compound of Preparation 63 (800mg, 1.6mmol) in ethanol and the reaction mixture stirred at room temperature for 18 hours, then evaporated under reduced pressure. The residue was partitioned between aqueous sodium carbonate solution (20ml) and ethyl acetate (20ml), the phases separated and the aqueous phase extracted with ethyl acetate (2x20ml). The combined organic solutions were washed with brine (20ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residual orange oil was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 98:2), followed by trituration with ether, to afford the title compound (550mg, 57%) as a colourless foam. Found: C, 59.07; H, 6.37; N, 18.18. $C_{30}H_{38}N_8O_4S$ requires C, 59.39; H, 6.31; N, 18.47%. δ ($CDCl_3$): 0.95 (3H,t), 0.99 (3H,d), 1.24 (3H,d), 1.58 (3H,t), 1.72 (2H,m), 2.27 (1H,dd), 2.73 (1H,dd), 2.92 (1H,m), 3.00 (4H,m), 3.20 (1H,dd), 3.48 (1H,dd), 3.85 (1H,m), 4.75 (2H,q), 5.22 (2H,m), 5.68 (2H,s), 5.74 (1H,m), 7.09 (1H,d), 7.22 (1H,m), 7.62 (1H,m), 8.58 (1H,d), 8.67 (1H,s), 9.08 (1H,s), 10.69 (1H,s). LRMS: m/z 607 $(M+1)^+$.

Example 50a

3-Ethyl-5-[5-(4-ethylpiperazine-1-ylsulphonyl)-2-(2-methoxy-1(R)-methylethoxy)pyridin-3-yl]-2-(1-methylimidazol-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a white foam (82%), from the title compounds of Preparations 165 and 170, following a similar procedure to that described in Example 11. Found: C, 52.14; H, 6.15; N, 19.73. $C_{27}H_{37}N_9O_5S;1.5H_2O$ requires C, 51.74; H, 6.43; N, 20.11%. δ ($CDCl_3$) : 1.02 (3H, t), 1.32 (3H, t), 1.50 (3H, d), 2.40 (2H, q), 2.56 (4H, m), 3.04-3.22 (6H, m), 3.54 (3H, s), 3.62-3.80 (5H, m), 5.59 (1H, m), 5.66 (2H, s), 6.83 (1H, s), 6.99 (1H, s), 8.60 (1H, s), 8.84 (1H, s), 10.87 (1H, s). LRMS: m/z 600 $(M+1)^+$

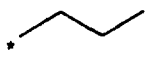
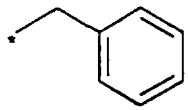
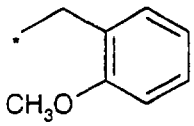
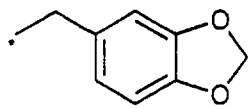
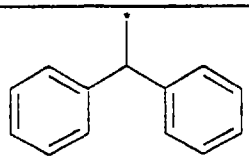
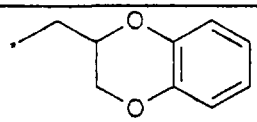
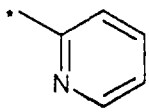
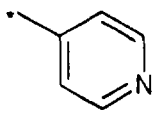
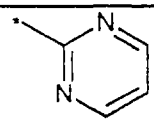
EXAMPLE 51 to 60



A group of analogues based on the structural formula identified above, in which the R^{10} substituent is varied, was obtained by the technique of high-speed analogue synthesis (HSAS) as described hereinafter.

A 0.4 M solution of triethylamine in dichloromethane (100µl, 40µmol) was added to each well of a 96-well plate containing the required range of 1-substituted piperazines (10µmol). A 0.1M solution of the title compound of Preparation 63 in dichloromethane (100µl, 10µmol) was added to each well, then the plate covered and shaken at room temperature for 18 hours. The reaction mixtures were filtered through a 96-well filtration block, which was washed with dichloromethane (1ml), then the filtrates evaporated under reduced pressure. The residues were dissolved in dimethylsulphoxide (1ml) and purified by HPLC using a 5µ Hypersil C18 column (10x0.46cm) with a flow rate of 4ml/min and an elution gradient of 0.1% trifluoroacetic acid in water: acetonitrile.

The following compounds were thus obtained:

Example	R^{10}	LRMS (m/z)	Retention time (min)
51		581 $(M+1)^+$	5.25
52		581 $(M+1)^+$	5.10
53		629 $(M+1)^+$	5.70
54		659 $(M+1)^+$	6.02
55		672 $(M)^+$	5.36
56		706 $(M+2)^+$	8.24
57		687 $(M+1)^+$	6.64
58		617 $(M+2)^+$	5.45
59		616 $(M+1)^+$	5.57
60		617 $(M+1)^+$	7.38

* = point of attachment of R^{10}

EXAMPLE 61

3-Ethyl-5-[2-(2-methoxyethoxy)-5-(3,4,5-trimethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a white solid (170mg, 47%) from the title compound of Preparation 64 and 1,2,6-trimethylpiperazine (J.Med.Chem., 1968, 11, 592), using the procedure of Example 50. Found: C, 55.78; H, 6.02; N, 18.42. $C_{28}H_{36}N_8O_5S$; 0.50 H_2O requires C, 55.22; H, 6.16; N, 18.58%. δ ($CDCl_3$): 1.09 (6H,d), 1.31 (3H,t), 2.01 (5H,m), 2.36 (2H,m), 3.04 (2H,q), 3.60 (5H,m), 3.88 (2H,t), 4.79 (2H,t), 5.68 (2H,s), 7.12 (1H,d), 7.22 (1H,m), 7.64 (1H,m), 8.58 (1H,d), 8.62 (1H,s), 8.95 (1H,s), 10.79 (1H,s). LRMS: m/z 597 $(M+1)^+$.

EXAMPLE 62

3-Ethyl-5-[2-(2-methoxyethoxy)-5-piperazin-1-ylsulphonyl)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A solution of the title compound of Preparation 64 (200mg, 0.40mmol) in dichloromethane (10ml) was added dropwise to a stirred solution of piperazine (136mg, 1.58mmol) and triethylamine (110µl, 0.79mmol) in dichloromethane (10ml) and the reaction mixture stirred at room temperature for 1 hour, then washed with water (10ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residual yellow solid was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (98:2 to 92:8), followed by trituration with dichloromethane, to give the title compound (189mg, 86%) as a white foam. Found: C, 52.75; H, 5.43; N, 19.18. $C_{25}H_{30}N_8O_5S$; 0.75 H_2O requires C, 52.85; H, 5.59; N, 19.72%. δ ($CDCl_3$): 1.30 (3H,t), 2.94-3.13 (10H,m), 3.58 (3H,s), 3.88 (2H,t), 4.79 (2H,t), 5.68 (2H,s), 7.10 (1H,d), 7.22 (1H,m), 7.62 (1H,m), 8.58 (1H,d), 8.62 (1H,s), 8.98 (1H,s), 10.82 (1H,s). LRMS: m/z 555 $(M+1)^+$.

EXAMPLE 63

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl]-2-methoxypyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A stirred mixture of the title compound of Example 1 (350mg, 0.63mmol), potassium bis(trimethylsilyl)amide (630mg, 3.15mmol) and n-propanethiol (5ml) was heated in a sealed vessel at 110°C for 48 hours, then allowed to cool and evaporated under reduced pressure. The residue was azeotroped with dichloromethane: methanol (95:5), then partitioned between water (10ml) and dichloromethane (15ml). The phases were separated, the aqueous phase extracted with dichloromethane (2x15ml) and the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. This residue was purified by column chromatography on silica gel, using dichloromethane: methanol (97:3) as eluant, to yield the title compound (170mg, 50%) as a yellow solid. Found: C, 54.50; H, 5.64; N, 19.93. $C_{25}H_{30}N_8O_4S$; 0.75 H_2O requires C, 54.38; H, 5.75; N, 20.29%. δ ($CDCl_3$): 1.02 (3H,t), 1.32 (3H,t,) 2.40 (2H,q), 2.55 (4H,m), 3.06 (2H,q), 3.14 (4H,m), 4.26 (3H,s), 5.68 (2H,s), 7.14 (1H,d), 7.22 (1H,m), 7.64 (1H,m), 8.58 (1H,d), 8.66 (1H,s), 9.05 (1H,s), 10.59 (1H,s). LRMS: m/z 540 $(M+2)^+$.

EXAMPLE 64

5-[2-Benzyloxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Potassium bis(trimethylsilyl)amide (360mg, 1.81mmol) was added to a stirred solution of the title compound of Example 1 (200mg, 0.36mmol) in benzyl alcohol (5ml) at 100°C and the reaction mixture stirred for 14 hours, then allowed to cool. The resulting mixture was partitioned between dichloromethane (10ml) and brine (10ml), the phases separated, the aqueous phase extracted with dichloromethane (2x10ml) and the combined organic solutions dried (Na_2SO_4) and evaporated under reduced pressure. The residual benzyl alcohol was removed by Kugelrohr distillation, then the crude

product purified by column chromatography on silica gel, using dichloromethane: methanol (97.5:2.5) as eluant, to provide the title compound (86mg, 39%) as a white solid. Found: C, 59.92; H, 5.64; N, 17.60. $C_{31}H_{34}N_8O_4S$; 0.40 H_2O requires C, 59.87; H, 5.64; N, 18.02%. δ ($CDCl_3$): 1.05 (3H,t), 1.29 (3H,t), 2.41 (2H,q), 2.56 (4H,m), 3.05 (2H,q), 3.15 (4H,m), 5.68 (2H,s) 5.75 (2H,s), 7.10 (1H,d), 7.24 (1H,m), 7.42 (3H,m), 7.52 (2H,m), 7.64 (1H,m), 8.58 (1H,d), 8.65 (1H,s), 9.02 (1H,s), 10.58 (1H,s). LRMS: m/z 615 $(M+1)^+$.

EXAMPLE 65

5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(furan-3-ylmethoxy)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Potassium bis(trimethylsilyl)amide (176mg, 0.88mmol) was added to a stirred suspension of the title compound of Example 26 (100mg, 0.17mmol) in 3-hydroxymethylfuran (4ml) and the reaction mixture heated under reflux for 24 hours then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using dichloromethane: methanol (95:5) as eluant, to furnish the title compound (33mg, 31%) as a pale yellow foam. δ ($CDCl_3$) 0.93 (3H,t), 1.04 (3H,t), 1.72 (2H,m), 2.41 (2H,q), 2.55 (4H,m), 2.99 (2H,t), 3.14 (4H,m), 5.63 (2H,s), 5.68 (2H,s), 6.60 (1H,s), 7.09 (1H,d), 7.22 (1H,m), 7.44 (1H,s), 7.64 (2H,m), 8.57 (1H,d), 8.68 (1H,s), 9.02 (1H,s), 10.53 (1H,s). LRMS: m/z 619 $(M+1)^+$.

EXAMPLE 66

5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(pyridin-2-ylmethoxy)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A stirred mixture of potassium bis(trimethylsilyl)amide (260mg, 1.32mmol) and 2-hydroxymethylpyridine (5ml) was heated at 100°C for 1 hour,

then the title compound of Example 26 (150mg, 0.26mmol) added and the reaction mixture stirred at 100°C for 14 hours. The resulting cool mixture was partitioned between dichloromethane (10ml) and brine (10ml), the phases separated and the aqueous phase extracted with dichloromethane (2x10ml). The combined organic solutions were dried ($MgSO_4$) and evaporated under reduced pressure, then the residual yellow oil purified by column chromatography on silica gel, using dichloromethane: ethyl acetate: methanol (47.5:47.5:5) as eluant, to afford the title compound (35mg, 21%) as a white solid. δ ($CDCl_3$): 0.94 (3H,t), 1.03 (3H,t), 1.73 (2H,m), 2.40 (2H,q), 2.55 (4H,m), 2.98 (2H,t), 3.14 (4H,m), 5.69 (2H,s), 5.92 (2H,s), 7.07 (1H,d), 7.21 (1H,m), 7.33 (2H,m), 7.62 (1H,m), 7.76 (1H,m), 8.58 (2H,m), 8.81 (1H,s), 8.85 (1H,d), 12.80 (1H,s). LRMS: m/z 630 $(M+1)^+$.

EXAMPLE 67

5-[2-(2-Dimethylaminoethoxy)-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A mixture of the title compound of Example 26 (200mg, 0.35mmol), potassium bis(trimethylsilyl)amide (352mg, 1.76mmol) and 2-dimethylaminoethanol (1.5ml) was stirred at 90°C for 18 hours, then allowed to cool. Water (5ml) was added, the mixture extracted with ethyl acetate (3x5ml) and the combined extracts dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (95:5 to 90:10), to give the title compound (147mg, 68%) as an off-white foam. Found: C, 56.35; H, 6.37; N, 20.12. $C_{29}H_{39}N_9O_4S$; 0.50 H_2O requires C, 56.29; H, 6.52; N, 20.37%. δ ($CDCl_3$): 0.94 (3H,t), 1.04 (3H,t), 1.72 (2H,m), 2.43 (8H,m), 2.56 (4H,m), 2.74 (2H,t), 2.95 (2H,t), 3.15 (4H,m), 4.80 (2H,t), 5.67 (2H,s), 7.07 (1H,d), 7.21 (1H,m), 7.61 (1H,m), 8.56 (1H,d), 8.62 (1H,s), 8.75 (1H,s), 12.23 (1H,s). LRMS: m/z 610 $(M+1)^+$.

EXAMPLE 68

5-{5-(4-Ethylpiperazin-1-ylsulphonyl)-2-[2-(morpholin-4-yl)ethoxy]pyridin-3-yl}-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A mixture of potassium bis(trimethylsilyl)amide (180mg, 0.88mmol) and 4-(2-hydroxyethyl)morpholine (4ml) was stirred at 100°C for 1 hour, then the title compound of Example 26 (100mg, 0.17mmol) added and the reaction mixture stirred at 110°C for 18 hours. The resulting, cool mixture was partitioned between water (10ml) and dichloromethane (20ml), the phases separated and the organic phase washed with water (10ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residual yellow oil was purified by column chromatography on silica gel, using an elution gradient of ethyl acetate: methanol (90:10 to 80:20), to yield the title compound (33mg, 30%) as a white solid. δ ($CDCl_3$): 0.95 (3H,t), 1.04 (3H,t), 1.74 (2H,m), 2.42 (2H,q), 2.56 (4H,m), 2.64 (4H,m), 2.90 (2H,t), 2.99 (2H,t), 3.15 (4H,m), 3.80 (4H,m), 4.75 (2H,t), 5.68 (2H,s), 7.12 (1H,d), 7.25 (1H,m), 7.63 (1H,m), 8.58 (1H,d), 8.62 (1H,s), 8.92 (1H,s), 11.16 (1H,s). LRMS: m/z 652 $(M+1)^+$.

EXAMPLE 69

5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(1-methylpiperidin-4-yloxy)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Caesium t-butoxide (76mg, 0.37mmol) was added to a stirred solution of the title compound of Preparation 119 (160mg, 0.24mmol) in 3-methylpentan-3-ol (5ml) and the reaction mixture stirred at 120°C for 3 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residue partitioned between dichloromethane (10ml) and water (10ml). The phases were separated, the aqueous phase extracted with dichloromethane (2x10ml) and the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. The residual yellow oil was purified by

column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (95:5 to 92.5:7.5), to provide the title compound as a yellow foam. δ ($CDCl_3$): 0.94 (3H,t), 1.03 (3H,t), 1.74 (2H,m), 2.10 (2H,m), 2.22 (2H,m), 2.42 (5H,m), 2.58 (6H,m), 2.78 (2H,m), 2.99 (2H,t), 3.13 (4H,m), 5.59 (1H,m), 5.67 (2H,s), 7.10 (1H,d), 7.22 (1H,m), 7.63 (1H,m), 8.57 (1H,d), 8.61 (1H,s), 9.00 (1H,s), 10.63 (1H,s). LRMS: m/z 636 $(M+1)^+$.

EXAMPLE 70

5-[2-Ethoxy-5-(4-ethyl-4-oxidopiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one

A mixture of the title compound of Example 1 (180mg, 0.32mmol), 3-chlorobenzoic acid (13mg, 0.08mmol) and dichloromethane (10ml) was stirred at room temperature for 20 minutes, 3-chloroperoxybenzoic acid (112mg, 0.32mmol) added and the reaction mixture stirred for a further 18 hours, then partitioned between dichloromethane (20ml) and aqueous sodium bicarbonate solution (10ml). The phases were separated, the aqueous phase extracted with dichloromethane (2x20ml) and the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using dichloromethane: methanol (80:20) as eluant, to furnish the title compound (82mg, 45%) as a white powder. Found: C, 52.73; H, 5.67; N, 17.69. $C_{26}H_{32}N_8O_5S$; 0.50 CH_2Cl_2 requires C, 52.08; H, 5.44; N, 18.34%. δ ($CDCl_3$): 1.30 (3H,t), 1.40 (3H,t), 1.58 (3H,t), 3.02 (2H,q), 3.20 (2H,m), 3.32 (4H,m), 3.48 (2H,m), 3.72 (2H,m), 4.76 (2H,q), 5.68 (2H,s), 7.08 (1H,d), 7.22 (1H,m), 7.63 (1H,m), 8.58 (1H,d), 8.65 (1H,s), 9.03 (1H,s), 10.70 (1H,s).

EXAMPLE 71

5-[5-(4-Ethyl-4-oxidopiperazin-1-ylsulphonyl)-2-n-propoxypyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

3-Chloroperoxybenzoic acid (93mg, 0.27mmol) was added to a stirred

solution of the title compound of Example 28 (155mg, 0.27mmol) in dichloromethane (2ml) and the reaction mixture stirred at room temperature for 2 hours, then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using dichloromethane:methanol:0.88 aqueous ammonia (90:10:1) as eluant, to afford the title compound (40mg, 25%) as a solid. δ ($CDCl_3$): 0.93 (3H,t), 1.14 (3H,t), 1.41 (3H,t), 1.72 (2H,m), 2.00 (2H,m), 2.97 (2H,t), 3.15 (2H,m), 3.31 (4H,m), 3.50 (2H,m), 3.70 (2H,m), 4.65 (2H,t), 5.68 (2H,s), 7.06 (1H,d), 7.24 (1H,m), 7.64 (1H,m), 8.58 (1H,d), 8.66 (1H,s), 9.06 (1H,s), 10.67 (1H,s). LRMS: m/z 598 $(M+1)^+$.

EXAMPLE 72

3-Ethyl-5-[5-(4-ethyl-4-oxidopiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one

and

EXAMPLE 73

3-Ethyl-5-[5-(4-ethyl-4-oxidopiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-(1-oxidopyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

3-Chlorobenzoic acid (15mg, 0.096mmol) was added to a stirred solution of the title compound of Example 4 (223mg, 0.38mmol) in dichloromethane (3ml) and the mixture stirred at room temperature for 30 minutes. 3-Chloroperoxybenzoic acid (132mg, 0.38mmol) was then added and the reaction mixture stirred at room temperature for 14 hours, then partitioned between dichloromethane (5ml) and aqueous sodium bicarbonate solution (5ml). The phases were separated, the aqueous phase extracted with dichloromethane

(3x10ml) and the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (90:10 to 80:20), to give the first title compound (78mg, 34%) as a solid. Found: C, 51.77; H, 5.82; N, 17.33. $C_{27}H_{34}N_8O_6S$; 1.75 H_2O requires C, 51.46; H, 6.00; N, 17.78%. δ ($CDCl_3$): 1.28 (3H,t), 1.42 (3H,t), 3.02 (2H,q), 3.18 (2H,m), 3.30 (4H,m), 3.50 (2H,m), 3.56 (3H,s), 3.72 (2H,m), 3.88 (2H,t), 4.80 (2H,t), 5.68 (2H,s), 7.08 (1H,d), 7.22 (1H,m), 7.64 (1H,m), 8.58 (1H,d), 8.68 (1H,s), 8.99 (1H,s), 10.84 (1H,s);

followed by the second title compound (50mg, 22%) as a solid. Found: C, 50.15; H, 5.81; N, 16.85. $C_{27}H_{34}N_8O_6S$; 2.0 H_2O requires C, 49.84; H, 5.89; N, 17.22%. δ ($CDCl_3$): 1.32 (3H,t), 1.42 (3H,t), 3.05 (2H,q), 3.18 (2H,m), 3.32 (4H,m), 3.53 (5H,m), 3.72 (2H,m), 3.86 (2H,t), 4.80 (2H,t), 5.81 (2H,s), 6.78 (1H,d), 7.22 (2H,m), 8.29 (1H,d), 8.66 (1H,s), 8.99 (1H,s), 10.90 (1H,s).

EXAMPLE 74

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-2-(2-morpholin-4-yl)ethyl-3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Potassium t-butoxide (110mg, 0.99mmol) was added to a stirred solution of the title compound of Preparation 120 (400mg, 0.66mmol) in 3-methylpentan-3-ol (20ml) and the reaction mixture heated under reflux for 3 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure, the residue suspended in water (10ml) and the suspension extracted with dichloromethane (3x10ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure, then the residual yellow oil purified by column chromatography on silica gel, using dichloromethane: methanol (97.5:2.5) as eluant, to yield the title compound (65mg, 17%) as a white foam. Found: C, 54.51; H, 6.95; N, 18.18.

$C_{27}H_{40}N_8O_5S$; 0.15 CH_2Cl_2 requires C, 54.51; H, 6.92; N, 18.14%. δ ($CDCl_3$):1.04 (6H,m), 1.58 (3H,t), 1.88 (2H,m), 2.41 (2H,q), 2.54 (8H,m), 2.99 (4H,m), 3.15 (4H,m), 3.68 (4H,m), 4.40 (2H,t), 4.75 (2H,q), 8.62 (1H,s), 9.04 (1H,s), 10.61 (1H,s). LRMS: m/z 589 $(M+1)^+$.

EXAMPLE 75

5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-(2-morpholin-4-yl)ethyl-3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a white solid (24%) from the title compound of Example 74 and 2-methoxyethanol, using the procedure of Example 66. Found: C, 53.81; H, 6.93; N, 16.89. $C_{28}H_{42}N_8O_6S$; 0.30 $C_4H_8O_2$; 0.20 H_2O requires C, 54.06; H, 6.96; N, 17.27%. δ ($CDCl_3$): 1.04 (6H,m), 1.87 (2H,m), 2.42 (2H,q), 2.55 (8H,m), 2.99 (4H,m), 3.16 (4H,m), 3.56 (3H,s), 3.69 (4H,m), 3.88 (2H,t), 4.40 (2H,t), 4.79 (2H,t), 8.63 (1H,s), 8.98 (1H,s), 10.78 (1H,s). LRMS: m/z 619 $(M+1)^+$.

EXAMPLE 76

3-t-Butyl-5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-1-(pyridin-2-yl)methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A stirred mixture of the title compound of Preparation 121 (150mg, 0.25mmol), potassium t-butoxide (71mg, 0.625mmol) and ethanol (10ml) was heated at 100°C for 18 hours in a sealed vessel, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residue partitioned between water (10ml) and ethyl acetate (15ml). The phases were separated, the aqueous phase extracted with ethyl acetate (2x15ml) and the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel, using dichloromethane: methanol (100:0 to 95:5) as eluant, to provide the title compound (140mg, 97%) as a white solid. Found: C, 56.30; H, 6.39; N, 18.43. $C_{28}H_{36}N_6O_4S$; H_2O requires C, 56.17; H, 6.40; N, 18.72%.

δ ($CDCl_3$): 1.04 (3H,t), 1.56 (12H,m), 2.42 (2H,q), 2.56 (4H,m), 3.16 (4H,m), 4.76 (2H,q), 5.95 (2H,s), 6.94 (1H,d), 7.18 (1H,m), 7.60 (1H,m), 8.58 (1H,d), 8.64 (1H,s), 9.08 (1H,s), 10.82 (1H,s). LRMS: m/z 581 $(M+1)^+$.

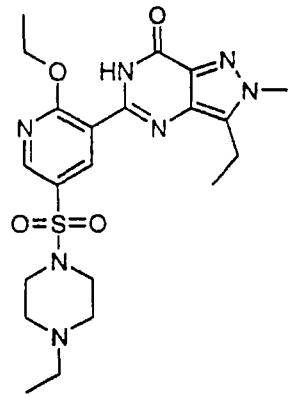
EXAMPLE 77

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-1-(2-morpholin-4-yl)ethyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a white solid (68%) from the title compound of Preparation 122, using the procedure of Example 74. Found: C, 54.59; H, 6.91; N, 18.08. $C_{27}H_{40}N_8O_5S$; 0.15 CH_2Cl_2 requires C, 54.59; H, 6.89; N, 18.08%. δ ($CDCl_3$): 1.01 (6H,m), 1.60 (3H,t), 1.84 (2H,m), 2.42 (2H,q), 2.53 (8H,m), 2.86 (2H,t), 2.94 (2H,t), 3.15 (4H,m), 3.62 (4H,m), 4.72 (4H,m), 8.63 (1H,s), 9.09 (1H,s), 10.81 (1H,s). LRMS: m/z 589 $(M+1)^+$.

EXAMPLE 78

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



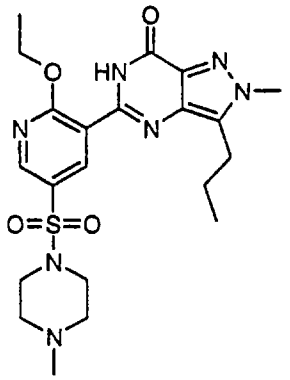
A mixture of the title compound of Preparation 152 (25.9g, 52.5mmol), and potassium bis(trimethylsilyl)amide (22.0g, 110.0mmol) in ethanol (1500ml) was heated at 120°C for 18 hours in a sealed vessel. The cooled solution was concentrated under reduced pressure, and pre-adsorbed onto silica gel. The crude product was purified by column chromatography on silica gel, using an elution gradient of ethyl acetate: diethylamine (97:3 to 95:5) and triturated with ether to afford the title compound (11.0g, 44%) as a white solid.

δ ($CDCl_3$) : 1.03 (3H, t), 1.40 (3H, t), 1.59 (3H, t), 2.41 (2H, q), 2.57 (4H, m), 3.04 (2H, q), 3.14 (4H, m), 4.09 (3H, s), 4.75 (2H, q), 8.62 (1H, s), 9.04 (1H, s), 10.64 (1H, s).

LRMS : m/z 476 $(M+1)^+$

EXAMPLE 79

5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)pyridin-3-yl]-2-methyl-3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



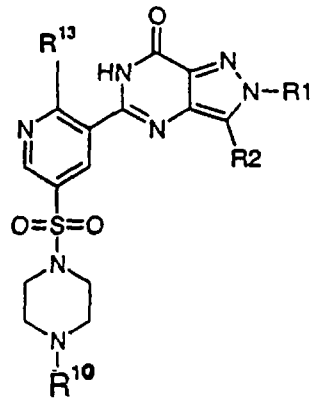
The title compound of Preparation 151 (500mg, 1.0mmol) was added to a solution of potassium bis(trimethylsilyl)amide (610mg, 3.06mmol) in ethanol (20ml), and the reaction heated at 110°C in a sealed vessel for 18 hours. The cooled mixture was evaporated under reduced pressure and the residue dissolved in water and neutralised using hydrochloric acid. This aqueous suspension was extracted with dichloromethane (3x30ml), the combined organic extracts washed with brine (3x30ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol (100:0 to 97.5:2.5), and triturated with ether, to afford the title compound (207mg, 44%) as an off-white solid.

δ ($CDCl_3$) : 1.03 (3H, t), 1.59 (3H, t), 1.83 (2H, m), 2.29 (3H, s), 2.53 (4H, m), 3.00 (2H, t), 3.16 (4H, m), 4.10 (3H, s), 4.75 (2H, q), 8.63 (1H, s), 9.06 (1H, s), 10.65 (1H, s).

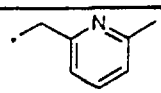
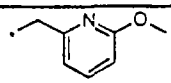
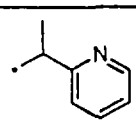
LRMS : m/z 476 $(M+1)^+$

EXAMPLES 80 TO 84

The compounds of the general formula:



were prepared from the appropriate pyrazole-5-carboxamides, i.e. Preparations 153, 154, 156, 157 and 155 respectively, following procedures similar to that described in Example 79. In Examples 80 to 84, R^1 is methyl and R^{13} is $-OR^3$.

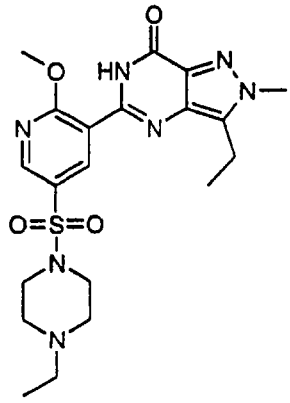
Ex	R1	R2	R3	R10	Data
80	CH_3	$(CH_2)_2CH_3$	CH_2CH_3	CH_2CH_3	Found: C, 53.97; H, 6.38; N, 19.75. $C_{22}H_{31}N_7O_4S$ requires C, 53.97; H, 6.38; N, 20.03% δ ($CDCl_3$) : 1.03 (6H, t), 1.58 (3H, t), 1.82 (2H, m), 2.41 (2H, q), 2.56 (4H, m), 2.99 (2H, t), 3.14 (4H, m), 4.09 (3H, s), 4.76 (2H, q), 8.63 (1H, s), 9.05 (1H, s), 10.64 (1H, s). LRMS : m/z 490 $(M+1)^+$
81	CH_2CH_3	CH_2CH_3	CH_2CH_3	CH_2CH_3	δ ($CDCl_3$) : 1.02 (3H, t), 1.40 (3H, t), 1.58 (6H, m), 2.41 (2H, q), 2.55 (4H, m), 3.00-3.18 (6H, m), 4.38 (2H, q), 4.75 (2H, q), 8.63 (1H, s), 9.04 (1H, s), 10.63 (1H, s). LRMS : m/z 490 $(M+1)^+$
82 [1,2]		CH_2CH_3	CH_2CH_3	CH_2CH_3	Found: C, 56.66; H, 6.03; N, 19.57 $C_{27}H_{34}N_8O_4S$;0.25 H_2O requires C, 56.78; H, 6.09; N, 19.62%. δ ($CDCl_3$) : 1.02 (3H, t), 1.30 (3H, t), 1.58 (3H, t), 2.41 (2H, q), 2.57 (7H, m), 3.04 (2H, q), 3.15 (4H, m), 4.77 (2H, q), 5.64 (2H, s), 6.80 (1H, d), 7.08 (1H, d), 7.50 (1H, m), 8.62 (1H, s), 9.02 (1H, s), 10.66 (1H, s). LRMS : m/z 567 $(M+1)^+$
83		CH_2CH_3	CH_2CH_3	CH_2CH_3	δ ($CDCl_3$) : 1.04 (3H, t), 1.40 (3H, t), 1.58 (3H, t), 2.42 (2H, q), 2.58 (4H, m), 3.01 (2H, q), 3.16 (4H, m), 3.80 (3H, s), 4.75 (2H,q), 5.82 (2H, s), 6.54 (1H, d), 6.60 (1H, d), 7.46 (1H, m), 8.64 (1H, s), 9.10 (1H, s), 10.85 (1H, s). LRMS : m/z 583 $(M+1)^+$
84 [1]		CH_2CH_3	CH_2CH_3	CH_2CH_3	δ ($CDCl_3$) : 1.03 (3H, t), 1.25 (3H, t), 1.58 (3H, t), 2.13 (3H, d), 2.40 (2H, q), 2.55 (4H, m), 3.01 (2H, q), 3.14 (4H, m), 4.77 (2H, q), 5.84 (1H, q), 7.19 (2H, m), 7.61 (1H, m), 8.56 (1H, d), 8.62 (1H, s), 9.00 (1H, s), 10.60 (1H, s). LRMS : m/z 567 $(M+1)^+$

1 = 1.5 equivalents of potassium bis(trimethylsilyl)amide were used

2 = dichloromethane:methanol:0.88 ammonia (96:4:0.4) was used as the chromatographic eluant

EXAMPLE 85

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-methoxypyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



A mixture of the title compound of Example 78 (100mg, 0.21mmol), and copper (II) sulphate heptahydrate (75mg, 0.3mmol) in saturated methanolic ammonia (20ml) was heated at 100°C for 4 hours in a sealed vessel. The cooled mixture was evaporated under reduced pressure and the residue suspended in aqueous sodium carbonate solution (20ml) and extracted with dichloromethane (3x20ml). The combined organic extracts were washed with brine (3x20ml), dried (Na_2SO_4) and evaporated under reduced pressure to give a green solid. The crude product was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 97:3) and recrystallised from hexane/ethyl acetate/methanol to afford the title compound (23mg, 24%) as a white solid.

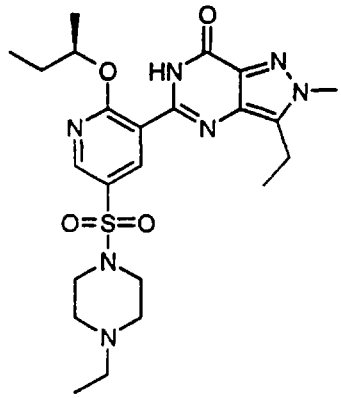
Found : C, 51.22; H, 5.81; N, 20.61. $C_{20}H_{27}N_7O_4S;0.5H_2O$ requires C, 51.05; H, 6.00; N, 20.84%

δ ($CDCl_3$) : 1.07 (3H, t), 1.40 (3H, t), 2.40-2.65 (6H, m), 3.04 (2H, q), 3.19 (4H, m), 4.09 (3H, s), 4.24 (3H, s), 8.65 (1H, s), 9.05 (1H, s), 10.58 (1H, s).

LRMS : m/z 462 $(M+1)^+$

EXAMPLE 86

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2- (1(R)-methyl-n-propoxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



The title compound of Example 78 (400mg, 0.84mmol) was added to a mixture of potassium bis(trimethylsilyl)amide (840mg, 4.2mmol) in (*R*)-2-butanol (4ml) and the mixture stirred at 110°C for 18 hours. The cooled mixture was concentrated under reduced pressure and the residue suspended in water (10ml) and neutralised using 2N hydrochloric acid. This aqueous suspension was extracted with ethyl acetate (3x30ml), the combined organic extracts washed with sodium hydroxide solution (20ml), brine (2x30ml), dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 97.5:2.5) and the product suspended in ether and evaporated under reduced pressure. This solid was recrystallised from hexane/ethyl acetate to afford the title compound (72mg, 17%) as a white solid.

$[\alpha]_D$ = -20.88° (c=0.083, dichloromethane)

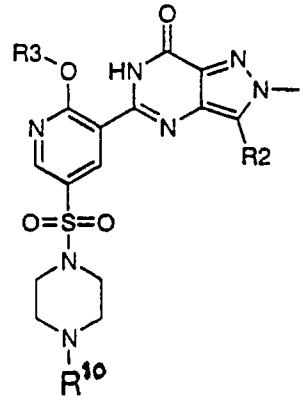
Found : C, 54.65; H, 6.63; N, 19.25. $C_{23}H_{33}N_7O_4S;0.5H_2O$ requires C, 53.89; H, 6.69; N, 19.13%

δ ($CDCl_3$) : 1.06 (6H, m), 1.40 (3H, t), 1.50 (3H, d), 1.86 (1H, m), 1.99 (1H, m), 2.42 (2H, q), 2.58 (4H, m), 3.04 (2H, q), 3.16 (4H, m), 4.09 (3H, s), 5.56 (1H, m), 8.62 (1H, s), 9.05 (1H, s), 10.70 (1H, s).

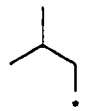
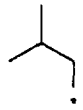
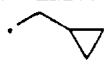
LRMS : m/z 504 $(M+1)^+$

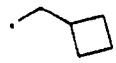
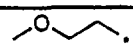
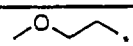
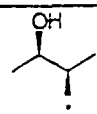
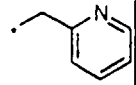
EXAMPLES 87 TO 97

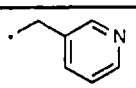
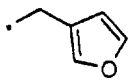
The compounds of the general formula wherein R^1 is methyl and R^{13} is $-OR^3$:



were prepared from the appropriate alcohols and pyrazolo[4,3-d]pyrimidin-7-ones, following procedures similar to that described in Example 86.

Ex	R2	R3	R10	Data
87	CH_2CH_3		CH_2CH_3	Found : C, 54.02; H, 6.59; N, 18.87 $C_{23}H_{33}N_7O_4S;0.5H_2O$ requires C, 53.89; H, 6.69; N, 19.13% δ ($CDCl_3$) : 1.02 (3H, t), 1.14 (6H, d), 1.40 (3H, t), 2.30 (1H, m), 2.42 (2H, q), 2.58 (4H, m), 3.03 (2H, q), 3.15 (4H, m), 4.09 (3H, s), 4.44 (2H, d), 8.62 (1H, s), 9.03 (1H, s), 10.62 (1H, s).
88	$(CH_2)_2CH_3$		CH_2CH_3	δ ($CDCl_3$) : 1.02 (6H, m), 1.14 (6H, d), 1.82 (2H, m), 2.30 (1H, m), 2.42 (2H, q), 2.56 (4H, m), 2.99 (2H, t), 3.16 (4H, m), 4.08 (3H, s), 4.45 (2H, d), 8.62 (1H, s), 9.03 (1H, s), 10.62 (1H, s). LRMS : m/z 518 $(M+1)^+$
89	CH_2CH_3		CH_2CH_3	Found : C, 55.11; H, 6.25; N, 19.45. $C_{23}H_{31}N_7O_4S$ requires C, 55.07; H, 6.23; N, 19.55%. δ ($CDCl_3$) : 1.04 (3H, t), 1.40 (3H, t), 1.90 (1H, m), 1.98 (1H, m), 2.30-2.44 (4H, m), 2.57 (6H, m), 3.02 (2H, q), 3.14 (4H, m), 4.09 (3H, s), 5.50 (1H, m), 8.60 (1H, s), 9.04 (1H, s), 10.68 (1H, s). LRMS : m/z 502 $(M+1)^+$
90 1	$(CH_2)_2CH_3$		CH_2CH_3	Found : C, 56.08; H, 6.45; N, 18.72. $C_{24}H_{33}N_7O_4S$ requires C, 55.90; H, 6.45; N, 19.01% δ ($CDCl_3$) : 0.47 (2H, m), 0.77 (2H, m), 1.02 (6H, m), 1.47 (1H, m), 1.83 (2H, m), 2.41 (2H, q), 2.56 (4H, m), 2.99 (2H, t), 3.15 (4H, m), 4.09 (3H, s), 4.50 (2H, d), 8.60 (1H, s), 9.05 (1H, s), 10.76 (1H, s). LRMS : m/z 516 $(M+1)^+$

91 2	$(CH_2)_2CH_3$		CH_2CH_3	Found : C, 56.53; H, 6.68; N, 18.43. $C_{25}H_{35}N_7O_4S$ requires C, 56.69; H, 6.66; N, 18.51% δ ($CDCl_3$) : 1.02 (6H, m), 1.82 (2H, m), 1.91-2.10 (4H, m), 2.26 (2H, m), 2.41 (2H, q), 2.57 (4H, m), 2.98 (3H, m), 3.14 (4H, m), 4.08 (3H, s), 4.62 (2H, d), 8.61 (1H, s), 9.02 (1H, s), 10.60 (1H, s). LRMS : m/z 530 $(M+1)^{+\cdot}$
92	CH_2CH_3		CH_2CH_3	Found : C, 52.20; H, 6.16; N, 19.26. $C_{22}H_{31}N_7O_5S$ requires C, 52.26; H, 6.18; N, 19.39% δ ($CDCl_3$) : 1.04 (3H, t), 1.40 (3H, t), 2.42 (2H, q), 2.56 (4H, m), 3.03 (2H, q), 3.15 (4H, m), 3.58 (3H, s), 3.86 (2H, t), 4.09 (3H, s), 4.79 (2H, t), 8.62 (1H, s), 9.00 (1H, s), 10.78 (1H, s). LRMS : m/z 506 $(M+1)^+$
93 3	$(CH_2)_2CH_3$		CH_2CH_3	Found : C, 52.86; H, 6.39; N, 18.67. $C_{23}H_{33}N_7O_5S$ requires C, 53.16; H, 6.40; N, 18.62% δ ($CDCl_3$) : 1.04 (6H, m), 1.82 (2H, m), 2.40 (2H, q), 2.55 (4H, m), 2.98 (2H, t), 3.14 (4H, m), 3.57 (3H, s), 3.85 (2H, t), 4.07 (3H, s), 4.78 (2H, t), 8.61 (1H, s), 8.99 (1H, s), 10.76 (1H, s). LRMS : m/z 520 $(M+1)^+$
94 3	CH_2CH_3		CH_2CH_3	Found : C, 53.16; H, 6.48; N, 18.32. $C_{23}H_{33}N_7O_5S;0.5H_2O$ requires C, 52.26; H, 6.48; N, 18.55% δ ($CDCl_3$) : 1.04 (3H, t), 1.38 (6H, m), 1.50 (3H, d), 2.41 (2H, q), 2.57 (4H, m), 2.96 (1H, s), 3.01 (2H, m), 3.15 (4H, m), 4.08 (3H, s), 4.18 (1H, m), 5.22 (1H, m), 8.60 (1H, s), 8.82 (1H, s), 11.27 (1H, s). $[\alpha]_D$ = +35.46° (c=0.073, dichloromethane)
95 2	$(CH_2)_2CH_3$		CH_2CH_3	δ ($CDCl_3$) : 1.04 (6H, m), 1.84 (2H, m), 2.41 (2H, q), 2.56 (4H m), 2.99 (2H, t), 3.15 (4H, m), 4.08 (3H, s), 5.91 (2H, s), 7.24-7.37 (2H, m), 7.76 (1H, m), 8.59 (1H, s), 8.83 (2H, m), 12.70 (1H, s). LRMS : m/z 553 $(M+1)^+$

96 [1]	$(CH_2)_2CH_3$		CH_2CH_3	Found : C, 55.22; H, 5.76; N, 19.42, $C_{26}H_{32}N_8O_4S;0.2CH_2Cl_2$ requires C, 55.24; H, 5.73; N, 19.67% δ ($CDCl_3$) : 1.01 (6H, m), 1.82 (2H, m), 2.41 (2H, q), 2.56 (4H, m), 2.98 (2H, t), 3.15 (4H, m), 4.09 (3H, s), 5.78 (2H, s), 7.38 (1H, m), 7.88 (1H, d), 8.61 (2H, m), 8.79 (1H, s), 9.02 (1H, s), 10.45 (1H, s). LRMS : m/z 553 $(M+1)^+$
97 [1]	$(CH_2)_2CH_3$		CH_2CH_3	δ ($CDCl_3$) : 1.02 (6H, m), 1.82 (2H, m), 2.41 (2H, q), 2.56 (4H, m), 2.98 (2H, t), 3.16 (4H, m), 4.06 (3H, s), 5.62 (2H, s), 6.60 (1H, s), 7.43 (1H, s), 7.62 (1H, s), 8.66 (1H, s), 9.02 (1H, s), 10.51 (1H, s). LRMS : m/z 542 $(M+1)^+$

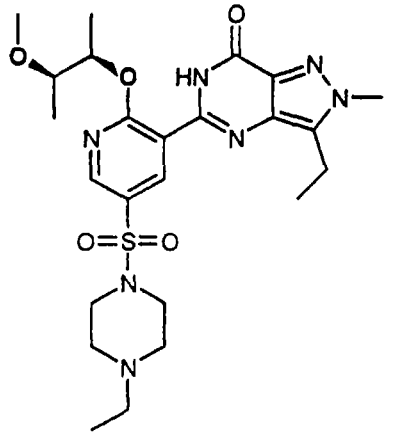
1 = dichloromethane:methanol:0.88 ammonia (100:0:0.5 to 99.5:1:0.5) used as chromatographic eluant, and the compound was isolated without crystallisation.

2 = dichloromethane:methanol:0.88 ammonia (100:0:0.5 to 99.5:1:0.5) used as chromatographic eluant, and the compound was triturated with ether.

3 = isolated without crystallisation

EXAMPLE 98

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-(R)-methoxy-1-(R)-methyl propoxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

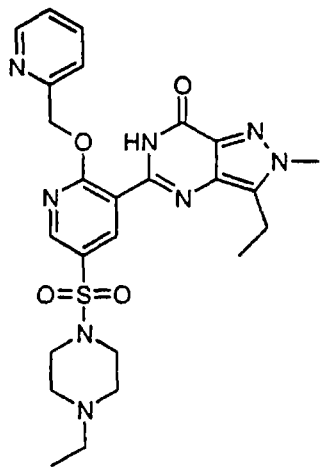


(R,R)-2,3 butanediol (7.78ml, 85mmol) was added dropwise to an ice-cold solution of sodium hydride (3.74g, 60% dispersion in mineral oil, 93.5mmol) in ether (800ml), and the solution stirred at room temperature for 30 minutes. Methyl iodide (5.6ml, 89.3mmol) was added dropwise and the reaction stirred under reflux for 48 hours. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (10.24ml, 85mmol) was added and stirring continued for a further 90 minutes under reflux. The cooled reaction was washed with aqueous ammonium chloride solution (500ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel using an elution gradient of ether: pentane (10:90 to 50:50) to give a pale yellow oil. The title compound of Example 78 (100mg, 0.2mmol) and potassium bis(trimethylsilyl)amide (121mg, 0.61mmol) in the intermediate alcohol (1ml), was heated at 110°C for 30 hours, then the reaction cooled and concentrated under reduced pressure. The residual brown solid was purified by column chromatography on silica gel using diethylamine: ethyl acetate (5:95) as eluant, and repeated using methanol: ethyl acetate (5:95) as eluant. The product was triturated with ether to afford the title compound (7mg, 6%) as a white solid.

δ ($CDCl_3$) : 1.03 (3H, t), 1.25 (3H, d), 1.40 (3H, t), 1.48 (3H, d), 2.41 (2H, q), 2.55 (4H, m), 3.03 (2H, q), 3.15 (4H, m), 3.52 (3H, s), 3.70 (1H, m), 4.09 (3H, s), 5.39 (1H, m), 8.60 (1H, s), 8.97 (1H, s). LRMS : m/z 534 $(M+1)^+$

EXAMPLE 99

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(pyridin-2-yl)methoxypyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



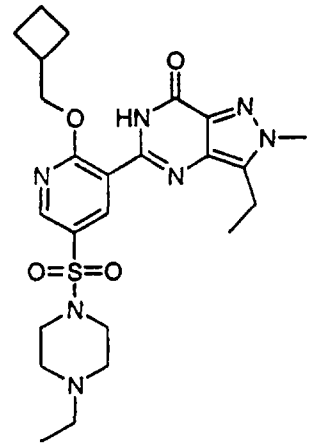
A mixture of the title compound of Example 78 (100mg, 0.2mmol), potassium bis(trimethylsilyl)amide (210mg, 1.1mmol) in pyridine-2-methanol (1ml) was heated to 110°C for 18 hours. The cooled mixture was partitioned between ethyl acetate (10ml) and water (10ml), and the phases separated. The aqueous layer was extracted with ethyl acetate (2x5ml) and dichloromethane (10ml), the combined organic solutions dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using methanol: ethyl acetate (10:90) as eluant, and triturated with ether, to afford the title compound (49mg, 43%) as a solid.

δ ($CDCl_3$) : 1.02 (3H, t), 1.40 (3H, t), 2.40 (2H, q), 2.55 (4H, m), 3.04 (2H, q), 3.14 (4H, m), 4.10 (3H, s), 5.90 (2H, s), 7.32 (2H, m), 7.76 (1H, m), 8.58 (1H, s), 8.82 (2H, m), 12.72 (1H, s).

LRMS : m/z 539 $(M+1)^+$.

EXAMPLE 100

5-[2-Cyclobutylmethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



Obtained (69%) from the title compound of Example 78 and cyclobutanemethanol, following a procedure similar to that described in Example 99.

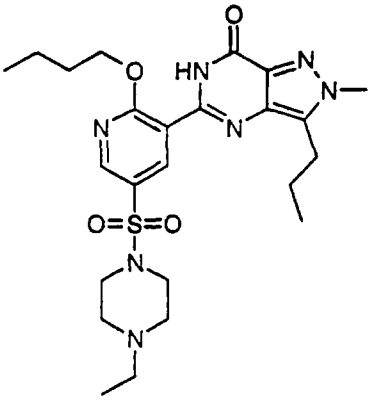
Found : C, 55.71; H, 6.44; N, 18.83. $C_{24}H_{33}N_7O_4S$ requires C, 55.90; H, 6.45; N, 19.01%.

δ ($CDCl_3$) : 1.03 (3H, t), 1.40 (3H, t), 1.98 (4H, m), 2.26 (2H, m), 2.42 (2H, q), 2.57 (4H, m), 3.02 (3H, m), 3.15 (4H, m), 4.10 (3H, s), 4.62 (2H, d), 8.62 (1H, s), 9.04 (1H, s), 10.61 (1H, s).

LRMS : m/z 516 $(M+1)^+$

EXAMPLE 101

5-[2-n-Butoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-2-methyl-3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



A mixture of the title compound of Example 90 (104mg, 0.2mmol) and potassium bis(trimethylsilyl)amide (200mg, 1.0mmol) in n-butanol (5ml) was stirred under reflux for 5 days. The cooled mixture was concentrated under reduced pressure, the residue suspended in ethyl acetate (20ml) and the mixture neutralised using 1M hydrochloric acid. The layers were separated, the organic phase washed with brine (10ml), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was triturated with ether, and the resulting solid, filtered and further purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (100:0:0.5 to 99:1:0.5) to afford the title compound, (86mg, 82%) as a solid.

δ ($CDCl_3$) : 1.02 (9H, m), 1.57 (2H, m), 1.82 (2H, m), 1.95 (2H, m), 2.42 (2H, q), 2.58 (4H, m), 2.99 (2H, t), 3.15 (4H, m), 4.08 (3H, s), 4.68 (2H, t), 8.62 (1H, s), 9.02 (1H, s), 10.62 (1H, s).

LRMS : m/z 518 $(M+1)^+$

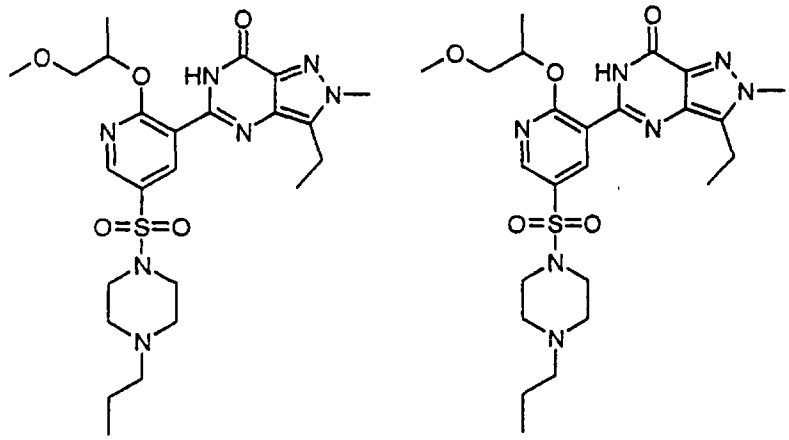
EXAMPLE 102

3-Ethyl-5-[2-(2-methoxy-1-methylethoxy)-5-(4-n-propylpiperazin-1-ylsulphonyl) pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (isomer 1)

and

EXAMPLE 103

3-Ethyl-5-[2-(2-methoxy-1-methylethoxy)-5-(4-n-propylpiperazin-1-ylsulphonyl) pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (isomer 2)



Potassium bis(trimethylsilyl)amide (325mg, 1.63mmol) was added to a solution of the title compound of Example 119 (200mg, 0.41mmol) in 1-methoxy-2-propanol (6ml) and the reaction stirred under reflux for 18 hours. The cooled mixture was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using dichloromethane: methanol (95:5) as eluant to give 193mg of a colourless oil. This product was further purified by HPLC using an AD250 column, using hexane:isopropanol:diethylamine (70:30:0.3) as eluant to afford, the title compound of Example 102 (58mg, 26%, 99.5%ee). δ ($CDCl_3$) : 0.86 (3H, t), 1.40 (5H, m), 1.50 (3H, d), 2.32 (2H, t), 2.56 (4H, m), 3.03 (2H, q), 3.15 (4H, m), 3.55 (3H, s), 3.66 (1H, m), 3.76 (1H, m), 4.08 (3H, s), 5.61 (1H, m), 8.61 (1H, s), 8.92 (1H, s), 10.82 (1H, s).

LRMS : m/z 534 $(M+1)^+$, and the title compound of Example 103 (47mg, 21%, 98.7%ee). δ ($CDCl_3$) : 0.86 (3H, t), 1.41 (5H, m), 1.50 (3H, d), 2.32 (2H, t), 2.56 (4H, m), 3.04 (2H, q), 3.14 (4H, m), 3.55 (3H, s), 3.66 (1H, m), 3.76 (1H, m), 4.08 (3H, s), 5.61 (1H, m), 8.60 (1H, s), 8.92 (1H, s), 10.82 (1H, s).

LRMS : m/z 534 $(M+1)^+$

EXAMPLE 104

(+)-5-[2-(2-Methoxy-1-methylethoxy)-5-(4-methylpiperazin-1-ylsulphonyl)pyridin-3-yl]-2-methyl-3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

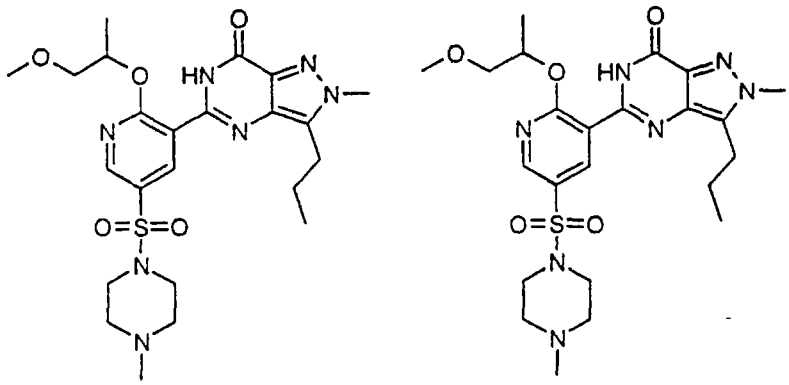
(isomer 1)

and

EXAMPLE 105

(-)-5-[2-(2-Methoxy-1-methylethoxy)-5-(4-methylpiperazin-1-ylsulphonyl)pyridin-3-yl]-2-methyl-3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

(isomer 2)



The title compound of Example 79 (198mg, 0.42mmol) was added to a solution of potassium bis(trimethylsilyl)amide (415mg, 2.1mmol) in 1-methoxy-2-propanol (5ml), and the reaction heated at 110°C for 72 hours. The cooled mixture was evaporated under reduced pressure, the residue dissolved in water and neutralised using 2M hydrochloric acid. This aqueous solution was extracted with ethyl acetate (3x30ml), the combined organic extracts washed with brine (3x20ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residual yellow oil was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol (100:0 to 97:3), and evaporated from ether to give a white solid.

The racemic product was purified by chiral HPLC using an AD250 column, and hexane: isopropanol:trifluoroacetic acid (80:20:0.5) as eluant. The first enantiomer was redissolved in water, basified using aqueous sodium carbonate solution, and this mixture extracted with ethyl acetate (3x20ml). The combined

organic extracts were washed with brine (2x20ml) dried (Na_2SO_4) and evaporated under reduced pressure. This product was then further purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 97:3), and evaporated from ether, to afford the title compound of Example 104 (39mg, 18%, 98.1%ee) as a colourless solid.

$[\alpha]_D$ = +30.31° (c=0.067, dichloromethane)

Found : C, 53.32; H, 6.49; N, 18.48. $C_{23}H_{33}N_7O_5S$ requires C, 53.16; H, 6.40; N, 18.87%.

δ ($CDCl_3$) : 1.02 (3H, t), 1.50 (3H, d), 1.82 (2H, m), 2.28 (3H, s), 2.53 (4H, m), 2.98 (2H, t), 3.16 (4H, m), 3.55 (3H, s), 3.66 (1H, m), 3.76 (1H, m), 4.07 (3H, s), 5.61 (1H, m), 8.61 (1H, s), 8.92 (1H, s), 10.82 (1H, s).

LRMS : m/z 520 $(M+1)^+$

The title compound of Example 105 was isolated using the same procedure as for Example 104, (26mg, 12%, 94.0%ee).

$[\alpha]_D$ = -30.31° (c=0.067, dichloromethane)

δ ($CDCl_3$) : 1.02 (3H, t), 1.51 (3H, d), 1.82 (2H, m), 2.29 (3H, s), 2.53 (4H, m), 2.98 (2H, t), 3.14 (4H, m), 3.55 (3H, s), 3.65 (1H, m), 3.77 (1H, m), 4.08 (3H, s), 5.61 (1H, m), 8.61 (1H, s), 8.92 (1H, s), 10.82 (1H, s).

LRMS : m/z 520 $(M+1)^+$

-80-

EXAMPLE 106

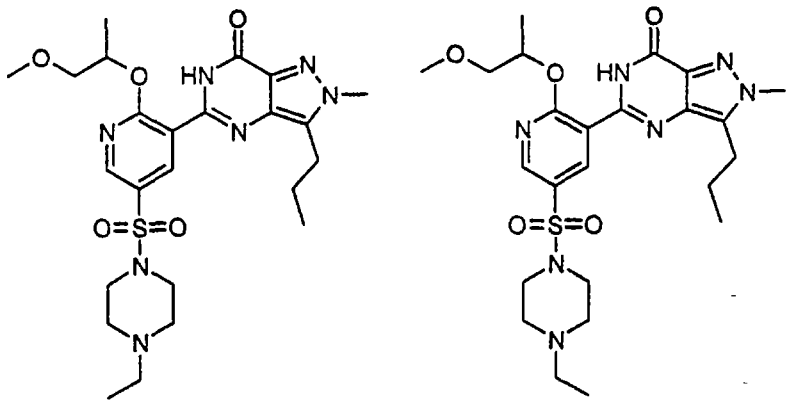
(+)-5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1-methylethoxy)pyridin-3-yl]-2-methyl -3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

and

EXAMPLE 107

(-)-5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1-methylethoxy)pyridin-3-yl]-2-methyl -3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

(isomers 1 and 2)



Potassium bis(trimethylsilyl)amide (1.47g, 7.4mmol) was added to a solution of the title compound of Example 80 (720mg, 1.5mmol) in 1-methoxy-2-propanol (10ml) and the reaction stirred under reflux for 72 hours. The cooled mixture was evaporated under reduced pressure and the residual brown gum purified by column chromatography on silica gel, using ethyl acetate: diethylamine (97:3) as eluant. This racemic mixture was purified by chiral HPLC using an AD 250 column, and hexane: isopropanol: diethylamine (70:30:0.3) as eluant, to give each enantiomer. The first enantiomer was partitioned between dichloromethane (20ml) and aqueous sodium carbonate solution (10ml), the phases separated, and the organic layer dried (Na_2SO_4), and evaporated under reduced pressure. The product was further purified by column chromatography on silica gel, using ethyl acetate: methanol (95:5) as eluant, to afford the title compound of Example 106 (130mg, 16%, 99.76%ee) as a white foam.

$[\alpha]_D$ = +15.65° (c=0.093, methanol).

Found : C, 53.47; H, 6.66; N, 17.92. $C_{24}H_{35}N_7O_5S;0.3H_2O$ requires C, 53.48; H, 6.66; N, 18.19%

δ ($CDCl_3$) : 1.02 (6H, m), 1.52 (3H, t), 1.82 (2H, m), 2.42 (2H, q), 2.57 (4H, m), 2.98 (2H, t), 3.14 (4H, m), 3.55 (3H, s), 3.65 (1H, m), 3.76 (1H, m), 4.08 (3H, s), 5.60 (1H, s), 8.61 (1H, s), 8.90 (1H, s), 10.81 (1H, s).

LRMS : m/z 534 $(M+1)^+$

The title compound of Example 107 was obtained (94mg, 12%, 97.2%ee) as a white foam, using the same procedure as in Example 106.

$[\alpha]_D$ = -14.52° (c=0.10, methanol)

Found : C, 53.66; H, 6.73; N, 17.89. $C_{24}H_{35}N_7O_5S;0.25H_2O$ requires C, 53.57; H, 6.65; N, 18.22%

δ ($CDCl_3$) : 1.03 (6H, m), 1.50 (3H, d), 1.82 (2H, m), 2.42 (2H, q), 2.57 (4H, m), 2.98 (2H, m), 3.17 (4H, m), 3.55 (3H, s), 3.65 (1H, m), 3.75 (1H, m), 4.08 (3H, s), 5.60 (1H, m), 8.60 (1H, s), 8.91 (1H, s), 10.81 (1H, s).

LRMS : m/z 534 $(M+1)^+$

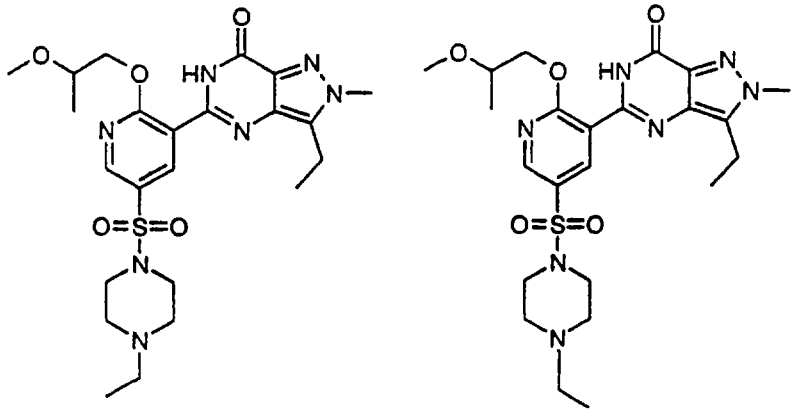
EXAMPLE 108

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-n-propoxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (isomer 1)

and

EXAMPLE 109

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-n-propoxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (isomer 2)



The title compounds were prepared from the title compound of Example 78, and 2-methoxy-1-propanol following a similar procedure to that described for Examples 104 and 105.

The racemate was further purified by HPLC using an AD250 column and hexane: ethanol:diethylamine (60:40:1) as eluant, to give isomer 1. This product was re-purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol (100:0 to 97:3) and triturated with ether to afford the title compound of Example 108 (8mg, 2%, 82%ee) as a white solid.

δ ($CDCl_3$) : 1.19-1.36 (6H, m), 1.40 (3H, t), 2.68-3.10 (8H, m), 3.32-3.59 (7H, m), 3.92 (1H, m), 4.09 (3H, s), 4.47 (1H, m), 4.72 (1H, m), 8.62 (1H, s), 8.97 (1H, s), 10.90 (1H, s).

LRMS : m/z 520 $(M+1)^+$

The title compound of Example 109 was isolated (5mg, 1%, 93%ee) as a white solid, using the same procedure as described for Example 108.

δ ($CDCl_3$) : 1.26 (3H, t), 1.32 (3H, d), 1.40 (3H, t), 2.80-3.10 (8H, m), 3.38-3.60 (7H, m), 3.92 (1H, m), 4.09 (3H, s), 4.48 (1H, m), 4.72 (1H, m), 8.61 (1H, s), 8.98 (1H, s), 10.89 (1H, s).

LRMS : m/z 520 $(M+1)^+$

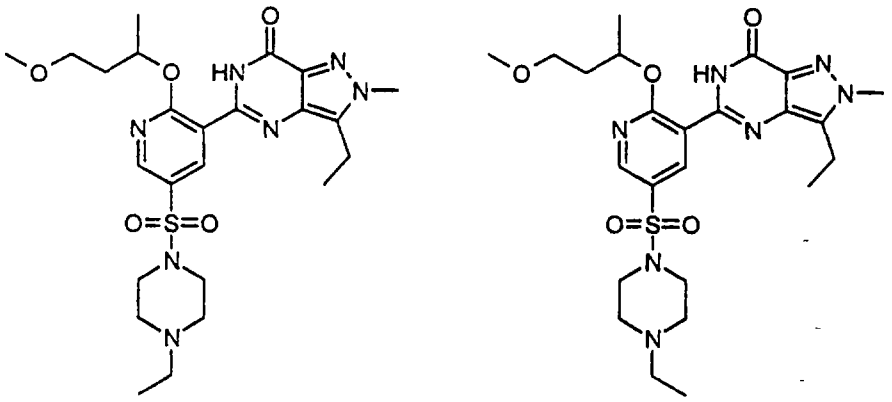
EXAMPLE 110

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(3-methoxy-1-methyl-n-propoxy)pyridin-3-yl]-2-methyl -2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

and

EXAMPLE 111

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(3-methoxy-1-methyl-n-propoxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (isomers 1 and 2)



A mixture of the title compound of Example 78 (330mg, 0.70mmol) and potassium bis(trimethylsilyl)amide (693mg, 3.47mmol) in the title compound of preparation 166 (2.5ml) was heated at 110°C for 16 hours. The cooled reaction was suspended in ethyl acetate (25ml), and washed with saturated ammonium chloride solution (5ml), then saturated sodium bicarbonate solution (10ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using methanol: dichloromethane (5:95) as eluant, and repeated using diethylamine: ethyl acetate (10:90) as eluant to give a gum.

This racemate was purified by HPLC using an AD250 column, and hexane: ethanol:diethylamine (85:15:1) as eluant to afford the title compound of Example 110 (25mg, 6.7%, 98.9%ee)

δ ($CDCl_3$) : 1.04 (3H, t), 1.39 (3H, t), 1.49 (3H, d), 2.04 (1H, m), 2.24 (1H, m), 2.42 (2H, q), 2.56 (4H, m), 3.01 (2H, m), 3.16 (4H, m), 3.33 (3H, s), 3.57 (1H, m), 3.68 (1H, m), 4.06 (3H, s), 5.75 (1H, m), 8.61 (1H, s), 8.88 (1H, s), 10.99 (1H, s).

LRMS : m/z 534 $(M+1)^+$

and the title compound of Example 111 (29mg, 7.8%, 99.7%ee).

δ ($CDCl_3$) : 1.03 (3H, t), 1.40 (3H, t), 1.48 (3H, d), 2.04 (1H, m), 2.24 (1H, m), 2.42 (2H, q), 2.58 (4H, m), 3.02 (2H, q), 3.16 (4H, m), 3.34 (3H, s), 3.57 (1H, m), 3.66 (1H, m), 4.08 (3H, s), 5.74 (1H, m), 8.60 (1H, s), 8.98 (1H, s), 10.98 (1H, s).

LRMS : m/z 534 $(M+1)^+$

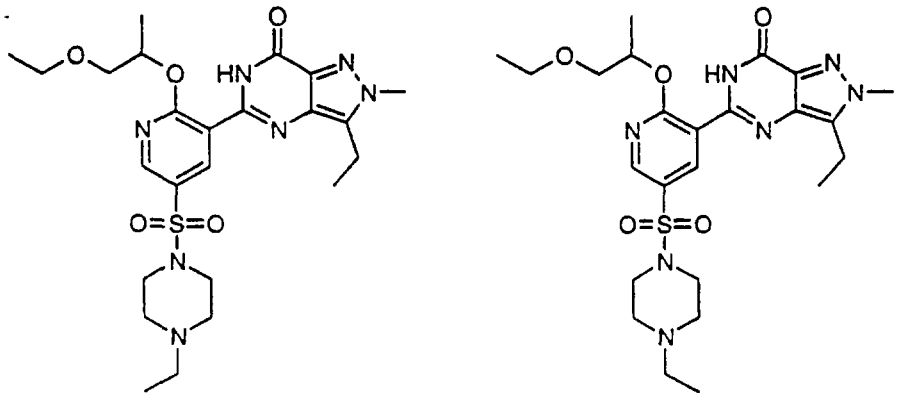
EXAMPLE 112

(+)-3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-ethoxy-1-methylethoxy)pyridin-3-yl]-2-methyl -2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (isomer 1)

and

EXAMPLE 113

(-)-3-Ethyl-5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-ethoxy-1-methylethoxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (isomer 2)



The racemate was prepared (70%) from the title compound of Example 78 and 1-ethoxy-2-propanol, following the procedure described for Examples 104 and 105.

This racemate was purified by chiral HPLC using an AD 250 column, and hexane: isopropanol:diethylamine (70:30:0.3) as eluant, to give enantiomer 1. This product was further purified by column chromatography on silica gel, using dichloromethane: methanol (97:3) as eluant, and evaporated from ether, to afford the title compound of Example 112 (52mg, 15%, 99.5%ee) as a foam.

$[\alpha]_D$ = +18.60° (c=0.067, dichloromethane)

Found : C, 53.20; H, 6.70; N, 17.78. $C_{24}H_{35}N_7O_5S;0.5H_2O$ requires C, 53.12; H, 6.69; N, 18.07%

δ ($CDCl_3$) : 1.04 (3H, t), 1.25 (3H, t), 1.40 (3H, t), 1.52 (3H, d), 2.42 (2H, q), 2.57 (4H, m), 3.02 (2H, q), 3.15 (4H, m), 3.60-3.82 (4H, m), 4.08 (3H, s), 5.60 (1H, m), 8.61 (1H, s), 8.94 (1H, s), 10.81 (1H, s).

LRMS : m/z 534 $(M+1)^+$

The title compound of Example 113 was isolated (11mg, 3%, 99.5%ee) following the same procedure to that described for Example 112.

$[\alpha]_D$ = -19.43° (c=0.070, dichloromethane)

Found : C, 53.34; H, 6.66; N, 17.86. $C_{24}H_{35}N_7O_5S;0.5H_2O$ requires C, 53.12; H, 6.69; N, 18.07%

δ ($CDCl_3$) : 1.04 (3H, t), 1.25 (3H, t), 1.40 (3H, t), 1.52 (3H, d), 2.42 (2H, q), 2.57 (4H, m), 3.03 (2H, q), 3.16 (4H, m), 3.60-3.82 (4H, m), 4.09 (3H, s), 5.60 (1H, m), 8.62 (1H, s), 8.92 (1H, s), 10.82 (1H, s).

LRMS : m/z 534 $(M+1)^+$

EXAMPLE 114

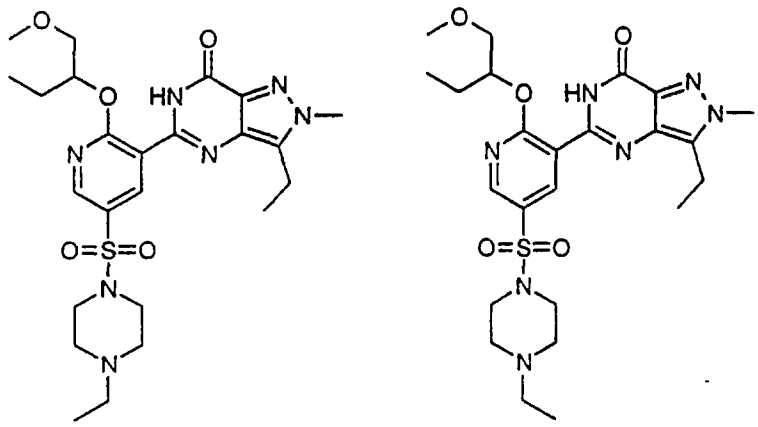
(+)-3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(1-methoxymethyl-n-propoxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

and

EXAMPLE 115

(-)-3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(1-methoxymethyl-n-propoxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

(isomers 1 and 2)



The title compounds of Examples 114 and 115 were obtained (11%, 93%ee) and (6.7%, 97%ee) respectively from the title compound of Example 78 and 1-methoxy-2-butanol, using the procedure described in Examples 108 and 109.

$[\alpha]_D$ = +37.04° (c=0.097, dichloromethane)

Found : C, 53.36; H, 6.73; N, 17.84. $C_{24}H_{35}N_7O_5S;0.5H_2O$ requires C, 53.12; H, 6.69; N, 18.07%

δ ($CDCl_3$) : 1.03 (6H, m), 1.39 (3H, t), 1.92 (2H, m), 2.42 (2H, q), 2.57 (4H, m), 3.02 (2H, q), 3.16 (4H, m), 3.51 (3H, s), 3.66 (1H, m), 3.77 (1H, m), 4.08 (3H, s), 5.57 (1H, m), 8.60 (1H, s), 8.88 (1H, s), 10.84 (1H, s).

LRMS : m/z 534 $(M+1)^+$; and α_D = -40.08° (c=0.093, dichloromethane)

Found : C, 53.44; H, 6.75; N, 17.76. $C_{24}H_{35}N_7O_5S;0.5H_2O$ requires C, 53.12; H, 6.69; N, 18.07%

δ ($CDCl_3$) : 1.03 (6H, m), 1.40 (3H, t), 1.92 (2H, m), 2.42 (2H, q), 2.57 (4H, m), 3.02 (2H, q), 3.16 (4H, m), 3.51 (3H, s), 3.68 (1H, m), 3.78 (1H, m), 4.10 (3H, s), 5.57 (1H, m), 8.61 (1H, m), 8.89 (1H, s), 10.83 (1H, s).

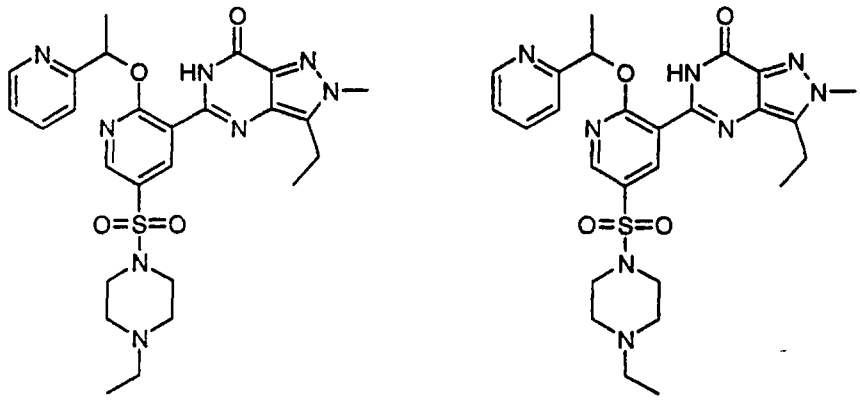
EXAMPLE 116

(-)-3-Ethyl-5-{5-(4-ethylpiperazin-1-ylsulphonyl)-2-[1-(pyridin-2-yl)ethoxy]pyridin-3-yl}-2-methyl -2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (isomer 1)

and

EXAMPLE 117

(+)-3-Ethyl-5-{5-(4-ethylpiperazin-1-ylsulphonyl)-2-[1-(pyridin-2-yl)ethoxy]pyridin-3-yl}-2-methyl -2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (isomer 2)



The title compounds of Example 116 and 117 were obtained as solids, (4%, 99.0%ee) and (2%, 99.0%ee) respectively, from the title compound of Example 78 and 1-(pyridin-2-yl) ethanol (Helv.Chim.Acta., 1955, 38, 1114), following a similar procedure to that described for Examples 112 and 113, except that hexane: isopropanol: diethylamine (70:30:1) was used as the HPLC eluant.

$[\alpha]_D$ = -90.11° (c=0.033, dichloromethane)

δ ($CDCl_3$) : 1.02 (3H, t), 1.40 (3H, t), 1.80 (3H, d), 2.41 (2H, q), 2.54 (4H, m), 3.00-3.17 (6H, m), 4.10 (3H, s), 6.69 (1H, q), 7.32 (2H, m), 7.75 (1H, m), 8.54 (1H, s), 8.75 (1H, s), 8.80 (1H, d), 13.14 (1H, s).

LRMS : m/z 553 $(M+1)^+$

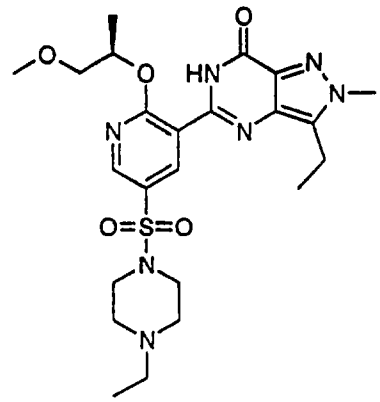
$[\alpha]_D$ = +82.02° (c=0.040, dichloromethane)

δ ($CDCl_3$) : 1.04 (3H, t), 1.40 (3H, m), 1.80 (3H, d), 2.41 (2H, q), 2.55 (4H, m), 3.00-3.18 (6H, m), 4.10 (3H, s), 6.69 (1H, q), 7.34 (2H, m), 7.75 (1H, m), 8.52 (1H, s), 8.76 (1H, s), 8.80 (1H, d), 13.16 (1H, s).

LRMS : m/z 553 $(M+1)^+$

EXAMPLE 118

(+)-3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1(R)-methyl ethoxy) pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



A mixture of the title compound of example 78 (2.0g, 4.2mmol) and potassium bis(trimethylsilyl)amide (4.2g, 21.0mmol) in the title compound of Preparation 165 (16ml), was heated at 110°C for 18 hours. The cooled mixture was concentrated under reduced pressure and the residue purified by column chromatography on silica gel using an elution gradient of diethylamine: methanol:ethyl acetate (2.5:0:97.5 to 0:10:90). The product was purified further by column chromatography on silica gel using methanol: ethyl acetate (2.5:97.5) as eluant to afford the title compound (640mg, 29%) as a solid.

Found : C, 53.16; H, 6.54; N, 18.37. $C_{23}H_{33}N_7O_5S;0.2CH_3CO_2C_2H_5$ requires C, 53.21; H, 6.49; N, 18.25%

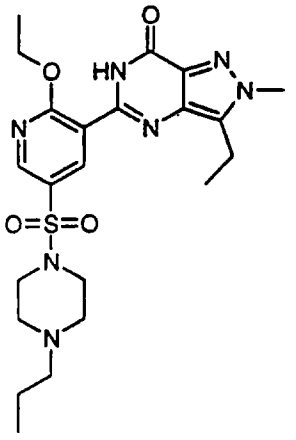
$[\alpha]_D$ = +16.6° (c=0.10 methanol)

δ ($CDCl_3$) : 1.04 (3H, t), 1.40 (3H, t), 1.52 (3H, d), 2.42 (2H, q), 2.57 (4H, m), 3.03 (2H, q), 3.15 (4H, m), 3.56 (3H, s), 3.66 (1H, m), 3.77 (1H, m), 4.09 (3H, s), 5.61 (1H, m), 8.62 (1H, s), 8.93 (1H, s), 10.82 (1H, s).

LRMS : m/z 520 $(M+1)^+$

EXAMPLE 119

5-[2-Ethoxy-5-(4-n-propylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

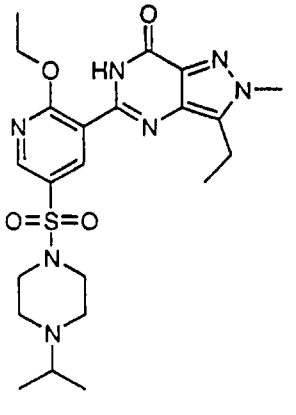


1-n-Propylpiperazine (308mg, 1.01mmol) and triethylamine (440ml, 3.2mmol) were added to a solution of the title compound of Preparation 164 (211mg, 0.53mmol) in dichloromethane (6ml), and the reaction mixture stirred at room temperature for 2 hours. The mixture was purified directly by column chromatography on silica gel, using dichloromethane: methanol (95:5) as eluant to afford the title compound (210mg, 85%) as a white foam.

δ ($CDCl_3$) : 0.86 (3H, t), 1.42 (5H, m), 1.58 (3H, t), 2.29 (2H, t), 2.56 (4H, m), 3.03 (2H, q), 3.14 (4H, m), 4.10 (3H, s), 4.76 (2H, q), 8.62 (1H, s), 9.04 (1H, s), 10.67 (1H, s). LRMS : m/z 490 $(M+1)^+$

EXAMPLE 120

5-{2-Ethoxy-5-[4-(prop-2-yl)piperazin-1-ylsulphonyl]pyridin-3-yl}-3-ethyl-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



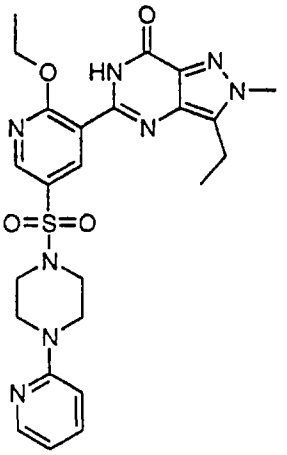
Obtained as a white solid (71%), from the title compound of Preparation 164 and 1-(prop-2-yl)-piperazine, following the procedure described in Example 119.

δ ($CDCl_3$) : 0.99 (6H, d), 1.40 (3H, t), 1.57 (3H, t), 2.62 (4H, m), 2.70 (1H, m), 3.02 (2H, q), 3.13 (4H, m), 4.08 (3H, s), 4.74 (2H, q), 8.62 (1H, s), 9.03 (1H, s), 10.64 (1H, s).

LRMS : m/z 490 $(M+1)^+$

EXAMPLE 121

5-{2-Ethoxy-5-[4-(pyridin-2-yl)piperazin-1-ylsulphonyl]pyridin-3-yl}-3-ethyl-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



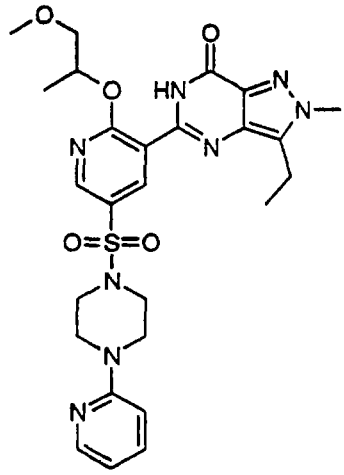
Obtained as a white solid (58%), from the title compound of Preparation 164 and 1-(pyridin-2-yl)piperazine, following the procedure described in Example 119.

δ ($CDCl_3$) : 1.41 (3H, t), 1.59 (3H, t), 3.05 (2H, q), 3.22 (4H, m), 3.70 (4H, m), 4.10 (3H, s), 4.75 (2H, q), 6.62 (2H, m), 7.47 (1H, m), 8.16 (1H, d), 8.64 (1H, s), 9.07 (1H, s), 10.65 (1H, s).

LRMS : m/z 525 $(M+1)^+$

EXAMPLE 122

3-Ethyl-5-{2-(2-methoxy-1-methylethoxy)-5-[4-(pyridin-2-yl)piperazin-1-ylsulphonyl]pyridin-3-yl}-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



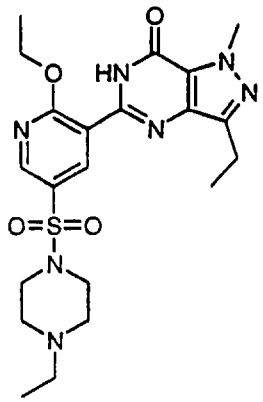
Potassium bis(trimethylsilyl)amide (76mg, 0.38mmol) was added to a solution of the title compound of Example 121 (50mg, 0.095mmol) in 1-methoxy-2-propanol (5ml) and the reaction heated under reflux for 18 hours. The cooled mixture was purified directly by column chromatography on silica gel, using dichloromethane: methanol (95:5) as eluant to afford the title compound (32mg, 59%) as a yellow oil.

δ ($CDCl_3$) : 1.40 (3H, t), 1.50 (3H, d), 3.04 (2H, q), 3.22 (4H, m), 3.54 (3H, s), 3.69 (6H, m), 4.09 (3H, s), 5.60 (1H, m), 6.63 (2H, m), 7.47 (1H, m), 8.16 (1H, d), 8.63 (1H, s), 8.94 (1H, s), 10.81 (1H, s).

LRMS : m/z 569 $(M+1)^+$

EXAMPLE 123

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-1-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



A mixture of the title compound of Preparation 158 (596mg, 1.21mmol) and potassium bis(trimethylsilyl)amide (723mg, 3.62mmol) in ethanol (20ml) was heated at 120°C for 18 hours in a sealed vessel. The cooled mixture was evaporated under reduced pressure and the residue purified by column chromatography on silica gel twice, using dichloromethane: methanol (95:5) as eluant. The product was triturated with ether to afford the title compound (358mg, 62%) as an off-white solid.

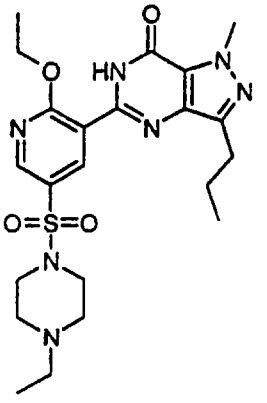
Found : C, 52.71; H, 6.00; N, 20.48. $C_{21}H_{29}N_7O_4S$ requires C, 53.04; H, 6.15; N, 20.62%

δ ($CDCl_3$) : 1.04 (3H, t), 1.40 (3H, t), 1.60 (3H, t), 2.42 (2H q), 2.58 (4H, m), 2.99 (2H, q), 3.16 (4H, m), 4.28 (3H, s), 4.78 (2H, q), 8.64 (1H, s), 9.08 (1H, s), 10.80 (1H, s).

LRMS : 476 $(M+1)^+$

EXAMPLE 124

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



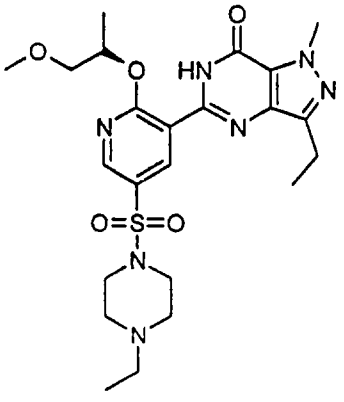
Obtained (42%) from the title compound of Preparation 159, following a similar procedure to that described in Example 123.

Found : C, 53.68; H, 6.34; N, 19.97. $C_{22}H_{31}N_7O_4S$ requires C, 53.97; H, 6.38; N, 20.03%

δ ($CDCl_3$) : 1.02 (6H, m), 1.60 (3H, t), 1.85 (2H, m), 2.42 (2H, q), 2.58 (4H, m), 2.95 (2H, t), 3.16 (4H, m), 4.29 (3H, s), 4.78 (2H, q), 8.63 (1H, s), 9.08 (1H, s), 10.78 (1H, s). LRMS : m/z 491 $(M+1)^+$

EXAMPLE 125

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1(R)-methylethoxy)pyridin-3-yl]-1-methyl -1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

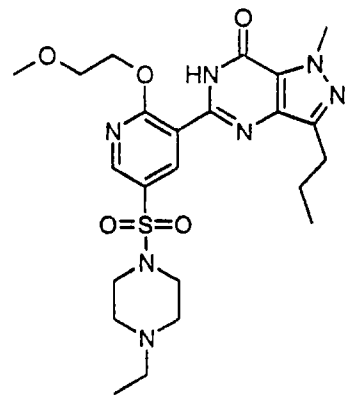


A mixture of the title compound of Example 123 (70mg, 0.15mmol) and potassium bis(trimethylsilyl)amide (150mg, 0.74mmol) in the title compound of Preparation 165 (1ml), was stirred at 110°C for 18 hours. The cooled mixture was concentrated under reduced pressure and the residue partitioned between water (5ml) and dichloromethane (5ml), and the mixture neutralised by the addition of solid carbon dioxide. The layers were separated, the aqueous phase extracted with dichloromethane (2x5ml), the combined organic solutions dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel, using ethyl acetate: diethylamine (97:3) as eluant to afford the title compound (62mg, 80%).

δ ($CDCl_3$) : 1.04 (3H, t), 1.39 (3H, t), 1.50 (3H, d), 2.42 (2H, q), 2.58 (4H, m), 2.98 (2H, q), 3.15 (4H, m), 3.58 (3H, s), 3.70 (2H, m), 4.28 (3H, s), 5.58 (1H, m), 8.62 (1H, s), 8.90 (1H, s), 11.07 (1H, s).
LRMS : m/z 520 $(M+1)^+$

EXAMPLE 126

5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



A mixture of the title compound of Example 124 (111mg, 0.23mmol) and potassium bis(trimethylsilyl)amide (226mg, 1.13mmol) in 2-methoxyethanol (5ml) was stirred under reflux for 18 hours. The cooled mixture was evaporated

under reduced pressure and the residue purified by column chromatography on silica gel, using dichloromethane: methanol (96:4) as eluant, and triturated with ether to afford the title compound (75mg, 64%) as a white crystalline solid.

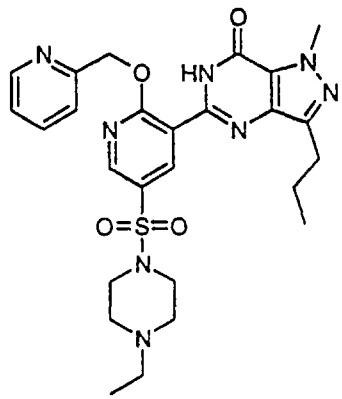
Found : C, 52.87; H, 6.35; N, 18.68. $C_{23}H_{33}N_7O_5S$ requires C, 53.16; H, 6.40; N, 18.87%

δ ($CDCl_3$) : 1.02 (6H, m), 1.85 (2H, m), 2.42 (2H, q), 2.57 (4H, m), 2.94 (2H, t), 3.16 (4H, m), 3.60 (3H, s), 3.86 (2H, t), 4.27 (3H, s), 4.78 (2H, t), 8.62 (1H, s), 9.00 (1H, s), 10.51 (1H, s).

LRMS : m/z 521 $(M+2)^+$

EXAMPLE 127

5-{5-(4-Ethylpiperazin-1-ylsulphonyl)-2-[(pyridin-2-yl)methoxy]pyridin-3-yl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



A mixture of the title compound of Example 124 (100mg, 0.20mmol) and potassium bis(trimethylsilyl)amide (204mg, 1.02mmol) in pyridine-2-methanol (2ml) was stirred at 110°C for 18 hours, then cooled. The solvent was removed by Kugelrohr distillation, and the residue was purified by column chromatography on silica gel, using dichloromethane: methanol (95:5) as eluant. This product was triturated with ether to afford the title compound (8mg, 7%) as a solid.

δ ($CDCl_3$) : 1.03 (6H, m), 1.87 (2H, m), 2.42 (2H, q), 2.56 (4H, m), 2.95 (2H, t), 3.16 (4H, m), 4.30 (3H, s), 5.94 (2H, s), 7.36 (2H, m), 7.68 (1H, m), 8.60 (1H, s), 8.86 (2H, d), 13.34 (1H, s).

LRMS : m/z 554 $(M+1)^+$

EXAMPLE 128

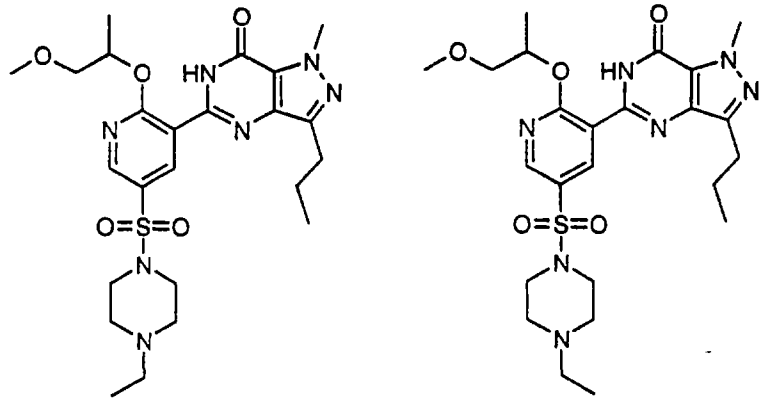
(+)-5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1-methylethoxy)pyridin-3-yl]-1-methyl 3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

and

EXAMPLE 129

(-)-5-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1-methylethoxy)pyridin-3-yl]-1-methyl 3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

(isomer 1 and isomer 2)



The title compounds of Examples 128 and 129 were prepared from Example 124 (17%, 99.5%ee) and (15%, 98.6%ee) respectively, following a procedure similar to that described in Examples 106 and 107, except that hexane :isopropanol : diethylamine :trifluoroacetic acid (85:15:0.2:0.3) was used as the HPLC eluant. $[\alpha]_D$ = +31.21° (c=0.067 dichloromethane)

Found : C. 53.77; H, 6.71; N, 17.89. $C_{24}H_{35}N_7O_5S;0.5H_2O$ requires C, 53.12; H, 6.69; N, 18.07%

δ ($CDCl_3$) : 1.02 (6H, m), 1.50 (3H, d), 1.84 (2H, m), 2.42 (2H, q), 2.58 (4H, m), 2.94 (2H, t), 3.17 (4H, m), 3.58 (3H, s), 3.72 (2H, m), 4.28 (3H, s), 5.58 (1H, m), 8.62 (1H, s), 8.90 (1H, s), 11.08 (1H, s); and

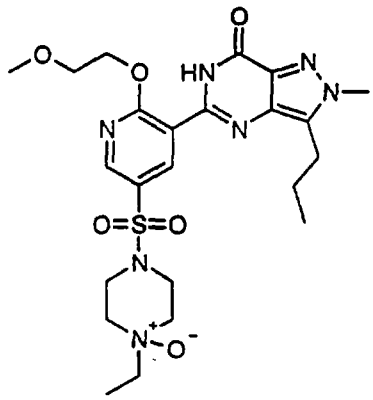
$[\alpha]_D$ = -34.10° (c=0.072 dichloromethane)

Found : C, 53.75; H, 6.67; N, 18.04. $C_{24}H_{35}N_7O_5S$ requires C, 54.02; H, 6.61; N, 18.37%

δ ($CDCl_3$) : 1.02 (6H, m), 1.50 (3H, d), 1.84 (2H, m), 2.42 (2H, q), 2.58 (4H, m), 2.94 (2H, t), 3.15 (4H, m), 3.59 (3H, s), 3.70 (2H, m), 4.28 (3H, s), 5.59 (1H, m), 8.62 (1H, s), 8.92 (1H, s), 11.17 (1H, s), respectively.

EXAMPLE 130

5-[5-(4-Ethyl-4-oxidopiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-methyl-3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



A mixture of the title compound of Example 93 (130mg, 0.25mmol) and 3-chloroperbenzoic acid (95mg, 0.275mmol) in dichloromethane (6ml) was stirred at room temperature for 2 ½ hours. The reaction mixture was washed with aqueous sodium bicarbonate solution (5ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residual foam was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol:0.88 ammonia (93:7:0 to 93:7:1) to afford the title compound (110mg, 82%) as a white solid.

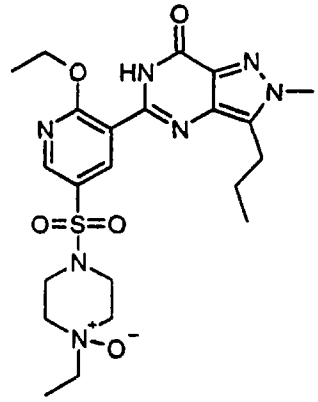
Found : C, 50.71; H, 6.27; N, 17.82. $C_{23}H_{33}N_7O_6S$ requires C, 50.72; H, 6.30; N, 18.00%

δ ($CDCl_3$) : 1.00 (3H, t), 1.40 (3H, t), 1.81 (2H, m), 2.98 (2H, t), 3.19 (2H, m), 3.33 (4H, m), 3.54 (5H, m), 3.70 (2H, m), 3.86 (2H, t), 4.06 (3H, s), 4.78 (2H, t), 8.63 (1H, s), 8.97 (1H, s), 10.87 (1H, s).

LRMS : m/z 536 $(M+1)^+$

EXAMPLE 131

5-[2-Ethoxy-5-(4-ethyl-4-oxidopiperazin-1-ylsulphonyl)pyridin-3-yl]-2-methyl-3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

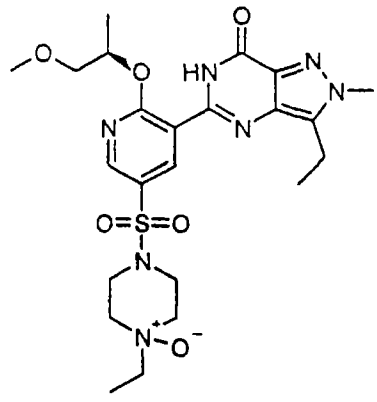


Obtained as a white foam (81%), from the title compound of Example 80 following the procedure described in Example 130.

δ ($CDCl_3$) : 1.00 (3H, t), 1.40 (2H, t), 1.38 (3H, t), 1.81 (2H, m), 2.97 (2H, t), 3.16 (2H, m), 3.30 (4H, m), 3.50 (2H, m), 3.70 (2H, m), 4.08 (3H, s), 4.74 (2H, q), 8.64 (1H, s), 9.00 (1H, s), 10.75 (1H, s). LRMS : m/z 506 $(M+1)^+$

EXAMPLE 132

3-Ethyl-5-[5-(4-ethyl-4-oxidopiperazin-1-ylsulphonyl)-2-(2-methoxy-1(R)-methyl ethoxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



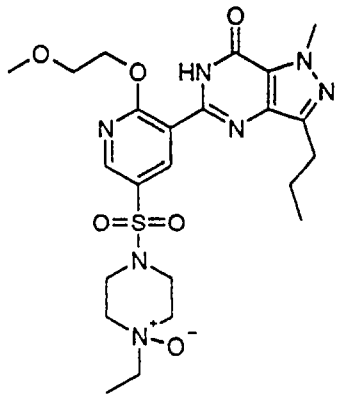
3-Chloroperbenzoic acid (95mg, 0.28mmol) was added to a solution of the title compound of Example 118 (130mg, 0.25mmol) in dichloromethane (2ml), and the reaction stirred at room temperature for 3 hours. The mixture was concentrated under reduced pressure and the residue was purified by column

chromatography on silica gel, using an elution gradient of dichloromethane:methanol:0.88 ammonia (95:5:0 to 90:10:1) to afford the title compound (130mg, 87%).

δ ($CDCl_3$) : 1.40 (6H, m), 1.52 (3H, d), 3.01 (2H, q), 3.22 (2H, ṁ), 3.34 (4H, m), 3.54 (5H, m), 3.73 (4H, m), 4.08 (3H, s), 5.62 (1H, m), 8.64 (1H, s), 8.94 (1H, s). LRMS : m/z 536 $(M+1)^+$

EXAMPLE 133

5-[5-(4-Ethyl-4-oxidopiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

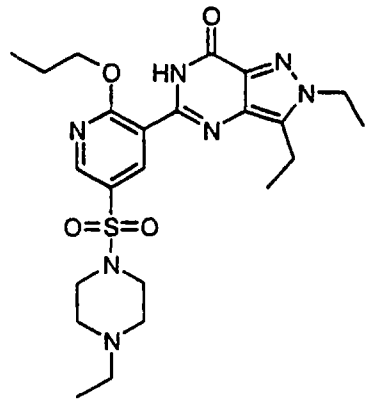


Obtained as a white solid (51%) from the title compound of Example 126 , using a similar procedure to that described in Example 130.

δ ($CDCl_3$) : 1.02 (3H, t), 1.41 (3H, t), 1.84 (2H, q), 2.92 (2H, t), 3.32 (2H, d), 3.36 (4H, m), 3.46-3.60 (5H, m), 3.74 (2H, m), 3.86 (2H, t), 4.29 (3H, s), 4.78 (2H, t), 8.64 (1H, s), 9.01 (1H, s), 11.05 (1H, s). LRMS : m/z 535 $(M)^+$

EXAMPLE 134

2,3-Diethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propoxypyridin-3-yl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



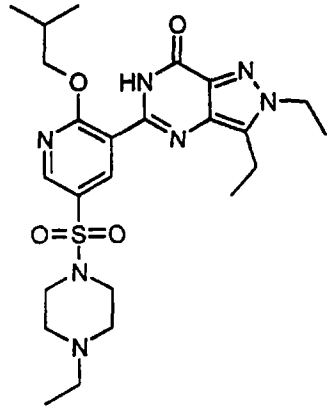
A mixture of the title compound of Example 81 (200mg, 0.41mmol), and potassium bis(trimethylsilyl)amide (407mg, 2.04mmol) in n-propanol (5ml) was stirred at 110°C for 18 hours and the cooled reaction, evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of ethyl acetate: diethylamine (100:0 to 95:5) and triturated with ether to afford the title compound (160mg, 68%) as a solid.

($CDCl_3$) : 1.02 (3H, t), 1.10 (3H, t), 1.42 (3H, t), 1.59 (3H, t), 2.00 (4H, m), 2.42 (2H, q), 2.58 (4H, m), 3.02 (2H, q), 3.14 (4H, m), 4.38 (2H, q), 4.63 (2H, t), 8.63 (1H, s), 9.04 (1H, s).

LRMS : m/z 504 $(M+1)^+$

EXAMPLE 135

5-[2-i-Butoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-2,3-diethyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



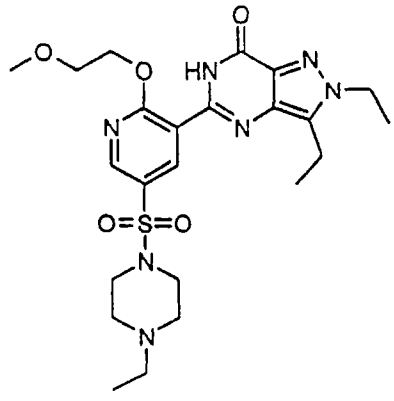
Obtained as a solid (65%) from the title compound of Example 81 and i-butanol, using the procedure described in Example 134.

δ ($CDCl_3$) : 1.02 (3H, t), 1.15 (6H, d), 1.42 (3H, t), 1.58 (3H, t), 2.30 (1H, m), 2.42 (2H, q), 2.57 (4H, m), 3.06 (2H, q), 3.16 (4H, m), 4.38 (2H, q), 4.45 (2H, d), 8.62 (1H, s), 9.03 (1H, s).

LRMS : m/z 518 $(M+1)^+$

EXAMPLE 136

2,3-Diethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



Obtained as a solid (33%) from the title compound of Example 81 and 2-methoxyethanol, using the procedure described in Example 134.

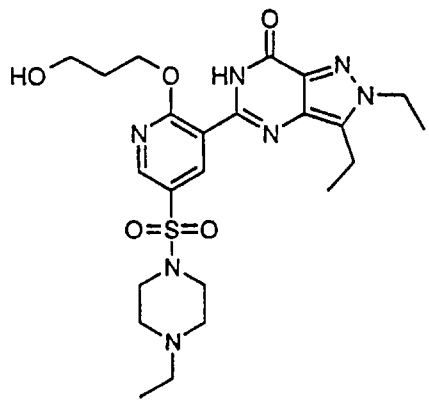
Found : C, 53.29; H, 6.20; N, 18.19. $C_{23}H_{33}N_7O_5S$ requires C, 53.16; H, 6.40; N, 18.87%

δ ($CDCl_3$) : 1.02 (3H, t), 1.42 (3H, t), 1.59 (3H, t), 2.44 (2H, q), 2.57 (4H, m), 3.05 (2H, q), 3.16 (4H, m), 3.58 (3H, s), 3.86 (2H, t), 4.28 (2H, q), 4.79 (2H, t), 8.62 (1H, s), 8.99 (1H, s).

LRMS : m/z 520 $(M+1)^+$

EXAMPLE 137

2,3-Diethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(3-hydroxy-n-propoxy)pyridin-3-yl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



A mixture of the title compound of Example 81 (200mg, 0.41mmol) and potassium bis(trimethylsilyl)amide (407mg, 2.04mmol) in 1,3-propanediol (3ml) was stirred at 110°C for 18 hours, then cooled and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of ethyl acetate: diethylamine (100:0 to 95:5). The product was partitioned between water (5ml) and dichloromethane (10ml), and the phases separated. The organic layer was washed with water (2x5ml), dried ($MgSO_4$), evaporated under reduced pressure and triturated with ether, to afford the title compound (90mg, 42%) as a solid.

δ ($CDCl_3$) : 1.02 (3H, t), 1.40 (3H, t), 1.57 (3H, t), 2.16 (2H, m), 2.42 (2H, q), 2.55 (4H, m), 3.02 (2H, q), 3.15 (4H, m), 4.00 (2H, t), 4.37 (2H, q), 4.80 (2H, t), 8.62 (1H, s), 8.96 (1H, s). LRMS : m/z 520 $(M+1)^+$

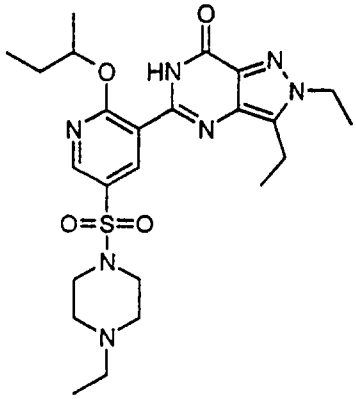
EXAMPLE 138

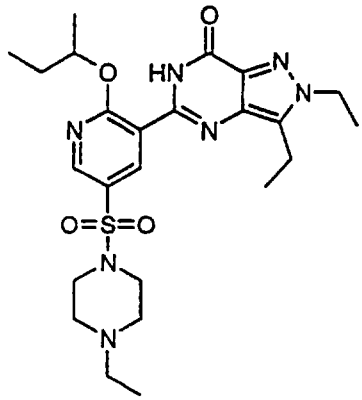
2,3-Diethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(1-methyl-n-propoxy)pyridin-3-yl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (isomer 1)

and

EXAMPLE 139

2,3-Diethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(1-methyl-n-propoxy)pyridin-3-yl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (isomer 2)





A mixture of the title compound of Example 81 (500mg, 1.02mmol) and potassium bis(trimethylsilyl)amide (1.01g, 5.11mmol) in 1-methyl-n-propanol (5ml) was stirred at 110°C for 18 hours, then cooled and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of ethyl acetate: diethylamine (100:0 to 95:5) and triturated with ether to give a solid. This racemate was further purified by chiral HPLC using an AD 250 column using hexane: isopropanol:diethylamine (90:10:1) as eluant, to afford the title compound of Example 138 (40mg, 8%, 95%ee) as a solid.

Found : C, 54.41; H, 6.71; N, 18.17; $C_{24}H_{35}N_7O_4S;0.2CH_2Cl_2$ requires C, 54.37; H, 6.67; N, 18.34%

δ ($CDCl_3$) : 1.04 (6H, m), 1.41 (3H, t), 1.50 (3H, d), 1.58 (3H, t0, 1.86 (1H, m), 1.98 (1H, m), 2.41 (2H, q), 2.58 (4H, m), 3.02 (2H, q), 3.15 (4H, m), 4.38 (2H, q), 5.55 (1H, m), 8.61 (1H, s), 9.02 (1H, s), 10.66 (1H, s);

and the title compound of Example 139 (70mg, 13%, 86%ee) as a solid.

Found : C, 55.91; H, 7.11; N, 18.55 $C_{24}H_{35}N_7O_4S$ requires C, 55.69; H, 6.82; N, 18.95%

δ ($CDCl_3$) : 1.05 (6H, m), 1.40 (3H, t), 1.50 (3H, d), 1.57 (3H, t), 1.84 (1H, m), 1.98 (1H, m), 2.42 (2H, q), 2.58 (4H, m), 3.04 (2H, q), 3.15 (4H, m), 4.38 (2H, q), 5.54 (1H, m), 8.61 (1H, s), 9.03 (1H, s), 10.67 (1H, s).

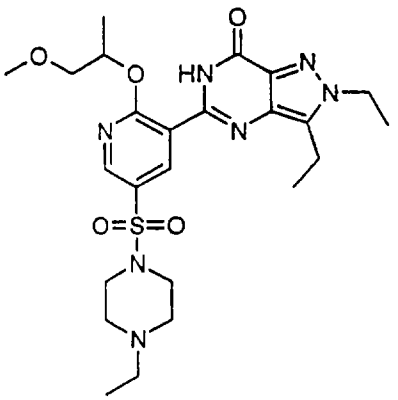
EXAMPLE 140

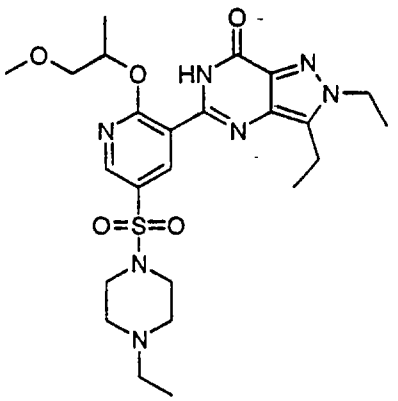
2,3-Diethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1-methylethoxy) pyridin-3-yl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (isomer 1)

and

EXAMPLE 141

2,3-Diethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1-methylethoxy) pyridin-3-yl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (isomer 2)





Obtained as solids (10%, 99.5%ee) and (10%, 99.1%ee) respectively, from the title compound of Example 81 and 1-methoxy-2-propanol (5ml), following a similar procedure to that described above, except, that hexane: isopropanol: diethylamine (70:30:1) was used as the HPLC eluant.

δ ($CDCl_3$) : 1.03 (3H, t), 1.40 (3H, t), 1.50 (3H, d), 1.58 (3H, t), 2.42 (2H, q), 2.58 (4H, m), 3.03 (2H, q), 3.15 (4H, m), 3.55 (3H, s), 3.64 (1H, m), 3.76 (1H, m), 4.37 (2H, q), 5.60 (1H, m), 8.60 (1H, s), 8.90 (1H, s).

LRMS : m/z 535 $(M+2)^+$

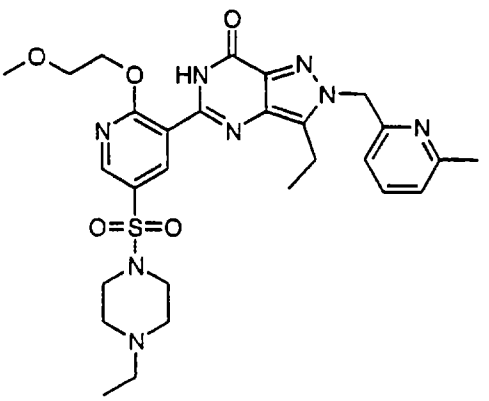
Found : C, 54.09; H, 6.91; N, 17.03. $C_{24}H_{35}N_7O_5S$ requires C, 54.02; H, 6.61; N, 18.38%

δ ($CDCl_3$) : 1.04 (3H, t), 1.40 (3H, t), 1.50 (3H, d), 1.58 (3H, t), 2.42 (2H, q), 2.58 (4H, m), 3.02 (2H, q), 3.12 (4H, m), 3.56 (4H, m), 3.65 (1H, m), 3.74 (1H, m), 4.37 (2H, q), 5.60 (1H, m), 8.60 (1H, s), 8.90 (1H, s).

LRMS : m/z 535 $(M+2)^+$, respectively.

EXAMPLE 142

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-(6-methyl-pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



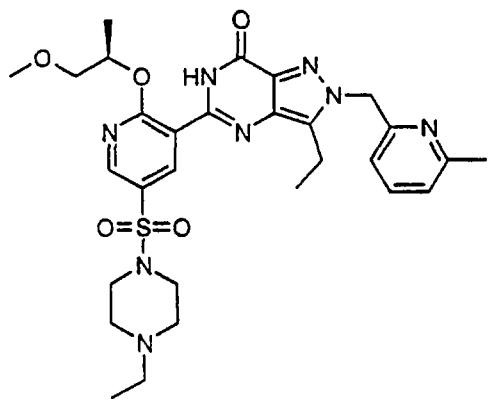
A mixture of the title compound of Example 82 (100mg, 0.176mmol), and potassium bis(trimethylsilyl)amide (175mg, 0.88mmol) in 2-methoxyethanol (1ml) was heated under reflux for 18 hours, then cooled. The solution was concentrated under reduced pressure and the residue partitioned between water (5ml) and dichloromethane (10ml), and the mixture neutralised using (2N) hydrochloric acid. The phases were separated, the aqueous layer extracted with dichloromethane (10ml), and the combined organic solutions dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel, using dichloromethane:methanol:0.88 ammonia (96:4:0.4) as eluant, and triturated with pentane, to afford the title compound (27mg, 26%) as an off-white solid.

Found : C, 56.14; H, 6.09; N, 18.53. $C_{28}H_{36}N_8O_5S$ requires C, 56.36; H, 6.08; N, 18.78%

δ ($CDCl_3$) : 1.02 (3H, t), 1.30 (3H, t), 2.42 (2H, q), 2.57 (7H, m), 3.04 (2H, q), 3.16 (4H, m), 3.58 (3H, s), 3.86 (2H, t), 4.79 (2H, t), 5.63 (2H, s), 6.78 (1H, d), 7.08 (1H, d), 7.48 (1H, m), 8.61 (1H, s), 8.98 (1H, s), 10.82 (1H, s).

EXAMPLE 143

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1(R)-methylethoxy)pyridin-3-yl]-2-(6-methylpyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



Obtained as a white solid (12%) from the title compounds of Examples 82 and 165, using a similar procedure to that described in Example 142, except the product was additionally purified by column chromatography on silica gel, using an elution gradient of ethyl acetate:methanol:0.88 ammonia (100:0:0 to 90:10:1), and then triturated with pentane.

δ ($CDCl_3$) :1.03 (3H, t), 1.30 (3H, t), 1.50 (3H, d), 2.42 (2H, q), 2.55 (6H, m), 3.02 (2H, q), 3.15 (4H, m), 3.56 (4H, m), 3.66 (1H, m), 3.76 (1H, m), 5.62 (3H, m), 6.78 (1H, d), 7.06 (1H, d), 7.49 (1H, m), 8.61 (1H, s), 8.90 (1H, s), 10.84 (1H, s).

LRMS : m/z 611 $(M+1)^+$

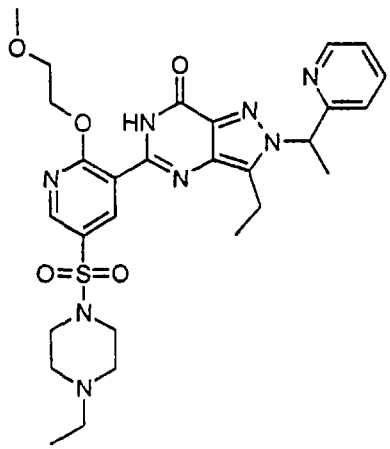
EXAMPLE 144

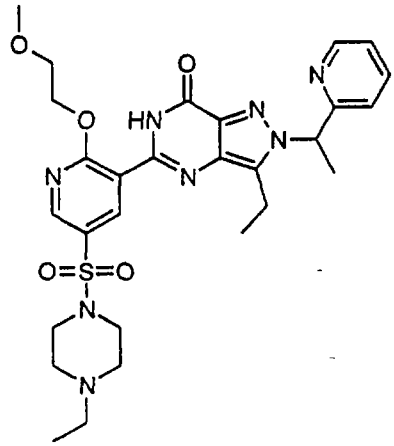
3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-[1-(pyridin-2-yl)ethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (isomer 1)

and

EXAMPLE 145

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-[1 -(pyridin-2-yl)ethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one(isomer2)





A mixture of the title compound of Example 84 (200mg, 0.35mmol) and potassium bis(trimethylsilyl)amide (350mg, 1.76mmol) in 2-methoxyethanol (5ml) was stirred at 120°C for 18 hours. The cooled mixture was concentrated under reduced pressure and the residue partitioned between aqueous saturated sodium bicarbonate solution (20ml) and ethyl acetate (20ml). The phases were separated, the aqueous layer extracted with ethyl acetate (2x10ml), and the combined organic solutions dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 95:5) to give a foam. This racemate was further purified by HPLC using an AD 250 column and hexane: isopropanol:diethylamine (50:50:1) as eluant to afford the title compound of Example 144 (24mg, 11%, 100.0%ee)

δ ($CDCl_3$) : 1.02 (3H, t), 1.25 (3H, t), 2.10 (3H, d), 2.40 (2H, q), 2.56 (4H, m), 3.00 (2H, q), 3.13 (4H, m), 3.58 (3H, s), 3.86 (2H, t), 4.77 (2H, t), 5.83 (1H, q), 7.18 (2H, m), 7.60 (1H, m), 8.55 (1H, d), 8.60 (1H, s), 8.96 (1H, s), 10.82 (1H, s).

LRMS : m/z 598 $(M+1)^+$

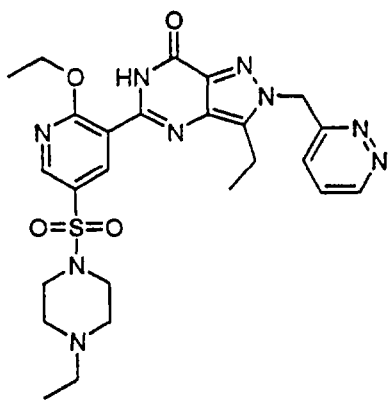
and the title compound of Example 145 (28mg, 13%, 99.8%ee).

δ ($CDCl_3$) : 1.00 (3H, t), 1.24 (3H, t), 2.10 (3H, d), 2.40 (2H, q), 2.55 (4H, m), 3.00 (2H, q), 3.14 (4H, m), 3 57 (3H, s), 3.84 (2H, t), 4.78 (2H, t), 5.82 (1H, q), 7.18 (2H, m), 7.60 (1H, m), 8.54 (1H, d), 8.60 (1H, s), 8.94 (1H, s), 10.82 (1H, s).

LRMS : m/z 598 $(M+1)^+$

EXAMPLE 146

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(pyridazin-3-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



A suspension of the title compound of Preparation 142 (1.12g, 4.55mmol) and triethylamine (1.5g, 13.7mmol) was added to an ice-cold suspension of the title compound of Preparation 28 (2.0g, 5.0mmol) in dichloromethane (25ml), and the reaction stirred at room temperature for 2 hours. The reaction mixture was washed with brine (15ml), saturated aqueous sodium bicarbonate solution (2x10ml), more brine (15ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel

using an elution gradient of dichloromethane:methanol:0.88 ammonia (99:0:1 to 96:3:1) to give a solid (1.73g).

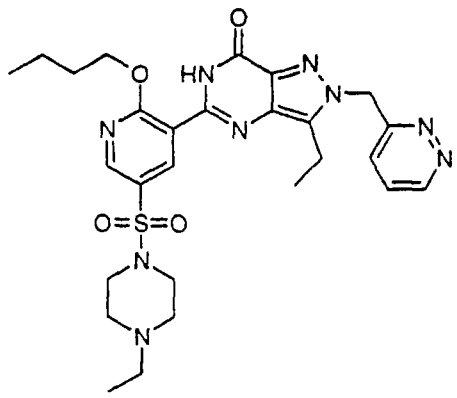
A mixture of this intermediate (829mg, 1.45mmol) and potassium bis(trimethylsilyl)amide (347mg, 1.74mmol) in 3-methyl-3-pentanol (3ml) was heated under reflux for 6 hours, and then stirred for 72 hours at room temperature. Additional potassium bis(trimethylsilyl)amide (87mg, 0.43mmol) was added, the reaction heated under reflux for a further 5 hours, then cooled, 2M hydrochloric acid (2ml) added and the mixture concentrated under reduced pressure. The residue was partitioned between dichloromethane (20ml) and water (10ml), the layers separated, the organic phase washed consecutively with water (10ml), saturated sodium bicarbonate solution (10ml), brine (10ml), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol (100:0 to 98:2) to afford the title compound (1.24g, 49%) as a light brown foam.

δ ($CDCl_3$) : 1.02 (3H, t), 1.36 (3H, t), 1.59 (3H, t), 2.40 (2H, q), 2.55 (4H, m), 3.14 (6H, m), 4.76 (2H, q), 5.90 (2H, s), 7.46 (1H, m), 7.56 (1H, m), 8.63 (1H, s), 9.01 (1H, s), 9.18 (1H, d), 10.70 (1H, s).

LRMS : m/z 554 $(M+1)^+$

EXAMPLE 147

5-[2-n-Butoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(pyridazin-3-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



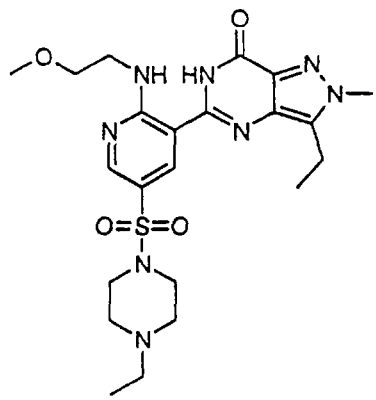
Potassium bis(trimethylsilyl)amide (35mg, 0.176mmol) was added to a solution of the title compound of Example 146 (80mg, 0.145mmol) in n-butanol (2ml), and the reaction stirred at 110°C for 6 ½ hours. The cooled mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate (20ml) and sodium bicarbonate solution (10ml). The phases were separated, the organic layer washed with additional sodium bicarbonate solution (10ml), brine (10ml), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (100:0:0 to 99.6:0.4:0.5) to afford the title compound (50mg, 59%) as a white foam.

δ ($CDCl_3$) : 1.04 (6H, m), 1.35 (3H, t), 1.58 (2H, m), 1.95 (2H, m), 2.41 (2H, q), 2.57 (4H, m), 3.10 (6H, m), 4.66 (2H, t), 5.90 (2H, s), 7.46 (1H, m), 7.56 (1H, m), 8.62 (1H, s), 9.01 (1H, s), 9.17 (1H, d), 10.79 (1H, s).

LRMS : m/z 582 $(M+1)^+$

EXAMPLE 148

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethylamino)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



A mixture of the title compound of Example 78 (200mg, 0.42mmol), and copper (II) sulphate pentahydrate (150mg, 0.60mmol) in 2-methoxyethylamine (2ml)

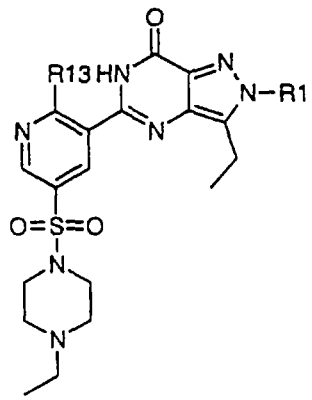
was heated under reflux for 2 hours, then cooled. The reaction was partitioned between dichloromethane (20ml) and aqueous sodium carbonate solution (5ml), and the layers separated. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol (98:2 to 95:5) to afford the title compound (150mg, 69%).

δ ($CDCl_3$) : 1.04 (3H, t), 1.40 (3H, t), 2.42 (2H, q), 2.55 (4H, m), 2.92 (3H, s), 3.01 (2H, q), 3.13 (4H, m), 3.50 (4H, m), 3.48 (3H, s), 3.68 (2H, t), 3.88 (2H, t), 4.07 (3H, s), 8.34 (1H, s), 8.58 (1H, s).

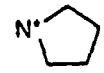
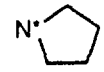
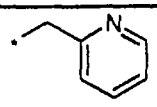
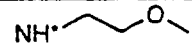
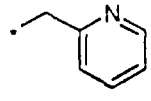
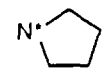
LRMS : m/z 519 $(M+1)^+$

EXAMPLES 149 TO 153

The compounds of the general formula:

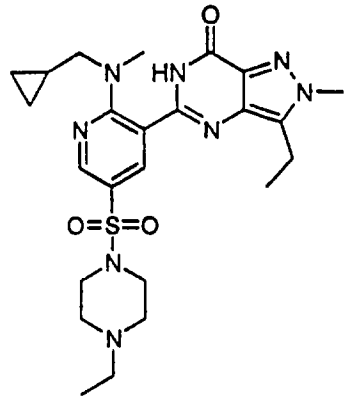


were prepared from the appropriate pyrazolo[4,3-d]pyrimidin-7-ones and amines, using procedures similar to that described in Example 148.

Example	R1	R13	Data
149	CH_3		δ ($CDCl_3$) : 1.02 (3H, t), 1.37 (3H, t), 2.26-2.42 (4H, m), 2.54 (4H, m), 3.01 (2H, q), 3.10 (4H, m), 4.05 (7H, m), 8.00 (1H, s), 8.57 (1H, s). LRMS : m/z 487 $(M+1)^+$
150	CH_3		δ ($CDCl_3$) : 1.02 (3H, t), 1.35 (3H, t), 1.89 (4H, m), 2.39 (2H, q), 2.55 (4H, m), 3.00 (2H, q), 3.11 (4H, m), 3.40 (4H, m), 4.08 (3H, s), 8.00 (1H, s), 8.57 (1H, s). LRMS : m/z 501 $(M+1)^+$
151	CH_2CH_3		Found : C, 55.53; H, 6.70; N, 21.52. $C_{24}H_{34}N_8O_3S$ requires C, 56.01; H, 6.66; N, 21.77% δ ($CDCl_3$) : 1.03 (3H, t), 1.38 (3H, t), 1.60 (3H, t), 1.88 (4H, m), 2.41 (2H, q), 2.57 (4H, m), 3.01 (2H,q), 3.10 (4H, m), 3.42 (4H, m), 4.38 (2H, q), 8.00 (1H, s), 8.58 (1H, s), 9.20 (1H, s). LRMS : m/z 515 $(M+1)^+$
152			Found : C, 54.63; H, 6.15; N, 20.97. $C_{27}H_{35}N_9O_4S$ requires C, 54.89; H, 6.14; N, 21.34% δ ($CDCl_3$) : 1.01 (3H, t), 1.33 (3H, t), 2.38 (2H, q), 2.54 (4H, m), 3.07 (2H, q), 3.16 (4H, m), 3.41 (3H, s), 3.65 (2H, t), 3.85 (2H, q), 5.67 (2H, s), 7.19 (1H, d), 7.25 (1H, m), 7.68 (1H, m), 8.14 (1H, s), 8.56 (1H, s), 8.58 (1H, d), 9.92 (1H, s), 10.07 (1H, m). LRMS : m/z 582 $(M+1)^+$
153			δ ($CDCl_3$) : 1.03 (3H, t), 1.26 (3H, t), 1.92 (4H, m), 2.41 (2H, q), 2.56 (4H, m), 3.02 (2H, q), 3.10 (4H, m), 3.42 (4H, m), 5.68 (2H, s), 7.19 (1H, d), 7.26 (1H, m), 7.67 (1H, m), 8.01 (1H, s), 8.58 (2H, m), 9.24 (1H, s). LRMS : m/z 578 $(M+1)^+$

EXAMPLE 154

5-[2-(N-Cyclopropylmethyl-N-methylamino)-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



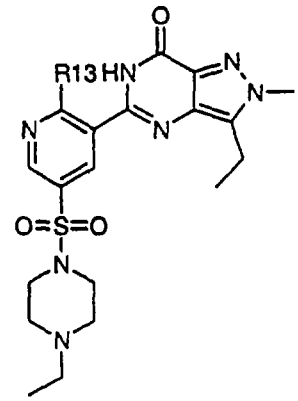
A mixture of the title compound of Example 78 (200mg, 0.42mmol), and N-cyclopropylmethyl-N-methylamine (600mg, 7.05mmol; obtained from the title compound of Preparation 168) and potassium bis(trimethylsilyl)amide (250mg, 1.26mmol) in N,N-dimethylformamide (2ml), was stirred at 100°C for 18 hours. The cooled mixture was partitioned between ethyl acetate (20ml) and aqueous sodium bicarbonate solution (10ml), and the phases separated. The organic layer was dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol (100:0 to 95:5) to afford the title compound (100mg, 46%) as a solid.

δ ($CDCl_3$) : 0.54 (2H, m), 0.71 (2H, m), 1.02 (3H, t), 1.37 (4H, m), 2.40 (2H, q), 2.56 (4H, m), 2.78-3.13 (11H, m), 4.08 (3H, s), 8.32 (1H, s), 8.60 (1H, s).

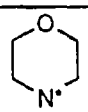
LRMS : m/z 515 $(M+1)^+$

EXAMPLES 155 TO 156

The compounds of the general formula:

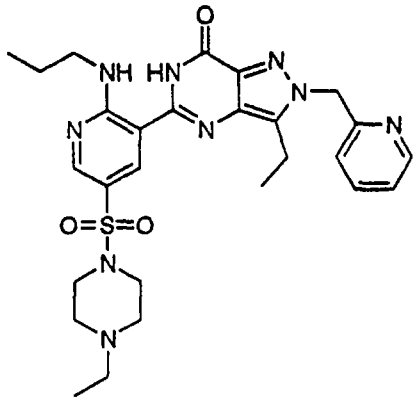


were prepared from the title compound of Example 78 and the appropriate amines, using procedures similar to that described in Example 154.

Example	R13	Data
155		δ ($CDCl_3$) : 1.01 (3H, t), 1.40 (3H, t), 1.58 (2H, m), 1.64 (2H, m), 1.77 (4H, m), 2.41 (2H, q), 2.55 (4H, m), 3.02 (2H, q), 3.12 (4H, m), 3.26 (2H, m), 4.10 (3H, s), 8.55 (1H, s), 8.63 (1H, s), 10.63 (1H, s). LRMS : m/z 515 $(M+1)^+$
156		δ ($CDCl_3$) : 1.04 (3H, t), 1.40 (3H, t), 2.42 (2H, q), 2.58 (4H, m), 3.03 (2H, q), 3.16 (4H, m), 3.35 (4H, m), 3.86 (4H, m), 4.10 (3H, s), 8.55 (1H, s), 8.68 (1H, s), 10.40 (1H, s). LRMS : m/z 517 $(M+1)^+$

EXAMPLE 157

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propylaminopyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



A mixture of the title compound of Preparation 160 (226mg, 0.39mmol) and potassium *t*-butoxide (112mg, 1.0mmol) in n-propanol (20ml), was stirred under reflux for 5 days, then cooled. Saturated ammonium chloride solution (5ml) was added, this solution poured into ethyl acetate (50ml), and the layers separated. The organic phase was washed with sodium bicarbonate solution (20ml), then brine (20ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 94:6) to give an oil. This was crystallised from ether to afford the title compound (9mg, 4%) as a white solid.

δ ($CDCl_3$) : 1.00 (3H, t), 1.18 (3H, t), 1.28 (3H, t), 1.70 (2H, m), 2.38 (2H, q), 2.50 (4H, m), 3.00 (2H, q), 3.07 (4H, m), 3.57 (2H, q), 5.62 (2H, s), 7.19 (1H, m), 7.63 (1H, m), 8.02 (1H, s), 8.55 (2H, m), 9.60 (1H, s), 9.80 (1H, s).

LRMS : m/z 566 $(M+1)^+$

PREPARATION 1

2-Ethoxypyridine-3-carboxylic acid

A solution of potassium *t*-butoxide (44.9g, 0.40mol) in absolute ethanol (300ml) was added slowly to a solution of 2-chloronicotinic acid (30g, 0.19mol) in absolute ethanol (100ml) and the reaction mixture heated in a sealed vessel at 170°C for 20 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure, the residue dissolved in water (200ml) and the solution acidified to pH 3 with hydrochloric acid and extracted with dichloromethane (4x200ml). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the title compound (27.4g, 41%) as a white solid. δ ($CDCl_3$): 1.53 (3H,t), 4.69 (2H,q), 7.13 (1H,m), 8.37 (1H,d), 8.48 (1H,d).

PREPARATION 2

2-(2-Methoxyethoxy)pyridine-3-carboxylic acid

Obtained as a brown solid (92%) from 2-chloronicotinic acid and 2-methoxyethanol, using the procedure of Preparation 1. Found: C, 54.89; H, 5.61; N, 7.03. $C_9H_{11}NO_4$ requires C, 54.82; H, 5.62; N, 7.10%. δ ($CDCl_3$): 3.45 (3H,s), 3.79 (2H,t), 4.74 (2H,t), 7.14 (1H,m), 8.36 (1H,d), 8.46 (1H,d). LRMS: m/z 198 $(M+1)^+$.

PREPARATION 3

2-Ethoxypyridine-3-carboxylic acid ethyl ester

A suspension of the title compound of Preparation 1 (16.4g, 98mmol) and caesium carbonate (32g, 98mmol) in dimethylformamide (240ml) was stirred at room temperature for 2 hours. Ethyl iodide (7.85ml, 98mmol) was added and the reaction mixture stirred for 24 hours, then evaporated under reduced pressure. The residue was partitioned between aqueous sodium carbonate solution (100ml) and ethyl acetate (100ml), the phases separated and the

aqueous phase extracted with ethyl acetate (2x100ml). The combined organic solutions were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure to yield the title compound (18.0g, 94%) as a pale yellow oil. δ ($CDCl_3$): 1.41 (6H,m), 4.36 (2H,q), 4.48 (2H,q), 6.90 (1H,m), 8.12 (1H,d), 8.28 (1H,d).

PREPARATION 4

2-(2-Methoxyethoxy)pyridine-3-carboxylic acid ethyl ester

Obtained as a brown oil (98%) from the title compound of Preparation 2, using the procedure of Preparation 3. Found: C, 58.36; H, 6.74; N, 6.04. $C_{11}H_{15}NO_4$ requires C, 58.66; H, 6.71; N, 6.23%. δ ($CDCl_3$): 1.37 (3H,t), 3.44 (3H,s), 3.78 (2H,t), 4.34 (2H,q), 4.56 (2H,t), 6.92 (1H,m), 8.13 (1H,d), 8.26 (1H,d). LRMS: m/z 226 $(M+1)^+$.

PREPARATION 5

2-Ethoxy-5-nitropyridine-3-carboxylic acid ethyl ester

Ammonium nitrate (5.36g, 66mmol) was added portionwise to a stirred, ice-cooled solution of the title compound of Preparation 3 (4.66g, 22.3mmol) in trifluoroacetic anhydride (50ml) and the reaction mixture stirred for 18 hours at room temperature, then carefully poured into stirred ice-water (200g). The resulting suspension was stirred for 1 hour, then the precipitate collected, washed with water and dried under suction to provide the title compound (3.29g, 61%). δ ($CDCl_3$): 1.41 (3H,t), 1.48 (3H,t), 4.41 (2H,q), 4.62 (2H,q), 8.89 (1H,s), 9.16 (1H,s).

PREPARATION 6

2-(2-Methoxyethoxy)-5-nitropyridine-3-carboxylic acid ethyl ester

Ammonium nitrate (10.57g, 131mmol) was added portionwise to a stirred, ice-cooled solution of the title compound of Preparation 4 (14.80g,

65.7mmol) in trifluoroacetic anhydride (150ml) and the reaction mixture stirred for 3 hours at room temperature, then carefully poured onto stirred ice (120g). The resulting solution was extracted with dichloromethane (3x150ml), then the combined extracts dried ($MgSO_4$) and evaporated under reduced pressure. The residual orange oil was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 97:3), to furnish the title compound (11.49g, 65%) as a white solid. Found: C, 48.78; H, 5.13; N, 10.29. $C_{11}H_{14}N_2O_6$ requires C, 48.89; H, 5.22; N, 10.37%. δ ($CDCl_3$): 1.42 (3H,t), 3.46 (3H,s), 3.83 (2H,t), 4.41 (2H,q), 4.70 (2H,t), 8.92 (1H,s), 9.16 (1H,s). LRMS: m/z 271 $(M+1)^+$.

PREPARATION 7

5-Amino-2-ethoxypyridine-3-carboxylic acid ethyl ester

A stirred mixture of the title compound of Preparation 5 (5.3g, 22mmol), Raney nickel (2.50g) and ethanol (150ml) was hydrogenated at 345kPa (50psi) and 50°C for 18 hours, then allowed to cool and filtered. The filtrate was combined with an ethanol wash (150ml) of the filter pad and then evaporated under reduced pressure. The residue was triturated with dichloromethane and the resulting solid collected and dried to afford the title compound (4.56g, 98%) as a tan-coloured solid. Found: C, 57.12; H, 6.79; N, 12.98. $C_{10}H_{14}N_2O_3$ requires C, 57.13; H, 6.71; N, 13.33%. δ ($CDCl_3$): 1.39 (6H, 2xd), 3.41 (2H,s), 4.35 (4H,m), 7.55 (1H,s), 7.78 (1H,s). LRMS: m/z 211 $(M+1)^+$.

PREPARATION 8

2-Ethoxy-5-nitropyridine-3-carboxylic acid

5M Aqueous sodium hydroxide solution (4ml, 20mmol) was added dropwise to a stirred solution of the title compound of Preparation 5 (5.1g, 20mmol) in ethanol (100ml) and the reaction mixture stirred at room temperature for 18 hours, then evaporated under reduced pressure. The

residue was suspended in water (50ml) and the stirred suspension acidified to pH 3 with hydrochloric acid. The resulting aqueous solution was extracted with ethyl acetate (3x100ml), then combined extracts washed with brine (100ml), dried (Na_2SO_4) and evaporated under reduced pressure to afford a beige solid. The crude product was crystallised from hexane-ethyl acetate to give the title compound (3.32g, 78%) as beige crystals. δ ($CDCl_3$): 1.55 (3H,t), 4.78 (2H,q), 9.17 (1H,s), 9.23 (1H,s).

PREPARATION 9

2-(2-Methoxyethoxy)-5-nitropyridine-3-carboxylic acid

1M Aqueous sodium hydroxide solution (40ml, 40mmol) was added to a stirred, ice-cooled solution of the title compound of Preparation 6 (4.0g, 14.8mmol) in 1,4-dioxan (40ml) and the reaction mixture stirred for 1.5 hours, then concentrated under reduced pressure to half its volume and acidified with hydrochloric acid to pH 3. The resulting suspension was extracted with dichloromethane (3x50ml), then the combined extracts dried ($MgSO_4$) and evaporated under reduced pressure to yield the title compound (2.61g, 73%) as a buff-coloured solid. Found: C, 44.11; H, 4.04; N, 11.46. $C_9H_{10}N_2O_6$ requires C, 44.63; H, 4.16; N, 11.57%. δ ($CDCl_3$): 3.47 (3H,s), 3.83 (2H,t), 4.82 (2H,t), 9.15 (1H,s), 9.21 (1H,s). LRMS: m/z 243 $(M+1)^+$.

PREPARATION 10

2-Aminopyridine-5-sulphonic acid

2-Aminopyridine (80g, 0.85mol) was added portionwise over 30 minutes to stirred oleum (320g) and the resulting solution heated at 140°C for 4 hours, then allowed to cool. The reaction mixture was poured onto stirred ice (200g) and this mixture stirred at ice-salt bath temperature for a further 2 hours.

The resulting suspension was filtered, then the collected solid washed successively with ice-water (200ml) and cold industrial methylated spirit (IMS) (200ml) and, finally, dried under suction to provide the title compound (111.3g, 75%) as a solid. LRMS: m/z 175 $(M+1)^+$.

PREPARATION 11

2-Amino-3-bromopyridine-5-sulphonic acid

Bromine (99g, 0.62mol) was added dropwise, over 1 hour, to a stirred, hot solution of the title compound of Preparation 10 (108g, 0.62mol) in water (600ml), at such a rate as to maintain steady reflux. When the addition was complete, the reaction mixture was allowed to cool and then filtered. The resulting solid was washed with water and dried under suction to furnish the title compound (53.4g, 34%). δ ($DMSOd_6$): 8.08 (1H,s), 8.14 (1H,s). LRMS: m/z 253 $(M)^+$.

PREPARATION 12

3-Bromo-2-chloropyridine-5-sulphonyl chloride

A solution of sodium nitrite (7.6g, 110mmol) in water (30ml) was added dropwise to a stirred, ice-cooled solution of the title compound of Preparation 11 (25.3g, 100mmol) in 20% hydrochloric acid (115ml), at such a rate as to maintain the temperature below 6°C. The reaction mixture was stirred for 30 minutes at 0°C for a further 1 hour at room temperature, then evaporated under reduced pressure. The residue was dried under vacuum at 70°C for 72 hours, then a mixture of the resulting solid, phosphorus pentachloride (30g, 144mmol) and phosphorus oxychloride (1ml) was heated at 125°C for 3 hours and then allowed to cool. The reaction mixture was poured onto stirred ice (100g) and the resulting solid collected and washed with water. The crude product was dissolved in dichloromethane, then the solution dried ($MgSO_4$) and evaporated under reduced pressure to afford the title compound (26.58g, 91%) as a yellow solid. δ ($CDCl_3$): 8.46 (1H,s), 8.92 (1H,s).

PREPARATION 13

3-Bromo-2-chloro-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine

A solution of 1-ethylpiperazine (11.3ml, 89mmol) and triethylamine (12.5ml, 89mmol) in dichloromethane (150ml) was added dropwise to a stirred, ice-cooled solution of the title compound of Preparation 12 (23g, 79mmol) in dichloromethane (150ml) and the reaction mixture stirred at 0°C for 1 hour, then evaporated under reduced pressure. The residual brown oil was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (99:1 to 97:3), to give the title compound (14.5g, 50%) as an orange solid. δ ($CDCl_3$): 1.05 (3H,t), 2.42 (2H,q), 2.55 (4H,m), 3.12 (4H,m), 8.24 (1H,s), 8.67 (1H,s).

PREPARATION 14

3-Bromo-5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridine

A 0.5M solution of potassium bis(trimethylsilyl)amide in toluene (8.1ml, 4.07mmol) was added to a stirred, ice-cooled solution of 2-methoxyethanol (416µl, 5.4mmol) in anhydrous tetrahydrofuran (30ml) and the resulting solution stirred at 0°C for 1 hour. Next, the title compound of Preparation 13 (1.0g, 2.71mmol) was added portionwise and the reaction mixture stirred at room temperature for 2 hours, then diluted with ethyl acetate (40ml). The resulting mixture was washed with water (10ml), dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow oil which was purified by column chromatography on silica gel, using dichloromethane: methanol (97:3) as eluant, to provide the title compound (1.02g, 92%) as a colourless oil. Found: C, 40.83; H, 5.32; N, 9.99. $C_{14}H_{22}BrN_3O_4S$ requires C, 41.18; H, 5.43; N, 10.29%. δ ($CDCl_3$): 1.04 (3H,t), 2.42 (2H,q), 2.53 (4H,m), 3.07 (4H,m), 3.46 (3H,s), 3.78 (2H,t), 4.60 (2H,t), 8.10 (1H,s), 8.44 (1H,s). LRMS: m/z 408 $(M)^+$.

PREPARATION 15

3-Bromo-2-(2-ethoxyethoxy)-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine

Sodium metal (93mg, 4mmol) was added to a stirred solution of 2-ethoxyethanol (537µl, 5.5mmol) in anhydrous tetrahydrofuran (5ml). When the sodium had dissolved, the title compound of Preparation 13 (1.0g, 2.7mmol) was added portionwise and the reaction mixture stirred for 18 hours at room temperature, then concentrated under reduced pressure. The residue was partitioned between ethyl acetate (10ml) and brine (10ml), the phases separated and the aqueous phase extracted with ethyl acetate (2x10ml). The combined organic solutions were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure, then the residue purified by column chromatography on silica gel, using an elution gradient of hexane: dichloromethane: methanol (50:50:0 to 0:98:2), to furnish the title compound (985mg, 86%) as a yellow oil. δ ($CDCl_3$): 1.03 (3H,t), 1.22 (3H,t), 2.40 (2H,q), 2.54 (4H,m), 3.07 (4H,m), 3.61 (2H,q), 3.82 (2H,t), 4.59 (2H,t), 8.10 (1H,s), 8.43 (1H,s). LRMS: m/z 423 $(M+1)^+$.

PREPARATION 16

3-Bromo-5-(4-ethylpiperazin-1-ylsulphonyl)-2-(3-methoxyprop-1-oxy)pyridine

Obtained as an oil (95%) from the title compound of Preparation 13 and 3-methoxypropan-1-ol, using the procedure of Preparation 15. δ ($CDCl_3$): 1.04 (3H,t), 2.09 (2H,m), 2.42 (2H,q), 2.52 (4H,m), 3.08 (4H,m), 3.37 (3H,s), 3.57 (2H,t), 4.54 (2H,t), 8.09 (1H,s), 8.45 (1H,s). LRMS: m/z 423 $(M+1)^+$.

PREPARATION 17

3-Bromo-5-(4-ethylpiperazin-1-ylsulphonyl)-2-(tetrahydrofuran-3(S)-yloxy)pyridine

A mixture of a 2M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (1.83ml, 3.66mmol), (S)-(+)-3-hydroxytetrahydrofuran (272µl,

6mmol) and tetrahydrofuran (40ml) was stirred for 30 minutes at room temperature. Next, the title compound of Preparation 13 (750mg, 2mmol) was added and the reaction mixture stirred for 18 hours, then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of hexane: ethyl acetate (25:75 to 0:100), to afford the title compound (430mg, 51%) as an oil. δ ($CDCl_3$): 1.06 (3H,t), 2.20 (1H,m), 2.30 (1H,m), 2.42 (2H,q), 2.56 (4H,m), 3.08 (4H,m), 3.94 (2H,m), 4.02 (1H,m), 4.11 (1H,m), 5.62 (1H,m), 8.12 (1H,s), 8.44 (1H,s). LRMS: m/z 420 $(M)^+$.

PREPARATION 18

2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine-3-carboxylic acid ethyl ester

Sodium nitrite (2.22g, 32.1mmol) was added to a stirred solution of the title compound of Preparation 7 (4.5g, 21.4mmol) in a mixture of concentrated hydrochloric acid (90ml) and glacial acetic acid (90ml) at -20°C and the resulting mixture stirred for 2 hours, whilst allowing the temperature to rise to 0°C. The mixture was cooled again to -20°C, liquid sulphur dioxide (50ml) and a solution of copper(II) chloride (8.4g, 62.5mmol) in a mixture of water (9ml) and acetic acid (80ml) added, then the reaction mixture stirred for 30 minutes at 0°C, followed by a further 2 hours at room temperature. The resulting mixture was poured onto stirred ice (80g) and the aqueous solution thus obtained was extracted with dichloromethane (3x50ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude sulphonyl chloride as a brown oil.

1-Ethylpiperazine (10.9ml, 85.6mmol) was added to a stirred solution of the sulphonyl chloride in ethanol (60ml) and the reaction mixture stirred for 18

hours at room temperature, then evaporated under reduced pressure. The residue was partitioned between water (20ml) and dichloromethane (30ml), the separated aqueous phase extracted with dichloromethane (2x30ml), then the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. The residual brown oil was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 98:2), to yield the title compound (5.0g, 63%) as a pale brown oil. Found: C, 51.40; H, 6.77; N, 11.15. $C_{16}H_{25}N_3O_5S$ requires C, 51.74; H, 6.78; N, 11.31%. δ ($CDCl_3$): 1.02 (3H,t), 1.39 (3H,t), 1.45 (3H,t), 2.40 (2H,q), 2.54 (4H,m), 3.08 (4H,m), 4.38 (2H,q), 4.55 (2H,q), 8.37 (1H,s), 8.62 (1H,s). LRMS: m/z 372 $(M+1)^+$.

PREPARATION 19

5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridine-3-carboxylic acid ethyl ester

Triethylamine (3ml, 19mmol) and tetrakis (triphenylphosphine) palladium (0) (260mg, 0.22mmol) were added to a solution of the title compound of Preparation 14 (1.30g, 3mmol) in ethanol (15ml) and the mixture heated under carbon monoxide at 100°C and 1034 kPa (150psi) in a sealed vessel for 18 hours, then allowed to cool. The reaction mixture was filtered and the filtrate evaporated under reduced pressure to provide a yellow solid. The crude product was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 97.3), to furnish the title compound (1.10g, 92%) as a yellow oil. δ ($CDCl_3$): 1.02 (3H,t), 1.38 (3H,t), 2.40 (2H,q), 2.53 (4H,m), 3.08 (4H,m), 3.43 (3H,s), 3.80 (2H,t), 4.38 (2H,q), 4.63 (2H,t), 8.40 (1H,s), 8.61 (1H,s). LRMS: m/z 402 $(M+1)^+$.

PREPARATION 20

2-(2-Ethoxyethoxy)-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine-3-carboxylic acid ethyl ester

Obtained as a gum (96%) from the title compound of Preparation 15, using the procedure of Preparation 19. δ ($CDCl_3$): 1.03 (3H,t), 1.22 (3H,t), 1.38 (3H,t), 2.40 (2H,q), 2.52 (4H,m), 3.08 (4H,m), 3.60 (2H,q), 3.83 (2H,t), 4.38 (2H,q), 4.62 (2H,t), 8.40 (1H,s), 8.62 (1H,s). LRMS: m/z 416 $(M+1)^+$.

PREPARATION 21

5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(3-methoxyprop-1-oxy)-pyridine-3-carboxylic acid ethyl ester

A mixture of triethylamine (5ml, 35.9mmol), tetrakis (triphenylphosphine) palladium (0) (200mg, 0.17mmol), the title compound of Preparation 16 (1.08g, 2.54mmol) and ethanol (25ml) was heated under carbon monoxide at 100°C and 1034 kPa (150psi) in a sealed vessel for 18 hours, then allowed to cool. The mixture was filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in ethyl acetate (40ml) and the solution washed consecutively with saturated aqueous sodium bicarbonate solution (20ml), brine (20ml) and 2M hydrochloric acid (5x10ml). The combined acidic extracts were basified using solid sodium bicarbonate and the solution extracted with ethyl acetate (2x25ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to afford the title compound (640mg, 68%) as an oil. δ ($CDCl_3$): 1.05 (3H,t), 1.39 (3H,t), 2.09 (2H,m), 2.41 (2H,q), 2.54 (4H,m), 3.08 (4H,m), 3.36 (3H,s), 3.58 (2H,t), 4.39 (2H,q), 4.57 (2H,t), 8.40 (1H,s), 8.64 (1H,s). LRMS: m/z 416 $(M+1)^+$.

PREPARATION 22

5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(tetrahydrofuran-3(S)-yloxy)pyridine-3-carboxylic acid ethyl ester

Obtained as a yellow oil (78%) from the title compound of Preparation 17, using the procedure of Preparation 19. δ ($CDCl_3$): 1.05 (3H,t), 1.39 (3H,t), 2.20 (1H,m), 2.30 (1H,m), 2.42 (2H,q), 2.55 (4H,m), 3.09 (4H,m), 3.97 (3H,m), 4.14 (1H,m), 4.38 (2H,q), 5.70 (1H,m), 8.41 (1H,s), 8.62 (1H,s). LRMS: m/z 414 $(M+1)^+$.

PREPARATION 23

2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine-3-carboxylic acid

A mixture of the title compound of Preparation 18 (4.96g, 13.35mmol), 2M aqueous sodium hydroxide solution (25ml, 50mmol) and ethanol (25ml) was stirred at room temperature for 2 hours. The resulting mixture was concentrated under reduced pressure to half its volume, washed with ether and acidified to pH 5 using 4M hydrochloric acid. This aqueous solution was extracted with dichloromethane (3x30ml), then the combined extracts dried ($MgSO_4$) and evaporated under reduced pressure to give the title compound (4.02g, 88%) as a tan-coloured solid. δ ($DMSOd_6$): 1.18 (3H,t), 1.37 (3H,t), 3.08 (2H,q), 3.17-3.35 (8H,m), 4.52 (2H,q), 8.30 (1H,s), 8.70 (1H,s).

PREPARATION 24

2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine-3-carboxylic acid sodium salt

1M Aqueous sodium hydroxide solution (85ml, 85mmol) was added slowly to a stirred, ice-cooled solution of the title compound of Preparation 18 (30.2g, 85mmol) in ethanol (300ml) and the reaction mixture stirred at room

temperature for 18 hours. The resulting mixture was evaporated under reduced pressure and the residue partitioned between water (225ml) and ethyl acetate (250ml). The phases were separated, then the aqueous phase washed with ethyl acetate (2x200ml) and evaporated under reduced pressure to yield the title compound (29.6g, 81%) as a white solid. δ ($DMSOd_6$): 0.90 (3H,t), 1.25 (3H,t), 2.24 (2H,q), 2.40 (4H,m), 2.82 (4H,m), 4.39 (2H,q), 7.76 (1H,s), 8.28 (1H,s).

PREPARATION 25

4-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridine-3-carboxylic acid hydrochloride

A solution of the title compound of Preparation 19 (1.18g, 2.94mmol) in a mixture of ethanol (10ml) and 1M aqueous sodium hydroxide solution (10ml, 10mmol) was stirred for 1 hour at room temperature. The resulting mixture was concentrated under reduced pressure to half its volume and the residual aqueous solution washed with ethyl acetate (10ml), then acidified to pH 3 with dilute hydrochloric acid. The acidic solution was extracted with dichloromethane: methanol (95:5) (6x20ml), then the combined extracts dried ($MgSO_4$) and evaporated under reduced pressure to provide the title compound (995mg, 82%) as a white foam. δ ($DMSOd_6$): 1.06 (3H,t), 2.28 (2H,q), 2.75-3.20 (8H,m), 3.28 (3H,s), 3.69 (2H,t), 4.56 (2H,t), 8.29 (1H,s), 8.68 (1H,s). LRMS: m/z 374 $(M+1)^+$.

PREPARATION 26

2-(2-Ethoxyethoxy)-5-4-(ethylpiperazin-1-ylsulphonyl)pyridine-3-carboxylic acid hydrochloride

A mixture of the title compound of Preparation 20 (859mg, 2.07mmol), 1M aqueous sodium hydroxide solution (4.6ml, 4.6mmol) and 1,4-dioxan (5ml)

was stirred at room temperature for 2 hours. The 1,4-dioxan was removed by evaporation under reduced pressure and the pH of the remaining aqueous solution was adjusted to 3 with hydrochloric acid. The resulting solution was evaporated under reduced pressure, the residue triturated with hot ethanol and the mixture filtered. The filtrate was then evaporated under reduced pressure to furnish the title compound (760mg, 87%) as a tan-coloured solid. δ ($DMSOd_6$): 1.08 (3H,t), 1.18 (3H,t), 2.98 (2H,m), 3.07 (4H,m), 3.37 (2H,m), 3.48 (2H,q), 3.72 (4H,m), 4.55 (2H,t), 8.30 (1H,s), 8.72 (1H,s). LRMS: m/z 387 $(M)^+$.

PREPARATION 27

5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(3-methoxyprop-1-oxy)pyridine-3-carboxylic acid hydrochloride

Obtained as a solid (87%) from the title compound of Preparation 21, using the procedure of Preparation 26. δ ($DMSOd_6$): 1.17 (3H,t), 1.96 (2H,m), 3.08 (2H,q), 3.22 (3H,s), 3.33 (8H,m), 3.48 (2H,t), 4.48 (2H,t), 8.30 (1H,s), 8.73 (1H,s). LRMS: m/z 388 $(M+1)^+$.

PREPARATION 28

2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine-3-carboxylic acid chloride hydrochloride

Oxalyl chloride (0.77ml, 8.85mmol) was added dropwise to a stirred, ice-cooled solution of the title compound of Preparation 23 (1.52g, 4.42mmol) and dimethylformamide (2 drops) in dichloromethane (30ml) and the reaction mixture stirred for 18 hours at room temperature, then evaporated under reduced pressure. The residue was triturated with ethyl acetate and the

resulting solid collected, washed with ether and dried under suction to afford the title compound (1.68g, 95%). Found: C, 41.51; H, 5.27; N, 10.32. $C_{14}H_{21}Cl_2N_3O_4S$; 0.10 CH_2Cl_2 requires C, 41.73; H, 5.02; N, 10.36%. δ ($CDCl_3$): 1.46 (6H,m), 2.95 (2H,q), 3.11 (2H,m), 3.48 (2H,m), 3.55 (2H,m), 3.92 (2H,m), 4.60 (2H,q), 8.58 (1H,s), 8.66 (1H,s), 13.16 (1H,s).

PREPARATION 29

5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridine-3-carboxylic acid chloride hydrochloride

Oxalyl chloride (270µl, 3.13mmol) was added dropwise to a stirred, ice-cooled suspension of the title compound of Preparation 25 (390mg, 1.04mmol), dimethylformamide (100µl) and dry dichloromethane (20ml), then the reaction mixture stirred for 3 hours at room temperature. The resulting mixture was evaporated under reduced pressure and the residue azeotroped with toluene (2 x 20ml) to give the title compound (390mg, 95%) as a white solid. δ ($DMSOd_6$): 1.20 (3H,t), 2.92 (2H,q), 3.08 (4H,m), 3.30 (3H,s), 3.49 (2H,m), 3.70 (2H,t), 3.76 (2H,m), 4.58 (2H,t), 8.32 (1H,s), 8.72 (1H,s), 14.20 (1H,s).

PREPARATION 30

Ethyl 3-ethyl-1H-pyrazole-5-carboxylate

Ethanolic sodium ethoxide solution (21% w/w; 143ml, 0.39mol) was added dropwise to a stirred, ice-cooled solution of diethyl oxalate (59.8ml, 0.44mol) in absolute ethanol (200ml) under nitrogen and the resulting solution stirred for 15 minutes. Butan-2-one (39ml, 0.44mol) was then added dropwise, the cooling bath removed, the reaction mixture stirred for 18 hours at room temperature and then for 6 hours at 40°C, then the cooling bath reintroduced. Next, glacial acetic acid (25ml, 0.44mol) was added dropwise, the resulting solution stirred for 30 minutes at 0°C, hydrazine hydrate (20ml, 0.44mol)

added dropwise, then the reaction mixture allowed to warm to room temperature and maintained there over a period of 18 hours, before being evaporated under reduced pressure. The residue was partitioned between dichloromethane (300ml) and water (100ml), then the organic phase separated, washed with water (2x100ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the title compound (66.0g). δ ($CDCl_3$): 1.04 (3H,t), 1.16 (3H,t), 2.70 (2H,q), 4.36 (2H,q), 6.60 (1H,s). LRMS: m/z 169 $(M+1)^+$.

PREPARATION 31

3-Ethyl-1H-pyrazole-5-carboxylic acid

Aqueous sodium hydroxide solution (10M; 100ml, 1.0mol) was added dropwise to a stirred suspension of the title compound of Preparation 30 (66.0g, 0.39mol) in methanol (400ml) and the resulting solution heated under reflux for 4 hours. The cool reaction mixture was concentrated under reduced pressure to ca. 200ml, diluted with water (200ml) and this mixture washed with toluene (3x100ml). The resulting aqueous phase was acidified with concentrated hydrochloric acid to pH 4 and the white precipitate collected and dried by suction to provide the title compound (34.1g). δ ($DMSOd_6$): 1.13 (3H,t), 2.56 (2H,q), 6.42 (1H,s).

PREPARATION 32

4-Nitro-3-n-propyl-1H-pyrazole-5-carboxylic acid

Fuming sulphuric acid (17.8ml) was added dropwise to stirred, ice-cooled fuming nitric acid (16.0ml), the resulting solution heated to 50°C, then 3-n-propyl-1H-pyrazole-5-carboxylic acid (Chem. Pharm. Bull., 1984, 32, 1568; 16.4g, 0.106mol) added portionwise over 30 minutes whilst maintaining the reaction temperature below 60°C. The resulting solution was heated for 18

hours at 60°C, allowed to cool, then poured onto ice. The white precipitate was collected, washed with water and dried by suction to yield the title compound (15.4g), m.p. 170-172°C. Found: C, 42.35; H, 4.56; N, 21.07. $C_7H_9N_3O_4$ requires C, 42.21; H, 4.55; N, 21.10%. δ ($DMSOd_6$): 0.90 (3H,t), 1.64 (2H,m), 2.83 (2H,m), 14.00 (1H,s).

PREPARATION 33

3-Ethyl-4-nitro-1H-pyrazole-5-carboxylic acid

Obtained from the title compound of Preparation 31, by analogy with Preparation 32, as a brown solid (64%). δ ($DMSOd_6$): 1.18 (3H,t), 2.84 (2H,m), 13.72 (1H,s).

PREPARATION 34

4-Nitro-3-n-propyl-1H-pyrazole-5-carboxamide

A solution of the title compound of Preparation 32 (15.4g, 0.077mol) in thionyl chloride (75ml) was heated under reflux for 3 hours and then the cool reaction mixture evaporated under reduced pressure. The residue was azeotroped with tetrahydrofuran (2x50ml) and subsequently suspended in tetrahydrofuran (50ml), then the stirred suspension ice-cooled and treated with gaseous ammonia for 1 hour. Water (50ml) was added and the resulting mixture evaporated under reduced pressure to give a solid which, after trituration with water and drying by suction, furnished the title compound (14.3g), m.p. 197-199°C. Found: C, 42.35; H, 5.07; N, 28.38. $C_7H_{10}N_4O_3$ requires C, 42.42; H, 5.09; N, 28.27%. δ ($DMSOd_6$): 0.90 (3H,t), 1.68 (2H,m), 2.86 (2H,t), 7.68 (1H,s), 8.00 (1H,s).

PREPARATION 35

3-Ethyl-4-nitro-1H-pyrazole-5-carboxamide

Obtained from the title compound of Preparation 33, by analogy with Preparation 34, as a white solid (90%). δ ($DMSOd_6$): 1.17 (3H,t), 2.87 (2H,m), 7.40 (1H,s), 7.60 (1H,s), 7.90 (1H,s). LRMS: m/z 185 $(M+1)^+$.

PREPARATION 36

4-Amino-3-n-propyl-1H-pyrazole-5-carboxamide

A stirred mixture of the title compound of Preparation 34 (10.0g, 0.050mol), 10% palladium on charcoal (1.5g) and ethanol (400ml) was hydrogenated for 18 hours at 345kPa (50psi) and 50°C, then filtered. The filtrate was combined with an ethanol wash (200ml) of the filter pad and then evaporated under reduced pressure to give an orange solid which, on crystallisation from ethyl acetate-methanol, afforded the title compound (6.8g) as a white solid, m.p. 196-201°C. Found: C, 48.96; H, 6.98; N, 32.08. $C_7H_{12}N_4O$; 0.25 H_2O requires C, 48.68; H, 7.30; N, 32.44%. δ ($DMSOd_6$): 0.88 (3H,t), 1.55 (2H,m), 2.46 (2H,t), 4.40 (2H,s), 7.00 (1H,s), 7.12 (1H,s), 12.20 (1H,s).

PREPARATION 37

4-Amino-3-ethyl-1H-pyrazole-5-carboxamide

Obtained from the title compound of Preparation 35, by analogy with Preparation 36, as a brown solid (80%). δ ($DMSOd_6$): 1.08 (3H,t), 2.45 (2H,q), 4.50 (1H,s), 6.88 (1H,s), 7.10 (1H,s), 7.26 (2H,s). LRMS: m/z 155 $(M+1)^+$.

PREPARATION 38a

3-Ethyl-4-nitro-1-(pyridin-2-yl)methylpyrazole-5-carboxamide

and

PREPARATION 38b

3-Ethyl-4-nitro-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

A mixture of the title compound of Preparation 35 (20.0g, 109mmol), 2-(chloromethyl)pyridine hydrochloride (17.9g, 109mmol), caesium carbonate (74.7g, 222mmol) and dimethylformamide (120ml) was stirred for 18 hours at room temperature, then evaporated under reduced pressure. The residue was partitioned between water (100ml) and dichloromethane (100ml) and the phases separated. The aqueous layer was extracted with dichloromethane (3 x 100ml) and the combined extracts dried ($MgSO_4$) and evaporated under reduced pressure. The residue was crystallised from dichloromethane-methanol to yield the first title compound (1-isomer; 6.5g, 21%). δ ($CDCl_3$): 1.24 (3H,t), 2.90 (2H,q), 5.54 (2H,s), 6.03 (1H,s), 7.27 (1H,m), 7.36 (1H,d), 7.76 (1H,m), 8.52 (1H,d), 8.58 (1H,s).

The mother liquor was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 95:5), to provide the second title compound (2-isomer; 17.36g, 58%) as a white solid. δ ($CDCl_3$): 1.16 (3H,t), 3.06 (2H,q), 5.48 (2H,s), 5.88 (1H,s), 7.19 (1H,d), 7.27 (1H,m), 7.70 (1H,m), 8.57 (1H,d).

PREPARATION 39a

4-Nitro-3-n-propyl-1-(pyridin-2-yl)methylpyrazole-5-carboxamide

and

PREPARATION 39b

4-Nitro-3-n-propyl-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

2-(Chloromethyl)pyridine hydrochloride (24.6g, 150mmol) was added portionwise to a stirred solution of the title compound of Preparation 34 (30.0g, 150mmol) and caesium carbonate (123.5g, 380mmol) in dimethylformamide (300ml) and the reaction mixture stirred at room temperature for 18 hours, then evaporated under reduced pressure. The residue was suspended in water and the resulting solid collected and dried under suction. The crude product was purified by two column chromatographic operations on silica gel, respectively using dichloromethane: methanol (98:2) and ethyl acetate: pentane (20:80) as eluants, to furnish the first title compound (1-isomer; 424mg, 1%) as a white solid. Found: C, 53.74; H, 5.20; N, 23.91. $C_{13}H_{15}N_5O_3$ requires C, 53.97; H, 5.23; N, 24.21%. δ ($CDCl_3$): 0.94 (3H,t), 1.68 (2H,m), 2.86 (2H,t), 5.55 (2H,s), 6.07 (1H,s), 7.35 (1H,d), 7.75 (1H,m), 8.51 (1H,d), 8.56 (1H,s). LRMS: m/z 290 $(M+1)^+$;

and the second title compound (2-isomer; 16.7g, 38%) as a white solid. δ ($DMSOd_6$): 0.84 (3H,t), 1.46 (2H,m), 2.95 (2H,t), 5.49 (2H,s), 7.31 (2H,m), 7.60 (1H,s), 7.79 (1H,m), 7.90 (1H,s), 8.49 (1H,d).

PREPARATION 40

4-Amino-3-ethyl-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

A stirred mixture of the title compound of Preparation 38b (16.36g, 59mmol), 10% palladium on charcoal (4g) and ethanol (150ml) was hydrogenated at 345kPa (50psi) for 4 hours, then filtered. The filtrate was combined with an ethyl acetate wash (150ml) of the filter pad and then

concentrated under reduced pressure to a volume of ca. 70ml. The resulting precipitate was collected and dried under suction to afford the title compound (12.6g, 87%) as a white solid. δ ($CDCl_3$): 1.03 (3H,t), 2.53 (2H,q), 4.00 (2H,s), 5.22 (1H,s), 5.36 (2H,s), 6.60 (1H,s), 6.81 (1H,d), 7.20 (1H,m), 7.62 (1H,m), 8.57 (1H,d). LRMS: m/z 246 $(M+1)^+$.

PREPARATION 41

4-Amino-3-n-propyl-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

A stirred mixture of the title compound of Preparation 39b (1.0g, 3.46mmol), Raney nickel (1g) and ethanol (50ml) was hydrogenated at 345kPa (50psi) and 50°C for 18 hours, then allowed to cool and filtered. The filtrate was combined with an ethanol wash (50ml) of the filter pad and then evaporated under reduced pressure to give the title compound (830mg, 93%) as a crystalline solid. δ ($DMSOd_6$): 0.79 (3H,t), 1.33 (2H,m), 3.28 (2H,t), 4.60 (2H,s), 5.30 (2H,s), 6.88 (1H,d), 6.98 (1H,s), 7.13 (1H,s), 7.30 (1H,m), 7.74 (1H,m), 8.50 (1H,d). LRMS: m/z 274 $(M)^+$.

PREPARATION 42

4-Amino-3-ethyl-1-(pyridin-2-yl)methylpyrazole-5-carboxamide

Obtained as a solid (94%) from the title compound of Preparation 38a, using the procedure of Preparation 40. δ ($CDCl_3$): 1.20 (3H,t), 2.52 (2H,q), 3.72 (2H,s), 5.50 (2H,s), 7.21 (1H,m), 7.34 (1H,d), 7.68 (1H,m), 8.49 (1H,d). LRMS: m/z 246 $(M+1)^+$.

PREPARATION 43

4-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-3-ethyl-1H-pyrazole-5-carboxamide hydrochloride

A mixture of the title compound of Preparation 28 (1.0g, 2.51mmol), Preparation 37 (387mg, 2.51mmol) and pyridine (15ml) was stirred at room

temperature for 18 hours. The resulting mixture was evaporated under reduced pressure and the residue triturated with ether to yield the title compound (1.05g, 87%) as a purple solid. Found: C, 44.82; H, 5.72; N, 18.62. $C_{20}H_{29}N_7O_5S$; HCl; H_2O requires C, 44.98; H, 6.04; N, 18.36%. δ ($DMSOd_6$): 1.17 (6H,m), 1.46 (3H,t), 2.77 (2H,q), 3.09 (2H,q), 3.49 (4H,m), 3.78 (4H,m), 4.68 (2H,q), 7.30 (1H,s), 7.49 (1H,s), 8.52 (1H,s), 8.76 (1H,s), 10.54 (1H,s). LRMS: m/z 480 $(M+1)^+$.

PREPARATION 44

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Potassium t-butoxide (943g, 8.41mmol) was added to a stirred suspension of the title compound of Preparation 43 (1.10g, 2.1mmol) in absolute ethanol (50ml) and the reaction mixture heated in a sealed vessel at 100°C for 18 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residue dissolved in water (15ml). The aqueous solution was acidified to pH 6 using hydrochloric acid and the resulting solid collected, washed with water and dried under suction. The crude product was purified by column chromatography on silica gel, using dichloromethane: methanol (97:3) as eluant, to provide the title compound (445mg, 46%) as a yellow solid. Found: C, 51.95; H, 5.89; N, 20.87. $C_{20}H_{27}N_7O_4S$ requires C, 52.05; H, 5.90; N, 21.24%. δ ($DMSOd_6$): 0.92 (3H,t), 1.30 (6H,m), 2.30 (2H,q), 2.42 (4H,m), 2.86 (2H,q), 2.95 (4H,m), 4.49 (2H,q), 8.20 (1H,s), 8.64 (1H,s), 12.19 (1H,s), 13.80 (1H,s). LRMS: m/z 462 $(M+1)^+$.

PREPARATION 45

4-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-3-ethyl-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

Alternative A

A mixture of the title compounds of Preparation 28 (1.0g, 2.5mmol), Preparation 40 (620mg, 2.5mmol), triethylamine (1.35ml, 10mmol) and dichloromethane (50ml) was stirred at room temperature for 18 hours. The resulting mixture was poured into stirred water (50 ml), the phases separated and the aqueous phase extracted with dichloromethane (2 x 50ml). The combined organic solutions were dried ($MgSO_4$) and evaporated under reduced pressure, then the residue purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 95:5), to furnish the title compound (1.29g, 90%) as a foam. δ ($CDCl_3$): 1.00 (6H,m), 1.55 (3H,t), 2.37 (2H,q), 2.50 (4H,m), 2.87 (2H,q), 3.08 (4H,m), 4.77 (2H,q), 5.28 (1H,s), 5.45 (2H,s), 6.68 (1H,s), 6.90 (1H,d), 7.18 (1H,m), 7.61 (1H,m), 8.57 (1H,d), 8.62 (1H,s), 8.80 (1H,s), 10.57 (1H,s).

Alternative B

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (17.6g, 91.8mmol) was added portionwise over 5 minutes to a stirred, ice-cooled suspension of 1-hydroxybenzotriazole hydrate (12g, 88.9mmol) and the title compound of Preparation 24 (24g, 65.7mmol) in tetrahydrofuran (300ml), then the mixture stirred for 1 hour. N-Ethyldiisopropylamine (12.7g, 98.3mmol) and the title compound of Preparation 40 (12.9g, 52.6mmol) were added and the reaction mixture stirred at room temperature for 14 hours, then evaporated under reduced pressure. The residue was partitioned between water (100ml) and ethyl acetate (200ml), the phases separated and the organic phase washed consecutively with water (50ml), saturated aqueous sodium bicarbonate solution (50ml) and brine (50ml), then dried ($MgSO_4$) and concentrated under reduced pressure to a low volume. The resulting

suspension was cooled in ice for 1 hour, then the precipitate collected and dried under suction to afford the title compound (14.1g, 47%) as a white crystalline solid, m.p. 185-187°C . Found: C, 54.59; H, 6.05; N, 19.32. $C_{26}H_{34}N_8O_3S$ requires C, 54.72; H, 6.00; N, 19.63%.

PREPARATION 46

2-n-Propoxypyridine-3-carboxylic acid

Obtained as a pale brown oil (50%) from 2-chloronicotinic acid and n-propanol, using the procedure of Preparation 1. δ ($CDCl_3$): 1.08 (3H,t), 1.92 (2H,m), 4.56 (2H,t), 7.10 (1H,m), 8.35 (1H,d), 8.45 (1H,d).

PREPARATION 47

2-n-Propoxypyridine-3-carboxylic acid methyl ester

Diethyl azodicarboxylate (2.2ml, 14mmol) was added dropwise to a stirred solution of the title compound of Preparation 46 (2.30g, 12.7mmol), triphenylphosphine (3.67g, 14mmol) and methanol (0.60ml, 15mmol) in tetrahydrofuran (20ml) and the reaction mixture stirred for 18 hours at room temperature, then evaporated under reduced pressure. The residue was triturated with pentane: ether (80:20) and the mixture filtered. The filtrate was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using pentane: ether (50:50) as eluant, to give the title compound (2.2g, 89%) as a pale yellow oil. δ ($CDCl_3$): 1.07 (3H,t), 1.86 (2H,m), 3.92 (3H,s), 4.38 (2H,t), 6.93 (1H,m), 8.15 (1H,d), 8.30 (1H,d).

PREPARATION 48

5-Nitro-2-n-propoxypyridine-3-carboxylic acid methyl ester

Obtained as pale yellow needles (32%), after crystallisation from methanol, from the title compound of Preparation 47, using the procedure of Preparation 5. δ ($CDCl_3$): 1.04 (3H,t), 1.84 (2H,m), 3.92 (3H,s), 4.48 (2H,t), 8.88 (1H,s), 9.14 (1H,s).

PREPARATION 49

5-Amino-2-n-propoxypyridine-3-carboxylic acid methyl ester

A mixture of the title compound of Preparation 48 (1.8g, 7.46mmol), Raney nickel (500mg) and methanol (50ml) was hydrogenated at 345 kPa (50psi) and 50°C for 3 hours, then allowed to cool and filtered. The filtrate was combined with a methanol wash (100ml) of the filter pad and then evaporated under reduced pressure to yield the title compound (1.5g, 95%) as a brown oil. δ ($CDCl_3$): 1.04 (3H,t), 1.80 (2H,m), 3.40 (2H,s), 3.89 (3H,s), 4.28 (2H,t), 7.57 (1H,s), 7.80 (1H,s). LRMS: m/z 211 $(M+1)^+$.

PREPARATION 50

5-(4-Methylpiperazin-1-ylsulphonyl)-2-n-propoxypyridine-3-carboxylic acid methyl ester

Obtained as an oil (56%) from the title compound of Preparation 49 and 1-methylpiperazine, using the procedure of Preparation 18.

PREPARATION 51

5-(4-Methylpiperazin-1-ylsulphonyl)-2-n-propoxypyridine-3-carboxylic acid

Obtained as a white solid (82%) from the title compound of Preparation 50, using the procedure of Preparation 23. δ ($DMSOd_6$): 0.97 (3H,t), 1.74 (2H,m), 2.15 (3H,s), 2.38 (4H,m), 2.93 (4H,m), 4.37 (2H,t), 8.15 (1H,s), 8.56 (1H,s).

PREPARATION 52

3-Ethyl-4-[5-(4-methylpiperazin-1-ylsulphonyl)-2-n-propoxypyridin-3-ylcarboxamido]-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

Oxalyl chloride (550μl, 6.37mmol), followed by dimethylformamide (2 drops), were added carefully to a stirred, ice-cooled suspension of the title

compound of Preparation 51 (605mg, 1.59mmol) in dichloromethane (10ml) and the reaction mixture stirred at room temperature for 2 hours, then evaporated under reduced pressure. The residue was azeotroped with toluene to produce a powder.

A solution of crude acid chloride in dichloromethane (10ml) was added dropwise to a stirred, ice-cooled suspension of the title compound of Preparation 40 (430mg, 1.76mmol), triethylamine (558µl, 4mmol) and dichloromethane (10ml) and the reaction mixture stirred at room temperature for 1.5 hours. The resulting mixture was washed successively with saturated aqueous sodium bicarbonate solution and brine, then the organic phase dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel, using an elution gradient of hexane: ethyl acetate: methanol (70:30:0 to 0:90:10), to provide the title compound (695mg, 76%) as a solid. Found: C, 53.96; H, 6.09; N, 19.00. $C_{26}H_{34}N_8O_5S$ requires C, 54.22; H, 6.00; N, 19.64%. δ ($CDCl_3$): 1.07 (6H,m), 2.01 (2H,m), 2.26 (3H,s), 2.48 (4H,m), 2.88 (2H,q), 3.10 (4H,m), 4.67 (2H,t), 5.34 (1H,s), 5.48 (2H,s), 6.70 (1H,s), 6.94 (1H,d), 7.22 (1H,m), 7.66 (1H,m), 8.59 (1H,d), 8.65 (1H,s), 8.82 (1H,s), 10.48 (1H,s). LRMS: m/z 572 $(M+2)^+$.

PREPARATION 53

4-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-ylcarboxamido]-3-n-propyl-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

Obtained as a white foam (70%) from the title compounds of Preparation 29 and Preparation 41, using the procedure of Preparation 45A. δ ($CDCl_3$): 0.81 (3H,t), 1.02 (3H,t), 1.46 (2H,m), 2.39 (2H,q), 2.51 (4H,m), 2.82 (2H,t), 3.10 (4H,m), 3.39 (3H,s), 3.94 (2H,t), 4.85 (2H,t), 5.30 (1H,s), 5.46 (2H,s), 6.69 (1H,s), 6.90 (1H,d), 7.21 (1H,m), 7.65 (1H,m), 8.60 (1H,d), 8.65 (1H,s), 8.82 (1H,s), 10.46 (1H,s). LRMS: m/z 615 $(M+1)^+$.

PREPARATION 54

4-[2-(2-Ethoxyethoxy)-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-3-n-propyl-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

Obtained as a foam (69%) from the title compounds of Preparation 26 and Preparation 41, using the procedure of Preparation 52. Found: C, 55.13; H, 6.45; N, 17.27. $C_{29}H_{40}N_8O_6S$ requires C, 55.39; H, 6.41; N, 17.82%. δ ($CDCl_3$): 0.80 (3H,t), 1.02 (3H,t), 1.10 (3H,t), 1.45 (2H,m), 2.40 (2H,q), 2.50 (4H,m), 2.81 (2H,t), 3.09 (4H,m), 3.54 (2H,q), 3.98 (2H,t), 4.80 (2H,t), 5.30 (1H,s), 5.47 (2H,s), 6.70 (1H,s), 6.89 (1H,d), 7.22 (1H,m), 7.63 (1H,m), 8.59 (1H,d), 8.65 (1H,s), 8.82 (1H,s), 10.45 (1H,s). LRMS: m/z 629 $(M+1)^+$.

PREPARATION 55

4-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(3-methoxyprop-1-oxy)pyridin-3-ylcarboxamido]-3-n-propyl-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

Obtained as a foam (52%) from the title compounds of Preparation 27 and Preparation 41, using the procedure of Preparation 52. δ ($CDCl_3$): 0.82 (3H,t), 1.02 (3H,t), 1.44 (2H,m), 2.25 (2H,m), 2.40 (2H,q), 2.53 (4H,m), 2.84 (2H,t), 3.10 (4H,m), 3.29 (3H,s), 3.57 (2H,t), 4.79 (2H,t), 5.34 (1H,s), 5.47 (2H,s), 6.70 (1H,s), 6.92 (1H,d), 7.22 (1H,m), 7.66 (1H,m), 8.59 (1H,d), 8.65 (1H,s), 8.81 (1H,s), 10.45 (1H,s). LRMS: m/z 629 $(M+1)^+$.

PREPARATION 56

3-Ethyl-4-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(tetrahydrofuran-3(S)-yloxy)pyridin-3-ylcarboxamido]-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

A solution of the title compound of Preparation 22 (330mg, 0.80mmol) and 1M aqueous sodium hydroxide solution (800µl, 0.80mmol) in ethanol (3ml) was stirred for 3 hours at room temperature, then evaporated under reduced pressure.

A mixture of the resulting solid, the title compound of Preparation 40 (196mg, 0.80mmol), 1-hydroxybenzotriazole hydrate (135mg, 0.88mmol), N-ethyldiisopropylamine (307µl, 1.76mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (169mg, 0.88mmol) and tetrahydrofuran (15ml) was stirred for 72 hours at room temperature, then evaporated under reduced pressure. The residue was partitioned between ethyl acetate (50ml) and water (15ml), the phases separated and the organic phase dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (95:5 to 90:10), to furnish the title compound (382mg, 78%) as a foam. δ ($CDCl_3$): 1.05 (6H,m), 2.40 (3H,m), 2.54 (5H,m), 2.85 (2H,q), 3.11 (4H,m), 3.54 (1H,m), 4.15 (3H,m), 5.31 (1H,s), 5.48 (2H,s), 5.90 (1H,m), 6.69 (1H,s), 6.94 (1H,d), 7.24 (1H,m), 7.67 (1H,m), 8.60 (1H,m), 8.66 (1H,s), 8.87 (1H,s), 10.27 (1H,s). LRMS: m/z 613 $(M+1)^+$.

PREPARATION 57

4-(2-Ethoxy-5-nitropyridin-3-ylcarboxamido)-3-n-propyl-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

Oxalyl chloride (2.73ml, 31mmol) was added dropwise to a stirred suspension of the title compound of Preparation 8 (3.31g, 15.7mmol) in dichloromethane (50ml), followed by dimethylformamide (2 drops), and the reaction mixture stirred at room temperature for 3 hours. The resulting mixture was evaporated under reduced pressure and the residue azeotroped with hexane to give a white solid.

A solution of the crude acid chloride in dichloromethane (20ml) was added dropwise to a stirred suspension of the title compound of Preparation 41 (4.06g, 15.7mmol), triethylamine (4.37ml, 31mmol) and dichloromethane (80ml) and the reaction mixture stirred at room temperature for 20 hours. The

resulting mixture was evaporated under reduced pressure and the residue partitioned between saturated aqueous sodium bicarbonate solution (200ml) and dichloromethane (300ml). The phases were separated, and the aqueous phase extracted with dichloromethane (2 x 300ml). The combined organic solutions were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure to give a purple solid. The crude product was triturated with ether and the resulting solid collected and dried under suction to afford the title compound (6.26g, 88%) as an off-white solid. Found: C, 55.42; H, 5.05; N, 21.49. $C_{21}H_{23}N_7O_5$ requires C, 55.62; H, 5.11; N, 21.62%. δ ($CDCl_3$): 0.83 (3H,t), 1.46 (2H,m), 1.60 (3H,t), 2.89 (2H,t), 4.85 (2H,q), 5.32 (1H,s), 5.48 (2H,s), 6.72 (1H,s), 6.95 (1H,d), 7.24 (1H,m), 7.67 (1H,m), 8.60 (1H,d), 9.16 (1H,s), 9.30 (1H,s), 10.59 (1H,s). LRMS: m/z 454 $(M+1)^+$.

PREPARATION 58

3-Ethyl-4-[2-(2-methoxyethoxy)-5-nitropyridin-3-ylcarboxamido]-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

1-Hydroxybenzotriazole hydrate (1.87g, 12.2mmol), N-ethyl diisopropyl amine (2.13ml, 12.2mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.34g, 12.2mmol) and the title compound of Preparation 40 (3.0g, 12.2mmol) were added, in turn, to a stirred, ice-cooled suspension of the title compound of Preparation 9 (2.96g, 12.2mmol) in dichloromethane (80ml) and the reaction mixture stirred for 18 hours at room temperature. The resulting mixture was washed consecutively with water (25ml), 2M hydrochloric acid (2 x 25ml), saturated aqueous sodium bicarbonate solution (25ml) and brine (25ml), then dried ($MgSO_4$) and evaporated under reduced pressure. The residual solid was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (99:1 to 97:3) to give the title compound (3.36, 58%) as a white solid. Found: C, 53.41; H, 4.90; N, 20.65. $C_{21}H_{23}N_7O_6$ requires C, 53.72; H, 4.94; N, 20.89%. δ ($CDCl_3$): 1.08 (3H,t), 2.88 (2H,q), 3.40 (3H,s), 3.98 (2H,t), 4.90 (2H,t), 5.28 (1H,s), 5.48 (2H,s), 6.70

(1H,s), 6.92 (1H,d), 7.23 (1H,m), 7.66 (1H,m), 8.60 (1H,d), 9.15 (1H,s), 9.31 (1H,s), 10.50 (1H,s). LRMS: m/z 470 $(M+1)^+$.

PREPARATION 59

4-(5-Amino-2-ethoxypyridin-3-ylcarboxamido)-3-n-propyl-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

A stirred mixture of the title compound of Preparation 57 (5g, 11mmol), Raney nickel (2.5g) and ethanol (150ml) was hydrogenated at 345kPa (50psi) and 40°C for 3 hours, then for a further 72 hours at room temperature. The resulting mixture was filtered and the filtrate evaporated under reduced pressure to give a pale yellow solid. The crude product was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (99:1 to 95:5), followed by trituration with ether, to yield the title compound (4.4g, 94%) as a beige solid. Found: C, 59.42; H, 5.96; N, 22.98. $C_{21}H_{25}N_7O_3$ requires C, 59.56: H, 5.95; N, 23.15%. δ ($CDCl_3$): 0.78 (3H,t), 1.43 (2H,m), 1.52 (3H,t), 2.82 (2H,t), 3.49 (2H,s), 4.59 (2H,q), 5.30 (1H,s), 5.46 (2H,s), 6.70 (1H,s), 6.93 (1H,d), 7.22 (1H,m), 7.65 (1H,m), 7.78 (1H,s), 7.94 (1H,s), 8.58 (1H,d), 10.53 (1H,s).

PREPARATION 60

4-[5-Amino-2-(2-methoxyethoxy)pyridin-3-ylcarboxamido]-3-ethyl-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

A stirred mixture of the title compound of Preparation 58 (3.3g, 7.0mmol), Raney nickel (2g) and ethanol (120ml) was hydrogenated at 345kPa (50psi) and 50°C for 18 hours. The resulting mixture was filtered and the

filtrate evaporated under reduced pressure to provide the title compound (3.01g, 98%) as a pale grey foam. Found: C, 56.47, H, 5.82; N, 21.40. $C_{21}H_{25}N_7O_4$; 0.40 H_2O requires C, 56.47; H, 5.82; N, 21.95%. δ ($CDCl_3$): 1.06 (3H,t), 2.81 (2H,q), 3.38 (3H,s), 3.50 (2H,s), 3.92 (2H,t), 4.65 (2H,t), 5.33 (1H,s), 5.46 (2H,s), 6.70 (1H,s), 6.92 (1H,d), 7.22 (1H,m), 7.64 (1H,m), 7.76 (1H,s), 7.94 (1H,s), 8.60 (1H,d), 10.47 (1H,s). LRMS: m/z 440 $(M+1)^+$.

PREPARATION 61

5-(5-Amino-2-ethoxypyridin-3-yl)-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Potassium t-butoxide (2.32g, 20mmol) was added carefully to a stirred suspension of the title compound of Preparation 59 (2.11g, 5mmol) and 4Å molecular sieves in ethanol (50ml) and the reaction mixture heated under reflux for 18 hours, allowed to cool and filtered. The filtrate was evaporated under reduced pressure and the residue partitioned between 1M hydrochloric acid (30ml) and ethyl acetate (30ml). The phases were separated, the aqueous phase extracted with ethyl acetate (2x30ml) and the combined organic solutions washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residual brown oil was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 96:4), to furnish the title compound (1.22g, 60%) as a pale yellow solid. Found: C, 61.92; H, 5.69; N, 23.95. $C_{21}H_{23}N_7O_2$ requires C, 62.21; H, 5.72; N, 24.18%. δ ($CDCl_3$): 0.94 (3H,t), 1.51 (3H,t), 1.62 (2H,m), 2.95 (2H,t), 3.57 (2H,s), 4.50 (2H,q), 5.68 (2H,s), 7.06 (1H,d), 7.21 (1H,m), 7.60 (1H,m), 7.78 (1H,s), 8.16 (1H,d), 8.57 (1H,s), 11.07 (1H,s).

PREPARATION 62

5-[5-Amino-2-(2-methoxyethoxy)pyridin-3-yl]-3-ethyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Potassium bis(trimethylsilyl)amide (6.58g, 33.0mmol) was added to a stirred suspension of the title compound of Preparation 60 (2.90g, 6.60mmol) in 2-methoxyethanol (70ml) and the reaction mixture stirred under reflux for 18 hours. The resulting mixture was allowed to cool and then evaporated under reduced pressure to give a beige solid. The crude product was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (98:2 to 95:5), to afford the title compound (2.21g, 79%) as a white solid. Found: C, 59.10; H, 5.44; N, 22.86. $C_{21}H_{23}N_7O_3$ requires C, 59.85, H, 5.50; N, 23.26%. δ ($CDCl_3$): 1.28 (3H,t), 3.01 (2H,q), 3.53 (3H,s), 3.58 (2H,s), 3.82 (2H,t), 4.62 (2H,t,), 5.66 (2H,s), 7.08 (1H,d), 7.20 (1H,m), 7.61 (1H,m), 7.75 (1H,s), 8.09 (1H,s), 8.57 (1H,d), 11.14 (1H,s),. LRMS: m/z 422 $(M+1)^+$.

PREPARATION 63

5-(5-Chlorosulphonyl-2-ethoxypyridin-3-yl)-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3,d]pyrimidin-7-one

Sodium nitrite (295mg, 4.4mmol) was added portionwise to a stirred, ice-cooled solution of the title compound of Preparation 61 (900mg, 2.2mmol) in a mixture of glacial acetic acid (20ml) and concentrated hydrochloric acid (20ml) at such a rate as to maintain the temperature below -20°C . When the addition was complete, the mixture was allowed to warm slowly to 0°C over 2 hours and then re-cooled to -15°C. Liquid sulphur dioxide (22ml) and a solution of copper(II) chloride (860mg, 6.6mmol) in a mixture of water (2ml) and glacial acetic acid (14ml) were then added and the reaction mixture stirred at 0°C for

30 minutes, followed by a further 2 hours at room temperature. The resulting mixture was carefully poured into stirred ice-water (300ml) and the suspension thus obtained was extracted with dichloromethane (3x100ml). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure, then the residual oil triturated with ether to afford the title compound (720mg, 67%) as an off-white solid. δ ($CDCl_3$): 0.97 (3H,t), 1.60 (3H,t), 1.73 (2H,m), 3.01 (2H,t), 4.82 (2H,q), 5.70 (2H,s), 7.10 (1H,d), 7.22 (1H,m), 7.64 (1H,m), 8.58 (1H,d), 8.90 (1H,s), 9.29 (1H,s), 10.55 (1H,s).

PREPARATION 64

5-[5-Chlorosulphonyl-2-(2-methoxyethoxy)pyridin-3-yl]-3-ethyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Obtained as a cream solid (84%) from the title compound of Preparation 62, using the procedure of Preparation 63. δ ($CDCl_3$): 1.32 (3H,t), 3.08 (2H,q), 3.58 (3H,s), 3.89 (2H,t), 4.85 (2H,t), 5.69 (2H,s), 7.12 (1H,d), 7.22 (1H,m), 7.64 (1H,m), 8.57 (1H,d), 8.89 (1H,s), 9.26 (1H,s), 10.75 (1H,s). LRMS: m/z 505 $(M+1)^+$.

PREPARATION 65

3-Ethyl-4-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-ylcarboxamido]-1-(pyridin-2-yl)methylpyrazolo-5-carboxamide

Obtained as a white crystalline solid (44%) from the title compounds of Preparation 19 and Preparation 42, using the procedure of Preparation 56. δ ($CDCl_3$): 1.02 (3H,t), 1.20 (3H,t), 2.40 (2H,q), 2.52 (4H,m), 2.66 (2H,q), 3.10 (4H,m), 3.39 (3H,s), 3.90 (2H,t), 4.81 (2H,t), 5.62 (2H,s), 5.70 (1H,s), 7.26 (2H,m), 7.71 (1H,m), 8.53 (1H,d), 8.66 (1H,s), 8.82 (1H,s), 9.04 (1H,s). LRMS: m/z 601 $(M+1)^+$.

PREPARATION 66

3-Bromo-2-(1,3-dimethoxyprop-2-oxy)-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine

60% Sodium hydride dispersion in mineral oil (133mg, 3.33mmol) was added to a stirred, ice-cooled solution of 1,3-dimethoxypropan-2-ol (J. Amer. Chem. Soc., 1939, 61, 433; 400mg, 3.33mmol) in tetrahydrofuran (30ml) and the mixture stirred for 30 minutes. The title compound of Preparation 13 (500mg, 1.35mmol) was added and the reaction mixture stirred under reflux for 1 hour, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residue partitioned between water (30ml) and ethyl acetate (30ml). The phases were separated and the aqueous phase extracted with ethyl acetate (2x30ml), then the combined extracts washed with brine (30ml), dried ($MgSO_4$) and evaporated under reduced pressure to give the title compound (566mg, 93%) as a yellow solid. δ ($CDCl_3$): 1.06 (3H,t), 2.43 (2H,q), 2.55 (4H,m), 3.08 (4H,m), 3.40 (6H,2xs), 3.70 (4H, 2xd), 5.60 (1H,m), 8.10 (1H,s), 8.44 (1H,s). LRMS: m/z 452.

PREPARATION 67

2-(1,3-Dimethoxyprop-2-oxy)-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine-3-carboxylic acid ethyl ester

Obtained as a yellow solid (84%) from the title compound of Preparation 66, using the procedure of Preparation 19. δ ($CDCl_3$): 1.05 (3H,t), 1.40 (3H,t), 2.42 (2H,q), 2.55 (4H,m), 3.09 (4H,m), 3.40 (6H, 2xs), 3.70 (4H, 2xd), 4.37 (2H,q), 5.70 (1H,m), 8.40 (1H,s), 8.62 (1H,s). LRMS: m/z 446 $(M+1)^+$.

PREPARATION 68

3-Bromo-5-(4-ethylpiperazin-1-ylsulphonyl)-2-(tetrahydropyran-4-yloxy)pyridine

Obtained as a clear oil (70%) from the title compound of Preparation 13

and 4-hydroxytetrahydropyran, following the procedure of Preparation 14, after purification by column chromatography on silica gel, using ethyl acetate as eluant. δ ($CDCl_3$): 1.05 (3H,t), 1.88 (2H,m), 2.08 (2H,m), 2.42 (2H,q), 2.54 (4H,m), 3.08 (4H,m), 3.66 (2H,m), 3.99 (2H,m) 5.40 (1H,m), 8.10 (1H,s), 8.42 (1H,s). LRMS: m/z 434 $(M)^+$.

PREPARATION 69

5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(tetrahydropyran-4-yloxy)pyridine-3-carboxylic acid ethyl ester

Obtained as an oil (92%) from the title compound of Preparation 68, using the procedure of Preparation 19. δ ($CDCl_3$): 1.04 (3H,t), 1.40 (3H,t), 1.88 (2H,m), 2.08 (2H,m), 2.43 (2H,q), 2.55 (4H,m), 3.09 (4H,m), 3.66 (2H,m), 4.00 (2H,m), 4.40 (2H,q), 5.50 (1H,m), 8.40 (1H,s), 8.60 (1H,s). LRMS: m/z 427 $(M)^+$.

PREPARATION 70

5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(tetrahydropyran-4-yloxy)pyridine-3-carboxylic acid sodium salt

A mixture of the title compound of Preparation 69 (611mg, 1.4mmol), 1M aqueous sodium hydroxide solution (1.6ml, 1.6mmol) and ethanol (6ml) was stirred at room temperature for 6 hours, then evaporated under reduced pressure. The residue was dissolved in water (16ml), then the solution washed with ethyl acetate (2x10ml) and evaporated under reduced pressure to provide the title compound (520mg, 93%) as a tan-coloured solid. δ ($DMSOd_6$): 1.19 (3H,t), 1.70 (2H,m), 2.00 (2H,m), 2.80-3.88 (14H,m), 8.32 (1H,s), 8.73 (1H,s), 10.93 (1H,s). LRMS: m/z 400 $(M+1)^+$.

PREPARATION 71

2-(1,3-Dimethoxyprop-2-oxy)-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine-3-carboxylic acid sodium salt

Obtained as a solid (92%) from the title compound of Preparation 67, using the procedure of Preparation 70. LRMS: m/z 418 $(M+1)^+$.

PREPARATION 72

4-[2-(1,3-Dimethoxyprop-2-oxy)-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine-3-ylcarboxamido]-3-n-propyl-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

A mixture of the title compounds of Preparation 71 (418mg, 0.95mmol) and Preparation 41 (250mg, 1.0mmol), 1-hydroxybenzotriazole hydrate (270mg, 2.0mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (380mg, 2.0mmol), triethylamine (280µl, 2.0mmol) and tetrahydrofuran (10ml) was stirred at room temperature for 36 hours, then evaporated under reduced pressure. The residue was partitioned between dichloromethane (10ml) and brine (10ml), the phases separated, the aqueous phase extracted with dichloromethane (2x10ml) and the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. The residual yellow oil was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (98:2 to 96:4) to furnish the title compound (350mg, 56%) as an off-white solid. δ ($CDCl_3$): 0.81 (3H,t), 1.03 (3H,t), 1.44 (2H,m), 2.40 (2H,q), 2.52 (4H,m), 2.80 (2H,t), 3.10 (4H,m), 3.38 (6H,s), 3.78 (2H,dd), 3.92 (2H,dd), 5.31 (1H,s), 5.47 (2H,s), 5.93 (1H,m), 6.70 (1H,s), 6.92 (1H,d), 7.23 (1H,m), 7.65 (1H,m), 8.58 (1H,d), 8.65 (1H,s), 8.80 (1H,s), 10.26 (1H,s). LRMS: m/z 660 $(M+2)^+$.

PREPARATION 73

3-Bromo-5-(4-ethylpiperazin-1-ylsulphonyl)-2-(tetrahydrofuran-3(R)-yloxy)pyridine

Obtained as an oil (89%) from the title compound of Preparation 13 and (R)-(-)-3-hydroxytetrahydrofuran, using the procedure of Preparation 17. δ ($CDCl_3$): 1.05 (3H,t), 2.20 (1H,m), 2.30 (1H,m), 2.42 (2H,q), 2.54 (4H,m), 3.07 (4H,m), 3.94 (2H,m), 4.02 (1H,m), 4.10 (1H,m), 5.63 (1H,m), 8.11 (1H,s), 8.43 (1H,s). LRMS: m/z 421 $(M+1)^+$.

PREPARATION 74

5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(tetrahydrofuran-3(R)-yloxy)pyridine-3-carboxylic acid ethyl ester

Obtained as an oil (84%), from the title compound of Preparation 73, using the procedure of Preparation 19. δ ($CDCl_3$): 1.03 (3H,t), 1.40 (3H,t), 2.26 (2H,m), 2.42 (2H,q), 2.55 (4H,m), 3.10 (4H,m), 3.98 (3H,m), 4.12 (1H,m), 4.38 (2H,q), 5.70 (1H,m), 8.42 (1H,s), 8.62 (1H,s). LRMS: m/z 414 $(M+1)^+$.

PREPARATION 75

3-Ethyl-4-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(tetrahydrofuran-3(R)-yloxy)pyridin-3-ylcarboxamido]-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

Obtained as a foam (78%) from the title compounds of Preparation 74 and Preparation 40, using the procedure of Preparation 56. δ ($CDCl_3$): 1.04 (6H,m), 2.40 (3H,m), 2.52 (5H,m), 2.84 (2H,q), 3.10 (4H,m), 3.94 (1H,m), 4.15 (3H,m), 5.28 (1H,s), 5.48 (2H,s), 5.90 (1H,m), 6.68 (1H,s), 6.92 (1H,d), 7.22 (1H,m), 7.67 (1H,m), 8.60 (1H,d), 8.64 (1H,s), 8.86 (1H,s), 10.28 (1H,s). LRMS: m/z 613 $(M+1)^+$.

PREPARATION 76

4-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(tetrahydropyran-4-yloxy)pyridin-3-ylcarboxamido]-3-n-propyl-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

A mixture of the title compounds of Preparation 70 (520mg, 1.3mmol) and Preparation 41 (285mg, 1.1mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (250mg, 1.3mmol), 1-hydroxybenzotriazole hydrate (199mg, 1.3mmol), N-ethyldiisopropylamine (226µl, 1.3mmol) and tetrahydrofuran (20ml) was stirred for 1 week at room temperature. Ethyl acetate (150ml) was then added and the resulting mixture washed with brine (2x50ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of ethyl acetate: dichloromethane:methanol (32:64:4 to 0:95:5), to afford the title compound (603mg, 86%) as a white foam. δ ($DMSOd_6$): 0.74 (3H,t), 0.91 (3H,t), 1.39 (2H,m), 1.90 (2H,m), 2.05 (2H,m), 2.30 (2H,q), 2.42 (4H,m), 2.74 (2H,t), 2.95 (4H,m), 3.50 (2H,m), 3.85 (2H,m), 5.48 (2H,s), 5.52 (1H,m), 7.09 (1H,d), 7.35 (3H,m), 7.48 (1H,m), 8.39 (1H,s), 8.54 (1H,d), 8.65 (1H,s), 10.18 (1H,s). LRMS: m/z 641 $(M+1)^+$.

PREPARATION 77

4-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-3-n-propyl-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

A stirred mixture of the title compounds of Preparation 28 (3.07g, 7.71mmol) and Preparation 41 (2.0g, 7.71mmol) in pyridine (50ml) was heated at 50°C for 48 hours, then allowed to cool and evaporated under reduced pressure. The residue was partitioned between dichloromethane (100ml) and water (20ml), then the organic phase separated, dried ($MgSO_4$) and evaporated under reduced pressure. The residual brown foam was purified by column

chromatography on silica gel, using an elution gradient of ethyl acetate: methanol (100:0 to 90:10), to give the title compound (3.19g, 71%) as a white foam. Found: C, 54.66; H, 6.17; N, 18.38. $C_{27}H_{36}N_8O_5S$; 0.40 H_2O requires C, 54.79; H, 6.27; N, 18.93%. δ ($CDCl_3$): 0.82 (3H,t), 1.03 (3H,t), 1.45 (2H,m), 1.58 (3H,t), 2.40 (2H,q), 2.52 (4H,m), 2.86 (2H,t), 3.10 (4H,m), 4.79 (2H,q), 5.29 (1H,s), 5.46 (2H,s), 6.70 (1H,s), 6.93 (1H,d), 7.21 (1H,m), 7.64 (1H,m), 8.59 (1H,d), 8.64 (1H,s), 8.81 (1H,s), 10.56 (1H,s). LRMS: m/z 585 $(M+1)^+$.

PREPARATION 78

5-(4-Ethylpiperazin-1-ylsulphonyl)-2-propoxypyridine-3-carboxylic acid methyl ester

Obtained as an oil (53%) from the title compound of Preparation 49 and 1-ethylpiperazine, using the procedure of Preparation 18. δ ($CDCl_3$): 1.05 (6H,m), 1.86 (2H,m), 2.41 (2H,q), 2.54 (4H,m), 3.08 (4H,m), 3.92 (3H,s), 4.46 (2H,t), 8.40 (1H,s), 8.62 (1H,s). LRMS: m/z 372 $(M+1)^+$.

PREPARATION 79

5-(4-Ethylpiperazin-1-ylsulphonyl)-2-n-propoxypyridine-3-carboxylic acid

A mixture of the title compound of Preparation 78 (370mg, 1.0mmol), 2M aqueous sodium hydroxide solution (1ml, 2mmol) and methanol (10ml) was stirred at room temperature for 2 hours. The resulting mixture was treated with solid carbon dioxide in order to adjust its pH to 7 and then evaporated under reduced pressure. The residue was triturated with dichloromethane (3x50ml) and the combined organic solutions evaporated under reduced pressure to yield the title compound (340mg, 95%) as a white solid. LRMS: m/z 357 $(M)^+$.

PREPARATION 80

4-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-n-propoxypyridin-3-ylcarboxamido]-3-n-propyl-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

Oxalyl chloride (122µl, 5.6mmol) was added dropwise to a stirred solution of the title compound of Preparation 79 (478mg, 1.4mmol) and dimethylformamide (3 drops) in dichloromethane (10ml) and the reaction mixture stirred at room temperature for 18 hours, then evaporated under reduced pressure. The residue was azeotroped with dichloromethane (3x10ml), then added to a stirred, ice-cooled solution of the title compound of Preparation 41 (360mg, 1.4mmol) in pyridine (10ml) and the reaction mixture stirred at room temperature for 18 hours, then evaporated under reduced pressure. The residue was partitioned between water (50ml) and dichloromethane (50ml), the phases separated and the aqueous phase extracted with dichloromethane (2x50ml). The combined organic solutions were dried (Na_2SO_4) and evaporated under reduced pressure, then the crude product purified by column chromatography on silica gel, using ethyl acetate:methanol (80:20) as eluant, to provide the title compound (500mg, 37%) as a colourless glass. δ ($CDCl_3$): 0.81 (3H,t), 1.04 (3H,t), 1.27 (3H,t), 1.46 (2H,m), 2.00 (2H,m), 2.40 (2H,q), 2.53 (4H,m), 2.86 (2H,t), 3.09 (4H,m), 4.66 (2H,t), 5.27 (1H,s), 5.47 (2H,s), 6.68 (1H,s), 6.93 (1H,d), 7.21 (1H,m), 7.66 (1H,m), 8.59 (1H,d), 8.64 (1H,s), 8.80 (1H,s), 10.47 (1H,s). LRMS: m/z 599 $(M+1)^+$.

PREPARATION 81

2-(2-Benzyloxyethoxy)-3-bromo-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine

A mixture of a 2M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (4.1ml, 8.2mmol), 2-benzyloxyethanol (1.16ml, 8.2mmol) and tetrahydrofuran (5ml) was stirred at about 0°C for 1 hour. The title compound

of Preparation 13 (2.0g, 5.43mmol) was added and the reaction mixture stirred at room temperature for 5 hours, then evaporated under reduced pressure. The residue was suspended in ethyl acetate (10ml) and the suspension extracted with 2M hydrochloric acid (3x10ml). The combined extracts were basified with aqueous sodium bicarbonate solution and extracted with ethyl acetate (3x15ml). These combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure, then the crude product purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 95:5), to furnish the title compound (1.95g, 74%) as an oil. δ ($CDCl_3$): 1.02 (3H,t), 2.40 (2H,q), 2.52 (4H,m), 3.07 (4H,m), 3.88 (2H,t), 4.62 (4H,m), 7.26 (1H,m), 7.34 (4H,m), 8.09 (1H,s), 8.42 (1H,s). LRMS: m/z 486 $(M+2)^+$.

PREPARATION 82

2-(2-Benzyloxyethoxy)-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine-3-carboxylic acid ethyl ester

Obtained as an oil (42%) from the title compound of Preparation 81, using the procedure of Preparation 21. δ ($CDCl_3$): 1.04 (3H,t), 1.38 (3H,t), 2.42 (2H,q), 2.54 (4H,m), 3.08 (4H,m), 3.90 (2H,t), 4.38 (2H,q), 4.67 (4H,m), 7.28 (1H,m), 7.35 (4H,m), 8.41 (1H,s), 8.62 (1H,s). LRMS: m/z 478 $(M+1)^+$.

PREPARATION 83

2-(2-Benzyloxyethoxy)-5-(4-ethylpiperazin-1-ylsulphonyl)pyridine-3-carboxylic acid hydrochloride

Obtained as a pale yellow solid (88%) from the title compound of Preparation 82, using the procedure of Preparation 26. δ ($CDCl_3$): 1.45 (3H,t), 2.82 (2H,m), 3.09 (2H,q), 3.26 (2H,m), 3.64 (2H,m), 3.90 (4H,m), 4.64 (2H,s), 4.78 (2H,t), 7.33 (1H,m), 7.37 (4H,m), 8.58 (1H,s), 8.64 (1H,s), 12.17 (1H,s). LRMS: m/z 450 $(M+1)^+$.

PREPARATION 84

4-[2-(2-Benzyloxyethoxy)-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-3-n-propyl-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

Obtained as an orange solid (80%) from the title compounds of Preparation 83 and Preparation 41, using the procedure of Preparation 52. δ ($CDCl_3$): 0.80 (3H,t), 1.02 (3H,t), 1.42 (2H,m), 2.40 (2H,q), 2.54 (4H,m), 2.81 (2H,t), 3.10 (4H,m), 4.06 (2H,t), 4.57 (2H,s), 4.86 (2H,t), 5.26 (1H,s), 5.45 (2H,s), 6.68 (1H,s), 6.90 (1H,d), 7.17-7.27 (5H,m), 7.34 (1H,m), 7.63 (1H,m), 8.59 (1H,d), 8.62 (1H,s), 8.82 (1H,s), 10.50 (1H,s). LRMS: m/z 692 $(M+2)^+$.

PREPARATION 85

2-Benzyl-3-ethyl-4-nitropyrazole-5-carboxamide

Caesium carbonate (2.9g, 9.0mmol) was added to a stirred, ice-cooled solution of the title compound of Preparation 35 (1.7g, 8.8mmol) in dimethylformamide (20ml) and the suspension stirred for 30 minutes. Benzyl bromide (10.6ml, 9.0mmol) was added and the reaction mixture stirred at room temperature for 18 hours, then evaporated under reduced pressure. The residue was partitioned between ethyl acetate (125ml) and brine (100ml), the phases separated and the organic phase dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using ethyl acetate as eluant, to afford the title compound (1.13g, 47%) as a white solid. δ ($DMSOd_6$): 0.97 (3H,t), 2.96 (2H,q), 5.44 (2H,s), 7.24 (2H,m), 7.33 (3H,m), 7.68 (1H,s), 7.95 (1H,s). LRMS: m/z 274 $(M+1)^+$.

PREPARATION 86

4-Amino-2-benzyl-3-ethylpyrazole-5-carboxamide

Obtained as a pale pink solid (90%) from the title compound of Preparation 85, using the procedure of Preparation 40. δ ($DMSOd_6$): 0.87 (3H,t), 2.49 (2H,q), 4.46 (2H,s), 5.22 (2H,s), 6.85 (1H,s), 7.09 (3H,m), 7.25 (1H,m), 7.31 (2H,m). LRMS: m/z 245 $(M+1)^+$.

PREPARATION 87

2-Benzyl-4-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-3-ethylpyrazole-5-carboxamide

Obtained as a white crystalline foam (46%) from the title compounds of Preparation 18 and Preparation 86, using the procedure of Preparation 56. δ ($DMSOd_6$): 0.92 (6H,m), 1.44 (3H,t), 2.30 (2H,q), 2.41 (4H,m), 2.74 (2H,q), 2.95 (4H,m), 4.62 (2H,q), 5.40 (2H,s), 7.17 (2H,m), 7.31 (4H,m), 7.50 (1H,s), 8.39 (1H,s), 8.65 (1H,s), 10.38 (1H,s). LRMS: m/z 571 $(M+2)^+$.

PREPARATION 88a

3-Ethyl-1-(1-methylimidazol-2-yl)methyl-4-nitropyrazole-5-carboxamide

and

PREPARATION 88b

3-Ethyl-2-(1-methylimidazol-2-yl)methyl-4-nitropyrazole-5-carboxamide

A mixture of the title compound of Preparation 35 (2.2g, 11.95mmol), 2-chloromethyl-1-methylimidazole hydrochloride (J. Chem. Soc., 1957, 3305; 2.0g, 11.95mmol), caesium carbonate (8.5g, 26.3mmol) and dimethylformamide (100ml) was stirred at room temperature for 6 hours, then evaporated under reduced pressure. The residue was partitioned between water (150ml) and dichloromethane (150ml), the phases separated and the aqueous phase extracted with dichloromethane (2x150ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure, then the residue triturated with dichloromethane: methanol (90:10) and the resulting solid collected and dried under suction to give the first title compound (1-isomer; 305mg, 9%) as a cream solid. δ ($DMSOd_6$): 1.16 (3H,t), 2.82 (2H,q), 3.69 (3H,s), 5.40 (2H,s), 6.81 (1H,s), 7.13 (1H,s), 8.20 (1H,s), 8.50 (1H,s). LRMS: m/z 279 $(M+1)^+$.

The filtrate was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using dichloromethane:methanol:0.88 aqueous ammonia (90:10:1) as eluant, to yield the second title compound (2-isomer; 480mg, 14%) as a solid. δ ($CDCl_3$): 1.16 (3H,t), 3.20 (2H,q), 3.77 (3H,s), 5.48 (2H,s), 6.22 (1H,s), 6.68 (1H,s), 7.00 (1H,s), 7.25 (1H,s). LRMS: m/z 279 $(M+1)^+$.

PREPARATION 89

4-Amino-3-ethyl-2-(1-methylimidazol-2-yl)methylpyrazole-5-carboxamide

Obtained as a pink solid (92%) from the title compound of Preparation 88b, using the procedure of Preparation 40. δ ($CDCl_3$): 1.00 (3H,t), 2.68 (2H,q), 3.60 (3H,s), 5.34 (2H,s), 5.40 (1H,s), 6.55 (1H,s), 6.82 (1H,s), 6.98 (1H,s). LRMS: m/z 249 $(M+1)^+$.

PREPARATION 90

3-Ethyl-4-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-ylcarboxamido]-2-(1-methylimidazol-2-yl)methylpyrazole-5-carboxamide

Obtained as a solid (48%) from the title compounds of Preparation 29 and Preparation 89, using the procedure of Preparation 45A. δ ($CDCl_3$): 1.01 (3H,t), 1.10 (3H,t), 2.40 (2H,q), 2.52 (4H,m), 2.98 (2H,q), 3.08 (4H,m), 3.36 (3H,s), 3.66 (3H,s), 3.92 (2H,t), 4.82 (2H,t), 5.35 (1H,s), 5.42 (2H,s), 6.61 (1H,s), 6.86 (1H,s), 7.00 (1H,s), 8.64 (1H,s), 8.81 (1H,s), 10.33 (1H,s). LRMS: m/z 604 $(M+1)^+$.

PREPARATION 91a

1-(1-Methylimidazol-2-yl)methyl-4-nitro-3-n-propylpyrazole-5-carboxamide

and

PREPARATION 91b

2-(1-Methylimidazol-2-yl)methyl-4-nitro-3-n-propylpyrazole-5-carboxamide

A stirred mixture of the title compound of Preparation 34 (5.0g, 25.3mmol), 2-chloromethyl-1-methylimidazole hydrochloride (J. Chem. Soc., 1957, 3305; 4.6g, 27.7mmol), caesium carbonate (18.1g, 55.6mmol) and acetonitrile (100ml) was heated at 50°C for 5 hours, then allowed to cool. Ethyl acetate (300ml) was added and the mixture washed with water (2x400ml), dried ($MgSO_4$) and concentrated under reduced pressure to a volume of about 200ml. The resulting precipitate was collected and combined with the material produced by crystallisation from ethyl acetate of the residue obtained by evaporation under reduced pressure of the filtrate, to provide, after drying, the first title compound (1-isomer; 1.0g, 13%) as white crystals. δ ($DMSOd_6$): 0.89 (3H,t), 1.60 (2H,m), 2.76 (2H,t), 3.66 (3H,s), 5.39 (2H,s), 6.80 (1H,s), 7.12 (1H,s), 8.20 (1H,s), 8.48 (1H,s). LRMS: m/z 293 $(M+1)^+$.

The crystallisation mother liquor was evaporated under reduced pressure and the residue recrystallised from ethyl acetate to furnish the second title compound (2-isomer; 700mg, 9%) as a solid. δ ($DMSOd_6$): 0.92 (3H,t), 1.52 (2H,m), 3.04 (2H,t), 3.68 (3H,s), 5.49 (2H,s), 6.82 (1H,s), 7.14 (1H,s), 7.66 (1H,s), 7.93 (1H,s). LRMS: m/z 293 $(M+1)^+$.

PREPARATION 92

4-Amino-2-(1-methylimidazol-2-yl)methyl-3-n-propylpyrazole-5-carboxamide

A stirred mixture of the title compound of Preparation 91b (500mg, 1.71mmol), 10% palladium on charcoal (150mg) and ethanol (20ml) was

hydrogenated for 4 hours at 345kPa (50psi), then filtered. The filtrate was combined with a dichloromethane: methanol (80:20) wash (50ml) of the filter pad, evaporated under reduced pressure and the residue crystallised from ethyl acetate to afford the title compound (320mg, 71%) as a pale pink solid. δ ($CDCl_3$): 0.90 (3H,t), 1.40 (2H,m), 2.60 (2H,t), 3.58 (3H,s), 3.94 (2H,s), 5.32 (3H,m), 6.54 (1H,s), 6.82 (1H,s), 6.98 (1H,s).

PREPARATION 93

3-(2-Phenylethenyl)pyridazine

Zinc chloride (820mg, 6mmol) was added to a stirred mixture of benzaldehyde (6.11ml, 60mmol) and 3-methylpyridazine (2.83g, 30mmol) and the resulting mixture heated for 20 hours at 150°C. The cool reaction mixture was partitioned between dichloromethane (40ml) and 2M aqueous sodium hydroxide solution (20ml), then the organic phase separated, combined with a dichloromethane extract (80ml) of the aqueous phase, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using dichloromethane: methanol (99:1) as eluant, to give the title compound (59%) as a solid. δ ($CDCL_3$): 7.12 (1H,d), 7.34 (3H,m), 7.56 (2H,d), 7.72 (1H,d), 8.37 (1H,s), 8.50 (1H,s), 8.60 (1H,s). LRMS: m/z 183 $(M+1)^+$.

PREPARATION 94

3-Hydroxymethylpyridazine

Ozone was bubbled through a stirred solution of the title compound of Preparation 93 (3.60g, 0.02mol) in methanol (150ml) at -10°C. After 30 minutes the mixture was purged with nitrogen, sodium borohydride (750mg, 0.02mol) added portionwise and the resulting solution stirred for 2 hours at room temperature. The reaction mixture was acidified with 2M hydrochloric

acid, then basified with 0.880 aqueous ammonia solution and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (98:2 to 96:4), provided the title compound (76%) as a solid. δ ($CDCl_3$): 3.66 (1H,s), 4.92 (2H,s), 7.48 (2H,m), 9.06 (1H,d).

PREPARATION 95

3-Chloromethylpyridazine hydrochloride

Thionyl chloride (3.05ml, 42mmol) was added to an ice-cooled flask containing the title compound of Preparation 94 (920mg, 8mmol) and the reaction mixture stirred for 45 minutes at room temperature, then evaporated under reduced pressure. The residue was azeotroped with toluene (40ml) to furnish the crude title compound (1.4g) as a brown solid. δ ($DMSOd_6$): 4.98 (2H,s), 7.80 (1H,m), 7.90 (1H,d), 8.19 (1H,s), 9.22 (1H,d).

PREPARATION 96

4-Nitro-3-n-propyl-2-(pyridazin-3-yl)methylpyrazole-5-carboxamide

A mixture of the title compounds of Preparation 95 (700mg, 4.24mmol) and Preparation 34 (840mg, 4.24mmol), caesium carbonate (3.45g, 10.6mmol) and acetonitrile (30ml) was stirred at 80°C for 2 hours, then allowed to cool. Brine (30ml) was added, the mixture extracted with dichloromethane (2x80ml) and the combined extracts dried (Na_2SO_4) and evaporated under reduced pressure. The residual brown oil was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 90:10) to afford the title compound (480mg, 39%) as a yellow solid. δ ($CDCl_3$): 1.02 (3H,t), 1.60 (2H,m), 3.06 (2H,t), 5.72 (2H,s), 5.87 (1H,s), 7.25 (1H,s), 7.54 (2H,m), 9.20 (1H,s).

PREPARATION 97

4-Amino-3-n-propyl-2-(pyridazin-3-yl)methylpyrazole-5-carboxamide

Obtained as a pink gum (97%) from the title compound of Preparation 96, using the procedure of Preparation 40. δ ($CDCl_3$): 0.90 (3H,t), 1.47 (2H,m), 2.51 (2H,t), 5.25 (1H,s), 5.58 (2H,s), 6.58 (1H,s), 7.09 (1H,d), 7.43 (1H,m), 9.14 (1H,d). LRMS: m/z 261 $(M+1)^+$.

PREPARATION 98

4-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-3-n-propyl-2-(pyridazin-3-yl)methylpyrazole-5-carboxamide

Obtained as an orange gum (42%) from the title compounds of Preparation 28 and Preparation 97, using the procedure of Preparation 45A. δ ($CDCl_3$): 0.81 (3H,t), 1.01 (3H,t), 1.47 (2H,m), 1.55 (3H,t), 2.39 (2H,q), 2.50 (4H,m), 2.87 (2H,t), 3.07 (4H,m), 4.77 (2H,q), 5.58 (1H,s), 5.69 (2H,s), 6.71 (1H,s), 7.18 (1H,d), 7.45 (1H,m), 8.63 (1H,s), 8.79 (1H,s), 9.15 (1H,s), 10.52 (1H,s). LRMS: m/z 586 $(M+1)^+$.

PREPARATION 99

2-Methylpyrimidine-1-oxide

A freshly prepared solution of sodium metal (11.5g, 0.50mol) in ethanol (170ml) was added dropwise over 1 hour to a stirred suspension of hydroxylamine hydrochloride (34.75g, 0.50mol) and phenolphthalein (50mg) in ethanol (200ml) so as to maintain a colourless solution and the mixture stirred at room temperature for 3 hours. Acetonitrile (26ml, 0.50mol) was added and this mixture stirred for a further 2 hours at room temperature, then at 45°C for 48 hours. The resulting mixture was filtered and the filtrate concentrated under reduced pressure to a volume of ca. 100ml, then cooled to 0°C. The resulting

precipitate was collected and dried under suction to give the intermediate acetamidoxime (9.9g, 27%) as white crystals.

Boron trifluoride diethyl ether complex (9.5ml, 75mmol), followed by 1,1,3,3-tetramethoxypropane (11.5ml, 70mmol), were added to a stirred mixture of dimethylformamide (100ml) and toluene (100ml). The acetamidoxime (5.0g, 67.5mmol) was then added and the reaction mixture heated under reflux for 45 minutes, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residual brown oil partitioned between dichloromethane: methanol (80:20) (100ml) and aqueous sodium carbonate solution (100ml). The phases were separated, the aqueous phase extracted with dichloromethane: methanol (80:20) (10x50ml) and the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using dichloromethane: methanol (98:2) as eluant, to yield the title compound (2.5g, 34%) as an orange solid. δ ($CDCl_3$): 2.74 (3H,s), 7.19 (1H,m), 8.16 (1H,d), 8.39 (1H,d).

PREPARATION 100

2-Chloromethylpyrimidine

A stirred mixture of the title compound of Preparation 99 (2.5g, 22.7mmol) and phosphorous oxychloride (18ml, 193mmol) was heated under reflux for 2 hours, then allowed to cool. The resulting mixture was poured onto stirred ice and neutralised using solid sodium carbonate over 3 hours. The aqueous solution thus obtained was extracted with dichloromethane (3x100ml), then the combined extracts dried ($MgSO_4$) and evaporated under reduced pressure. The residual brown oil was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to

97:3), to provide the title compound (510mg, 17%). δ ($CDCl_3$): 4.72 (2H,s), 7.22 (1H,m), 8.75 (2H,d). LRMS: m/z 129 $(M+1)^+$.

PREPARATION 101a

4-Amino-3-n-propyl-1-(pyrimidin-2-yl)methylpyrazole-5-carboxamide

and

PREPARATION 101b

4-Amino-3-n-propyl-2-(pyrimidin-2-yl)methylpyrazole-5-carboxamide

Potassium hydroxide (393mg, 7mmol) was added to a stirred, ice-cooled solution of the title compound of Preparation 36 (1.2g, 6mmol) in dimethylformamide (10ml) and the mixture stirred for 1 hour at room temperature. The title compound of Preparation 100 (900mg, 7mmol) was then added and the reaction mixture stirred at room temperature for 18 hours, then evaporated under reduced pressure. The residue was partitioned between water (10ml) and dichloromethane (15ml), the phases separated and the aqueous phase extracted with dichloromethane (2x15ml). The combined organic solutions were dried ($MgSO_4$) and evaporated under reduced pressure, then the residue purified by column chromatography on silica gel, using dichloromethane: methanol (95:5) as eluant, to furnish a mixture of the title compounds (not separated) (1.06g, 67%) as a pale pink solid. Analysis of the ^1H nmr spectrum indicated a N1:N2 ratio (i.e. 1-isomer:2-isomer) of 22:78. δ ($DMSOd_6$): 0.81 (3H,t), 0.88 (3H,t), 1.38 (2H,m), 1.52 (2H,m), 2.48 (2H,t), 4.10 (2H,s), 4.44 (2H, s), 5.41 (2H,s), 5.73 (2H,s), 6.90 (1H,s), 7.06 (1H,s), 7.35 (1H,m), 7.42 (1H,m), 7.50 (2H,s), 8.68 (2H,d), 8.77 (2H,d). LRMS: m/z 261 $(M+1)^+$.

PREPARATION 102a

4-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-ylcarboxamido]-3-n-propyl-1-(pyrimidin-2-yl)methylpyrazole-5-carboxamide

and

PREPARATION 102b

4-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-ylcarboxamido]-3-n-propyl-2-(pyrimidin-2-yl)methylpyrazole-5-carboxamide

Triethylamine (1.12ml, 8.0mmol) was added to a stirred, ice-cooled suspension of the title compounds of Preparation 29 (680mg, 1.6mmol) and Preparations 101a/101b (417mg, 1.6mmol) in dichloromethane (20ml), then the reaction mixture stirred at room temperature for 18 hours, washed with water (10ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residual brown foam was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (98:2 to 95:5), to afford the first title compound (1-isomer; 56mg, 6%) as an orange gum. δ ($CDCl_3$): 0.96 (3H,t), 1.04 (3H,t), 1.76 (2H,m), 2.42 (2H,q), 2.54 (4H,m), 3.38 (3H,s), 3.86 (2H,t), 4.76 (2H,t), 6.13 (2H,s), 7.11 (1H,m), 8.44 (1H,s), 8.62 (2H,d), 8.78 (1H,s), 10.17 (1H,s). LRMS: m/z 616 $(M+1)^+$;

followed by the second title compound (2-isomer; 460mg, 47%) as an orange foam. δ ($CDCl_3$): 0.84 (3H,t), 1.03 (3H,t), 1.50 (2H,m), 2.40 (2H,q), 2.53 (4H,m), 2.88 (2H,t), 3.11 (4H,m), 3,39 (3H,s), 3.96 (2H,t), 4.85 (2H,q), 5.23 (1H,s), 5.58 (2H,s), 6.70 (1H,s), 7.25 (1H,m), 8.63 (1H,s), 8.74 (2H,d), 8.84 (1H,s), 10.52 (1H,s). LRMS: m/z 616 $(M+1)^+$.

PREPARATION 103a

4-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-3-n-propyl-1-(pyrimidin-2-yl)methylpyrazole-5-carboxamide

and

PREPARATION 103b

4-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-3-n-propyl-2-(pyrimidin-2-yl)methylpyrazole-5-carboxamide

Obtained as a mixture of isomers (88%) from the title compounds of Preparation 28 and Preparations 101a/101b using the procedure of Preparation 45A. LRMS: m/z 586 $(M+1)^+$.

PREPARATION 104

4-Amino-3-n-propyl-1-(pyridin-2-yl)methylpyrazole-5-carboxamide

Obtained as a solid (92%) from the title compound of Preparation 39a, using the procedure of Preparation 41. δ ($DMSOd_6$): 0.88 (3H,t), 1.55 (2H,m), 2.43 (2H,t), 4.18 (2H,s), 5.59 (2H,s), 6.73 (1H,d), 7.22 (1H,m), 7.57 (2H,s), 7.69 (1H,m), 8.47 (1H,d). LRMS: m/z 260 $(M+1)^+$.

PREPARATION 105

4-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-3-n-propyl-1-(pyridin-2-yl)methylpyrazole-5-carboxamide

Obtained as a brown foam (74%) from the title compounds of Preparation 28 and Preparation 104, using the procedure of Preparation 45A. δ ($CDCl_3$): 0.94 (3H,t), 1.02 (3H,t), 1.62 (5H,m), 2.40 (2H,q), 2.52 (4H,m), 2.64 (2H,t), 3.09 (4H,m), 4.77 (2H,q), 5.58 (2H,s), 5.71 (1H,s), 7.26 (1H,m), 7.40 (1H,d), 7.74 (1H,m), 8.52 (1H,d), 8.67 (1H,s), 8.82 (1H,s), 9.60 (1H,s), 9.96 (1H,s). LRMS: m/z 585 $(M+1)^+$.

PREPARATION 106

4-Amino-3-ethyl-1-(1-methylimidazol-2-yl)methylpyrazole-5-carboxamide

Obtained as a pink foam (95%) from the title compound of Preparation 88a, using the procedure of Preparation 40. δ ($DMSOd_6$): 1.09 (3H,t), 2.43 (2H,q), 3.72 (3H,s), 4.37 (2H,s), 5.44 (2H,s), 6.79 (1H,s), 7.08 (1H,s). LRMS: m/z 249 $(M+1)^+$.

PREPARATION 107

4-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-3-ethyl-1-(1-methylimidazol-2-yl)methylpyrazole-5-carboxamide

Obtained as a solid (78%) from the title compounds of Preparation 28 and Preparation 106, using the procedure of Preparation 45A. δ ($CDCl_3$): 1.01 (3H,t), 1.21 (3H,t), 1.60 (3H,t), 2.40 (2H,q), 2.53 (4H,m), 2.72 (2H,q), 3.08 (4H,m), 3.94 (3H,s), 4.76 (2H,q), 5.54 (2H,s), 5.93 (1H,s), 6.83 (1H,s), 6.92 (1H,s), 8.65 (1H,s), 8.82 (1H,s), 9.95 (1H,s), 10.27 (1H,s). LRMS: m/z 575 $(M+2)^+$.

PREPARATION 108

4-Amino-1-(1-methylimidazol-2-yl)methyl-3-n-propylpyrazole-5-carboxamide

Obtained as a cream solid (78%) from the title compound of Preparation 91a, using the procedure of Preparation 40. δ ($DMSOd_6$): 0.87 (3H,t), 1.52 (2H,m), 2.38 (2H,t), 3.70 (3H,s), 4.35 (2H,s), 5.44 (2H,s), 6.78 (1H,s), 7.08 (1H,s). LRMS: m/z 263 $(M+1)^+$.

PREPARATION 109

4-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-ylcarboxamido]-1-(1-methylimidazol-2-yl)methyl-3-n-propylpyrazole-5-carboxamide

Obtained (67%) from the title compounds of Preparation 25 and

Preparation 108, using the procedure of Preparation 52. δ ($CDCl_3$): 0.95 (3H,t), 1.02 (3H,t), 1.66 (2H,m), 2.40 (2H,q), 2.51 (4H,m), 2.63 (2H,t), 3.09 (4H,m), 3.39 (3H,s), 3.88 (3H,s), 3.93 (2H,t), 4.80 (2H,t), 5.56 (2H,s), 5.81 (1H,s), 6.83 (1H,s), 6.92 (1H,s), 8.65 (1H,s), 8.82 (1H,s), 9.60 (1H,s), 10.08 (1H,s).

PREPARATION 110

3-Bromo-5-(4-ethylpiperazin-1-ylsulphonyl)-2-(1-methylpiperidin-4-yloxy)pyridine

A mixture of 4-hydroxy-1-methylpiperidine (560mg, 4.89mmol), 60% sodium hydride dispersion in mineral oil (200mg, 4.89mmol) and tetrahydrofuran (30ml) was stirred at about 0°C for 30 minutes. The title compound of Preparation 13 (600mg, 1.63mmol) was added and the reaction mixture heated under reflux for 90 minutes, then allowed to cool. The resulting mixture was evaporated under reduced pressure, the residue suspended in ethyl acetate (50ml) and the suspension washed consecutively with 2M aqueous sodium hydroxide solution (2x20ml), water (20ml) and brine (20ml). The resulting solution was dried ($MgSO_4$) and evaporated under reduced pressure to give the title compound (660mg, 70%) as a yellow oil. δ ($CDCl_3$): 1.05 (3H,t), 1.92 (2H,m), 2.04 (2H,m), 2.33 (3H,s), 2.42 (4H,m), 2.55 (4H,m), 2.66 (2H,m), 3.08 (4H,m), 5.24 (1H,m), 8.09 (1H,s), 8.42 (1H,s). LRMS: m/z 447 $(M)^+$.

PREPARATION 111

5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(1-methylpiperidin-4-yloxy)pyridine-3-carboxylic acid ethyl ester

Triethylamine (2ml, 1.43mmol) and tetrakis(triphenylphosphine)-palladium(0) (200mg, 0.173mmol) were added to a stirred solution of the title compound of Preparation 110 (640mg, 1.43mmol) in ethanol (20ml) and the reaction mixture heated under carbon monoxide at 100°C and 1034kPa

(150psi) in a sealed vessel for 18 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using dichloromethane: methanol (96.5:3.5) as eluant, to yield the title compound (550mg, 87%) as an orange solid. δ ($CDCl_3$): 1.02 (3H,t), 1.40 (3H,t), 2.16 (2H,m), 2.41 (2H,q), 2.56 (6H,m), 2.72 (3H,s), 3.08 (4H,m), 3.19 (4H,m), 4.38 (2H,q), 5.60 (1H,m), 8.42 (1H,s), 8.62 (1H,s). LRMS: m/z 441 $(M+1)^+$.

PREPARATION 112

5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(1-methylpiperidin-4-yloxy)pyridine-3-carboxylic acid sodium salt

A mixture of the title compound of Preparation 111 (550mg, 1.25mmol), 1M aqueous sodium hydroxide solution (2.4ml, 2.40mmol) and ethanol (5ml) was stirred at room temperature for 18 hours, then evaporated under reduced pressure. The residue was partitioned between water (15ml) and ethyl acetate (15ml), the phases separated and the aqueous phase evaporated under reduced pressure to provide the title compound (510mg, 94%) as a white solid. δ ($DMSOd_6$): 0.93 (3H,t), 1.94 (2H,m), 2.10 (2H,m), 2.16 (3H,s), 2.29 (2H,q), 2.40 (4H,m), 2.68 (4H,m), 2.88 (4H,m), 5.08 (1H,m), 7.75 (1H,s), 8.28 (1H,s).

PREPARATION 113a

4-Amino-1-(2-morpholin-4-yl)ethyl-3-n-propylpyrazole-5-carboxamide

and

PREPARATION 113b

4-Amino-2-(2-morpholin-4-yl)ethyl-3-n-propylpyrazole-5-carboxamide

4-(2-Chloroethyl)morpholine (obtained by basification of the hydrochloride salt (2.67g, 14.35mmol)) was added to a stirred solution of the

title compound of Preparation 36 (2.0g, 11.96mmol) and potassium hydroxide (800mg, 14.35mmol) in dimethylformamide (20ml) and the reaction mixture heated under reflux for 18 hours, then allowed to cool. The resulting mixture was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using dichloromethane: methanol: glacial acetic acid (95:5:1) as eluant, to furnish the second title compound (2-isomer; 480mg, 14%). δ ($CDCl_3$): 0.98 (3H,t), 1.60 (2H,m), 2.48 (4H,m), 2.55 (2H,t), 2.76 (2H,t), 3.69 (4H,m), 3.94 (2H,s), 4.08 (2H,t), 5.19 (1H,s), 6.55 (1H,s). LRMS: m/z 282 $(M+1)^+$;

followed by the first title compound (1-isomer;350mg, 10%). δ ($CDCl_3$): 0.97 (3H,t), 1.64 (2H,m), 2.50 (6H,m), 2.81 (2H,t), 3.48 (2H,s), 3.64 (4H,m), 4.50 (2H,t).

PREPARATION 114

3-t-Butyl-1H-pyrazole-5-carboxylic acid hydrochloride

Hydrazine hydrate (1.7ml, 35mmol) was added dropwise to a stirred solution of 5,5-dimethyl-2,4-dioxohexanoic acid ethylester (J. Org. Chem., 1997, 62, 5908; 6.1g, 30.5mmol) in ethanol (20ml) and the reaction mixture stirred at room temperature for 4 hours, then evaporated under reduced pressure. The residue was partitioned between dichloromethane (20ml) and water (20ml), the phases separated and the aqueous phase extracted with dichloromethane (2x20ml). The combined organic solutions were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude ester as a yellow solid.

A mixture of this product, 1,4-dioxan (100ml) and 2M aqueous sodium hydroxide solution (25.5ml, 51mmol) was stirred at room temperature for 72 hours, then the pH of the reaction mixture adjusted to 2 with hydrochloric acid. The resulting mixture was evaporated under reduced pressure and the residue

triturated with hot ethanol. This mixture was filtered and the filtrate evaporated under reduced pressure to afford the title compound (5.06g, 81%) as an orange solid. δ ($DMSOd_6$): 1.26 (9H,s), 6.46 (1H,s).

PREPARATION 115

3-t-Butyl-4-nitro-1H-pyrazole-5-carboxylic acid

The title compound of Preparation 114 (1.5g, 7.3mmol) was added portionwise to stirred, ice-cooled concentrated sulphuric acid (7.5ml), the mixture warmed to 40°C and fuming nitric acid (1.13ml) then added dropwise, so as to maintain the internal temperature below 50°C. The reaction mixture was stirred at 50°C for 7 hours, allowed to cool and poured carefully onto ice/water (100g). The resulting suspension was stirred for 2 hours and filtered, then the collected solid washed with water and dried under suction to give the title compound (975mg, 63%) as a white solid. δ ($DMSOd_6$): 1.33 (9H,s). LRMS: m/z 231 $(M+18)^+$.

PREPARATION 116

3-t-Butyl-4-nitro-1H-pyrazole-5-carboxamide

Oxalyl chloride (1.59ml, 18.2mmol) was added dropwise to a stirred, ice-cooled solution of the title compound of Preparation 115 (970mg, 4.55mmol) and dimethylformamide (1 drop) in dichloromethane (20ml) and the reaction mixture stirred at room temperature for 3 hours, then evaporated under reduced pressure. The residue was azeotroped firstly with dichloromethane and then with 0.88 aqueous ammonia solution. The resulting material was triturated with hot ethanol, then acetonitrile, the mixture filtered and the filtrate evaporated under reduced pressure to yield the title compound (955mg, 99%) as a white solid. δ ($DMSOd_6$): 1.36 (9H,s), 7.60 (1H,s), 7.88 (1H,s). LRMS: m/z 230 $(M+18)^+$.

PREPARATION 117

3-t-Butyl-4-nitro-1-(pyridin-2-yl)methylpyrazole-5-carboxamide

A mixture of the title compound of Preparation 116 (960mg, 4.55mmol), caesium carbonate (3.7g, 11.36mmol) and 2-(chloromethyl)pyridine hydrochloride (821mg, 5.00mmol) in acetonitrile (20ml) was stirred at 70°C for 20 hours, then allowed to cool and filtered. The filtrate was evaporated under reduced pressure, then the residue purified by column chromatography on silica gel, using an elution gradient of ethyl acetate: methanol (100:0 to 95:5), to provide the title compound (300mg, 22%) as a yellow solid. δ ($DMSOd_6$): 1.35 (9H,s), 5.40 (2H,s), 7.18 (1H,d), 7.32 (1H,m), 7.80 (1H,m), 8.10 (1H,s), 8.46 (1H,s), 8.51 (1H,d). LRMS: m/z 304 $(M+1)^+$.

PREPARATION 118

4-Amino-3-t-butyl-1-(pyridin-2-yl)methylpyrazole-5-carboxamide

A stirred mixture of the title compound of Preparation 117 (290mg, 0.96mmol) and 10% palladium on charcoal (29mg) in ethanol (20ml) was hydrogenated at 345kPa (50psi) and room temperature for 7 hours, then filtered. The filter pad was washed with ethanol and the combined washings and filtrate evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of ethyl acetate: methanol (100:0 to 95:5), to furnish the title compound (220mg, 84%) as an orange solid. δ ($CDCl_3$): 1.36 (9H,s), 4.00 (2H,s), 5.50 (2H,s), 7.23 (1H,m), 7.38 (1H,d), 7.71 (1H,m), 8.50 (1H,d). LRMS: m/z 274 $(M+1)^+$.

PREPARATION 119

4-[5-(4-Ethylpiperazin-1-ylsulphonyl)-2-(1-methylpiperidin-4-yloxy)pyridin-3-ylcarboxamido]-3-n-propyl-2-(pyridin-2-yl)methylpyrazole-5-carboxamide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (350mg, 1.8mmol) was added to a stirred solution of 1-hydroxybenzotriazole hydrate

(250mg, 1.8mmol), triethylamine (350µl, 2.5mmol) and the title compounds of Preparation 112 (510mg, 1.18mmol) and Preparation 41 (330mg, 1.25mmol) in tetrahydrofuran (20ml) and the reaction mixture stirred at room temperature for 72 hours, then evaporated under reduced pressure. The residue was triturated several times with ethyl acetate to afford the title compound (175mg, 21%) as a white solid. δ ($CDCl_3$): 0.81 (3H,t), 1.04 (3H,t), 1.47 (2H,m), 2.17 (4H,m), 2.32 (5H,m), 2.40 (2H,q), 2.53 (4H,m), 2.76 (2H,m), 2.84 (2H,t), 3.10 (4H,m), 5.49 (3H,m), 5.64 (1H,s), 6.90 (2H,m), 7.22 (1H,m), 7.68 (1H,m), 8.60 (1H,d), 8.64 (1H,s), 8.82 (1H,s), 10.35 (1H,s). LRMS: m/z 654 $(M+1)^+$.

PREPARATION 120

4-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-2-(2-morpholin-4-yl)ethyl-3-n-propylpyrazole-5-carboxamide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (280mg, 1.5mmol) was added to a stirred solution of 1-hydroxybenzotriazole hydrate (200mg, 1.5mmol), triethylamine (278µl, 2.0mmol) and the title compounds of Preparation 23 (371mg, 1.0mmol) and Preparation 113b (250mg, 0.9mmol) in dichloromethane (20ml) and the reaction mixture stirred at room temperature for 18 hours. The resulting mixture was washed with water (10ml), dried ($MgSO_4$) and evaporated under reduced pressure, then the residue purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (97:3 to 95:5), to give the title compound (430mg, 68%) as a white solid. δ ($CDCl_3$): 0.93 (3H,t), 1.02 (3H,t), 1.58 (5H,m), 2.40 (2H,q), 2.52 (8H,m), 2.82 (2H,t), 2.90 (2H,t), 3.12 (4H,m), 3.72 (4H,m), 4.20 (2H,t), 4.79 (2H,q), 5.28 (1H,s), 6.63 (1H,s), 8.64 (1H,s), 8.82 (1H,s), 10.50 (1H,s).

PREPARATION 121

3-t-Butyl-4-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-1-(pyridin-2-yl)methylpyrazole-5-carboxamide

The title compound of Preparation 28 (384mg, 0.967mmol) was added dropwise to a stirred, ice-cooled solution of the title compound of Preparation

118 (220mg, 0.805mmol) and triethylamine (330µl, 2.42mmol) in dichloromethane (10ml) and the reaction mixture stirred at room temperature for 14 hours. The resulting mixture was washed with aqueous sodium bicarbonate solution (5ml) and brine (5ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by two column chromatography operations on silica gel, using an elution gradient of ethyl acetate: methanol (100:0 to 90:10) and then of dichloromethane: methanol (100:0 to 95:5), to yield the title compound (156mg, 32%) as a white solid. δ ($CDCl_3$): 1.02 (3H,t), 1.36 (9H,s), 1.55 (3H,t), 2.42 (2H,q), 2.55 (4H,m), 3.10 (4H,m), 4.77 (2H,q), 5.68 (3H,m), 7.02 (1H,d), 7.19 (1H,m), 7.65 (1H,m), 7.98 (1H,s), 8.56 (1H,d), 8.70 (1H,s), 8.87 (1H,s), 9.35 (1H,s). LRMS: m/z 599 $(M+1)^+$.

PREPARATION 122

4-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-1-(2-morpholin-4-yl)ethyl-3-n-propylpyrazole-5-carboxamide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.34g, 7.0mmol) was added to a stirred solution of 1-hydroxybenzotriazole hydrate (945mg, 7.0mmol), N-ethyldiisopropylamine (1.22ml, 7.0mmol) and the title compounds of Preparation 113a (1.82g, 6.5mmol) and Preparation 23 (428mg, 1.25mmol) in tetrahydrofuran (120ml) and the reaction mixture stirred at room temperature for 72 hours. The resulting mixture was evaporated under reduced pressure and the residue partitioned between aqueous sodium carbonate solution (50ml) and dichloromethane (100ml). The phases were separated, the aqueous phase extracted with dichloromethane (2x100ml) and the combined organic solutions washed with brine (3x50ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was triturated with ether, then crystallised from ethyl acetate-methanol, to provide the title compound (310mg, 42%) as a white solid. δ ($CDCl_3$): 0.92 (3H,t), 1.01 (3H,t), 1.54 (3H,t), 1.62 (2H,m), 2.36-2.60 (12H,m), 2.80 (2H,t), 3.08 (4H,m), 3.64 (4H,m), 4.49 (2H,t), 4.72 (2H,q), 5.78 (1H,s), 8.30 (1H,s), 8.66 (1H,s), 8.80 (1H,s), 9.49 (1H,s). LRMS: m/z 607 $(M+1)^+$.

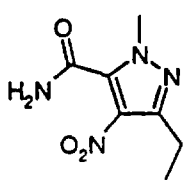
PREPARATION 123

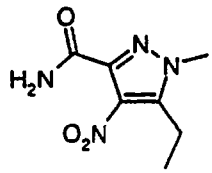
3-Ethyl-1-methyl-4-nitropyrazole-5-carboxamide

and

PREPARATION 124

3-Ethyl-2-methyl-4-nitropyrazole-5-carboxamide





A mixture of the title compound of Preparation 35 (100g, 0.54mol), and caesium carbonate (194g, 0.60mol) in N,N-dimethylformamide (1000ml) was stirred at room temperature for 45 minutes, then cooled in an ice-bath. Methyl iodide (37.2ml, 0.60mol) was added dropwise and once the addition was complete, the reaction was stirred at room temperature for 18 hours. The mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate (500ml) and water (300ml). The layers were separated, the aqueous phase extracted with ethyl acetate (4x500ml) and the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was recrystallised from dichloromethane/ethyl acetate to give some of the N1 isomer (17.0g, 16%).

The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel, using ethyl acetate: pentane (80:20) as eluant to afford the title compound of Preparation 123 (25.0g, 23%) as a white solid.

δ ($CDCl_3$) : 1.27 (3H, t), 2.94 (2H, q), 4.06 (3H, s), 6.00 (1H, br s), 7.56 (1H, br s).

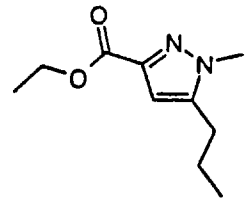
LRMS : m/z 216 $(M+18)^+$

and the title compound of Preparation 124 (28.4g, 27%) as a white solid.

δ ($CDCl_3$) : 1.29 (3H, t), 3.00 (2H, q), 3.92 (3H, s), 5.98 (1H, s), 7.32 (1H, s).

PREPARATION 125

2-Methyl-3-n-propyl-pyrazole-5-carboxylic acid ethyl ester

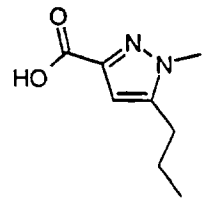


A solution of diethyloxalate (27.2ml, 0.2mol) in 2-pentanone (21.2ml, 0.2mol) was added dropwise to a solution of sodium (4.83g, 0.21mol) in ethanol (200ml), and the reaction stirred at 60°C for 5 hours, then cooled in an ice-bath. The solution was neutralised using acetic acid (11.5ml, 0.2mol) and N-methyl hydrazine (10.6ml, 0.2mol) then added dropwise. The mixture was stirred for a further 4 hours at room temperature and concentrated under reduced pressure. The residue was partitioned between dichloromethane (300ml) and water (200ml), and the phases separated. The aqueous layer was extracted with dichloromethane (3x100ml), the combined organic solutions were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel, using ethyl acetate: hexane (25:75) as eluant to give ethyl 1-methyl-3-n-propyl-pyrazole-5-carboxylate (6.1g) and the title compound (22.1g, 56%).

δ ($CDCl_3$) : 1.00 (3H, t), 1.40 (3H, t), 1.70 (2H, m), 2.60 (2H, t), 3.87 (3H, s), 4.40 (2H, q), 6.60 (1H, s).

PREPARATION 126

2-Methyl-3-n-propylpyrazole-5-carboxylic acid



A mixture of the title compound of Preparation 125 (21.5g, 0.11mol) in aqueous sodium hydroxide solution (50ml, 6N, 0.3mol) was heated under reflux for 3 hours. The cooled mixture was diluted with water (50ml) and acidified using

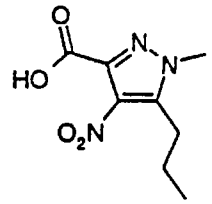
concentrated hydrochloric acid (25ml) and the resulting precipitate was filtered and dried to give the title compound (17.3g, 94%) as a pale yellow solid.

A portion (1g) of this solid, was recrystallised from water/ethanol.

m.p. 120-122°C. δ ($DMSOd_6$) : 0.95 (3H, t), 1.59 (2H, m), 2.60 (2H, t), 3.78 (3H, s), 6.48 (1H, s), 12.45 (1H, s).

PREPARATION 127

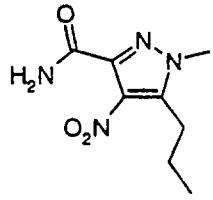
2-Methyl-4-nitro-3-n-propylpyrazole-5-carboxylic acid



Obtained as a solid (89%) from the title compound of Preparation 126, using a similar procedure to that described in Preparation 32. δ ($DMSOd_6$) : 0.95 (3H, t), 1.60 (2H, m), 2.96 (2H, t), 3.88 (3H, s), 13.75 (1H, s).

PREPARATION 128

2-Methyl-4-nitro-3-n-propylpyrazole-5-carboxamide

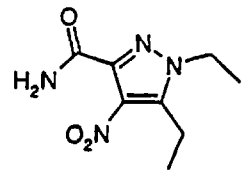


A mixture of the title compound of Preparation 127 (18.6g, 87.3mmol) in thionyl chloride (75ml), was heated under reflux for 2 hours. The cooled reaction mixture was concentrated under reduced pressure and the residue poured into an ice/ammonium hydroxide mixture. This was extracted with dichloromethane (4x100ml) and the combined organic extracts dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel, using dichloromethane:methanol:0.88 ammonia (95:5:1) as eluant to afford the title compound (6.8g, 37%) as a solid.

δ ($CDCl_3$) : 1.07 (3H, t), 1.72 (2H, m), 3.00 (2H, t), 3.97 (3H, s), 6.14 (1H, s), 7.40 (1H, s).

PREPARATION 129

2, 3-Diethyl-4-nitro-pyrazole-5-carboxamide



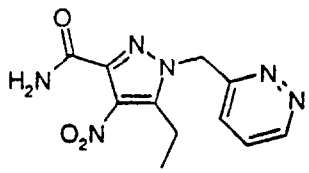
Ethyl iodide (7.2ml, 90.0mmol) was added to a suspension of the title compound of Preparation 35 (15.0g, 81.0mmol), and cesium carbonate (29.3g, 90.0mmol) in N,N-dimethylformamide (100ml) and the reaction stirred at room temperature for 18 hours. The mixture was concentrated under reduced pressure and the residue triturated with water (100ml), and the resulting solid filtered and dried. A suspension of this solid in ether (250ml) was heated at 35°C for an hour, and the precipitate filtered and dried. This was recrystallised from ethyl acetate to afford the title compound as a crystalline solid (5.8g, 34%).

δ ($CDCl_3$) : 1.30 (3H, t), 1.54 (3H, t), 3.00 (2H, q), 4.20 (2H, q), 5.92 (1H, s), 7.27 (1H, s).

LRMS : m/z 212 $(M)^+$

PREPARATION 130

3-Ethyl-4-nitro-2-(pyridazin-3-yl)methyl-pyrazole-5-carboxamide



A mixture of the title compounds of Preparation 35 (2.66g, 14.5mmol), and 95 (2.65g, 16.1mmol) and caesium carbonate (13.1g, 40.2mmol) in acetonitrile (100ml) was stirred under reflux for 18 hours. The cooled reaction was concentrated under reduced pressure, the residue suspended in water and extracted with dichloromethane (5x100ml). The combined organic extracts were dried (Na_2SO_4), adsorbed onto silica gel and the product isolated by column

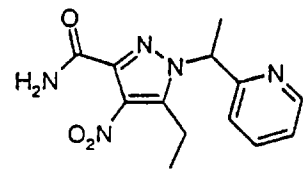
chromatography on silica gel, using an elution gradient of methanol: dichloromethane (5:95 to 10:90) to give 3-ethyl-4-nitro-1-(pyridazin-3-yl)methyl-pyrazole-5-carboxamide (1.31g), and the title compound (1.81g, 45%) as a pale yellow solid.

δ ($CDCl_3$) : 1.20 (3H, t), 3.11 (2H, q), 5.72 (2H, s), 5.89 (1H, s), 7.29 (1H, s), 7.55 (2H, m), 9.20 (1H, d).

LRMS : m/z 277 $(M+1)^+$

PREPARATION 131

3-Ethyl-4-nitro-2-[1-(pyridin-2yl)ethyl]-pyrazole-5-carboxamide



A mixture of 2-ethylpyridine (20.0g, 187mmol), N-bromosuccinimide (38.0g, 213mmol), and benzoyl peroxide (1.0g, 75% in water) in 1,1,1-trichloroethane (200ml), was heated under reflux for 3 hours. The cooled mixture was filtered, and the filtrate washed with water (2x100ml), aqueous sodium thiosulphate solution (100ml), and brine (100ml). The solution was dried ($MgSO_4$), filtered through charcoal, and then hydrobromic acid (25ml, 62%) added. This solution was concentrated under reduced pressure and azeotroped with toluene to give 2-(1-bromoethyl)pyridine hydrochloride as a dark oil (66.0g).

A mixture of the title compound of Preparation 35 (8.0g, 43.4mmol), caesium carbonate (35.0g, 107.4mmol) and the crude 2-(1-bromoethyl)pyridine hydrochloride (13.6g, 52.0mmol) in N,N-dimethylformamide (80ml) was stirred at room temperature for 20 hours. The mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate (150ml) and water (50ml). The layers were separated and the organic phase washed

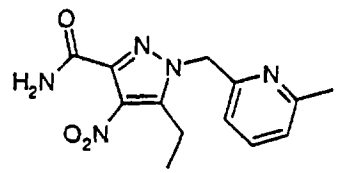
with more water (3x50ml), brine (50ml), then dried ($MgSO_4$) and evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel, using an elution gradient of pentane: ethyl acetate: methanol (90:10:0 to 0:100:0 to 0:90:10) to afford the N1 isomer (4.3g), and the title compound (5.7g, 45%).

δ ($CDCl_3$) : 1.14 (3H, t), 2.01 (3H, d), 3.00 (2H, q), 5.66 (2H, q), 5.88 (1H, s), 6.98 (1H, s), 7.18 (1H, d), 7.25 (1H, m), 7.68 (1H, m), 8.56 (1H, d).

LRMS : m/z 290 $(M+1)^+$

PREPARATION 132

3-Ethyl-2-(6-methylpyridin-2-yl)methyl-4-nitropyrazole-5-carboxamide



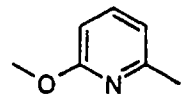
A mixture of the title compound of Preparation 35 (4.32g, 23.5mmol) and 6-methyl-2-picolyl chloride hydrochloride (5.0g, 23.4mmol) in N,N-dimethylformamide (50ml) was stirred at room temperature for 20 hours. The reaction mixture was concentrated under reduced pressure and the residue partitioned between water (50ml) and dichloromethane (50ml). The layers were separated and the aqueous phase extracted with dichloromethane (3x50ml), the combined organic solutions washed with brine (50ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, twice, using dichloromethane: methanol (95:5) as eluant and repeated using an elution gradient of pentane: ethyl acetate (50:50 to 0:100) to give the N1 isomer (1.0g) and the title compound (2.47g, 36%) as a white solid.

δ ($CDCl_3$) : 1.18 (3H, t), 2.53 (3H, s), 3.06 (2H, q), 5.42 (2H, s), 5.97 (1H, s), 6.90 (1H, d), 7.12 (1H, d), 7.22 (1H, s), 7.58 (1H, m).

LRMS : m/z 312 $(M+23)^+$

PREPARATION 133

2-Methoxy-6-methylpyridine

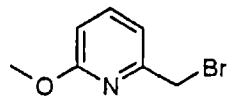


Trimethyloxonium tetrafluoroborate (10.0g, 67.6mmol) was added portionwise to a suspension of 6-methylpyridin-2-one (7.3g, 67.0mmol) in dichloromethane (100ml), and once addition was complete, the reaction was stirred at room temperature for 24 hours. Dichloromethane (50ml) and aqueous sodium hydroxide solution (50ml, 2N) were added and the layers separated. The aqueous phase was extracted with dichloromethane (2x50ml), the combined organic solutions washed with brine (50ml), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel, using an elution gradient of pentane: dichloromethane (66:34 to 0:100) to afford the title compound (2.25g, 27%) as a colourless oil.

δ ($CDCl_3$) : 2.49 (3H, s), 3.90 (3H, s), 6.38-6.73 (2H, m), 7.23-7.40 (1H, br d).

PREPARATION 134

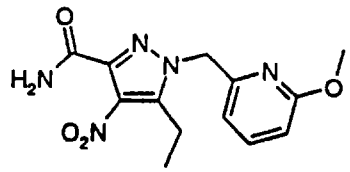
6-Bromomethyl-2-methoxypyridine



A mixture of the title compound of Preparation 133 (2.5g, 20.3mmol), N-bromosuccinamide (3.7g, 20.8mmol) and benzoyl peroxide (100mg, 0.41mmol) in 1,1,1-trichloroethane (50ml) was stirred under reflux for 3 hours, and a further 16 hours at room temperature. The reaction was washed with water (2x25ml), aqueous sodium thiosulphate solution (25ml), brine (25ml) and dried ($MgSO_4$) and evaporated under reduced pressure. The residue was shaken well with hydrobromic acid (62%, 2.4ml), and the suspension concentrated under reduced pressure, and azeotroped twice with toluene, to give the title compound as a yellow solid. δ ($CDCl_3$) : 3.95 (3H, s), 4.46 (2H, s), 6.63 (1H, d), 6.98 (1H, d), 7.53 (1H, m). LRMS : m/z 202/204 $(M+1)^+$

PREPARATION 135

3-Ethyl-2-(6-methoxypyridin-2-yl)methyl-4-nitro-pyrazole-5-carboxamide



A mixture of the title compound of Preparation 134 (5.2g, 18.4mmol), caesium carbonate (6.58g, 32.5mmol) and the title compound of Preparation 35 (3.4g, 18.4mmol) in N,N-dimethylformamide (30ml) was stirred at room temperature for 18 hours. The reaction was concentrated under reduced pressure, the residue partitioned between ether (100ml) and water (50ml), and the phases separated. The organic layer was washed with brine (20ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residual gum was triturated with ether, to give the title compound (640mg, 11%) as a white solid.

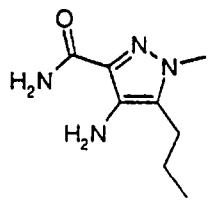
The filtrate was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using pentane: ethyl acetate (66:34) as eluant to give a further (280mg, 5%) of the title compound.

δ ($DMSOd_6$) : 1.18 (3H, t), 2.84 (2H, q), 3.68 (3H, s), 5.34 (2H, s), 6.73 (2H, m), 7.66 (1H, m), 8.17 (1H, s), 8.39 (1H, s).

LRMS : m/z 306 $(M+1)^+$

PREPARATION 136

4-Amino-2-methyl-3-n-propylpyrazole-5-carboxamide



A mixture of the title compound of Preparation 128 (6.17g, 29.0mmol) and tin (II) chloride dihydrate (32.8g, 145mmol) in industrial methylated spirits (IMS) (100ml) was heated under reflux for 2 hours. The cooled mixture was

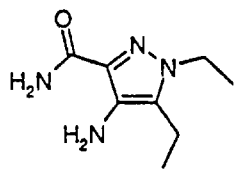
concentrated under reduced pressure to approximately half it's volume, basified to pH 9 using aqueous 2N sodium hydroxide solution, and extracted with dichloromethane (3x300ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure and the crude product recrystallised from ethyl acetate/methanol to afford the title compound (4.86g, 92%).

m.p.170-174°C

δ ($DMSOd_6$) : 0.90 (3H, t), 1.47 (2H, m), 2.50 (2H, t), 3.68 (3H, s), 4.43 (2H, s), 6.92 (1H, s), 7.04 (1H, s).

PREPARATION 137

4-Amino-2,3-diethyl-pyrazole-5-carboxamide



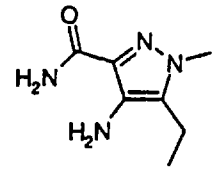
A mixture of the title compound of Preparation 129 (5.7g, 26.9mmol) and tin (II) chloride dihydrate (29.0g, 128mmol) in ethanol (200ml) was heated under reflux for 45 minutes. The cooled reaction mixture was evaporated under reduced pressure and re-dissolved in ethyl acetate (200ml). This solution was poured into a 10% aqueous solution of sodium carbonate (400ml), and the mixture stirred vigorously for an hour. The layers were separated and the aqueous phase was extracted with ethyl acetate (2x100ml). The combined organic solutions were dried (Na_2SO_4) and concentrated under reduced pressure to a volume of 50 ml, and the resulting crystals filtered off and dried, to afford the title compound (3.3g, 67%).

δ ($CDCl_3$) : 1.19 (3H, t), 1.40 (3H, t), 2.59 (2H, q), 3.94 (2H, s), 4.02 (2H, q), 5.20 (1H, s), 6.57 (1H, s).

LRMS : m/z 183 $(M+1)^+$

PREPARATION 138

4-Amino-3-ethyl-2-methylpyrazole-5-carboxamide

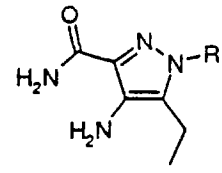


A mixture of the title compound of Preparation 124 (5.8g, 29.3mmol) and 10% palladium on charcoal (650mg) in ethanol (100ml) was hydrogenated at 60psi and room temperature for 20 hours. The reaction was filtered through Arbocel® and the filter pad washed well with hot ethanol (200ml). The combined filtrate was evaporated under reduced pressure to afford the title compound as a solid (4.7g, 95%).

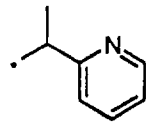
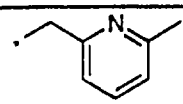
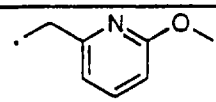
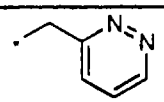
δ ($CDCl_3$) : 1.20 (3H, t), 2.59 (2H, q), 3.77 (3H, s), 3.95 (2H, s), 5.21 (1H, s), 6.54 (1H, s).

PREPARATIONS 139 TO 142

The compounds of the following tabulated Preparations of general formula:



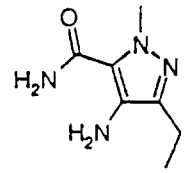
were prepared from the corresponding nitropyrazoles, using a similar procedure to that described in Preparation 138.

Preparation	R	LRMS: m/z	^{1}H nmr
139			δ ($CDCl_3$) : 0.98 (3H, t), 1.93 (3H, d), 2.50 (2H, q), 3.98 (2H, s), 5.23 (1H, s), 5.50 (1H, q), 6.68 (1H, s), 6.80 (1H, d), 7.17 (1H, m), 7.59 (1H, m), 8.54 (1H, d).
140		282 $(M+23)^+$	δ ($CDCl_3$) : 1.04 (3H, t), 2.55 (5H, m), 4.00 (2H, s), 5.19 (1H, s), 5.30 (2H, s), 6.52 (1H, d), 6.60 (1H, s), 7.03 (1H, d), 7.48 (1H, m).
141[1]		298 $(M+23)^+$	δ ($CDCl_3$) : 1.22 (3H, t), 2.57 (2H, q), 3.78 (2H, s), 3.84 (3H, s), 5.45 (2H, s), 6.68 (1H, d), 6.90 (1H, d), 7.58 (1H, m).
142		247 $(M+1)^+$	δ ($CDCl_3$) : 1.05 (3H, t), 2.58 (2H, q), 4.01 (2H, s), 5.28 (1H, br s), 5.59 (2H, s), 6.60 (1H, br s), 7.11 (1H, d), 7.42 (1H, m), 9.15 (1H, d).

1 = purified by column chromatography using ethyl acetate as eluant

PREPARATION 143

4-Amino-3-ethyl-1-methyl-pyrazole-5-carboxamide



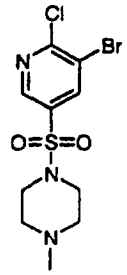
A mixture of the title compound of Preparation 123 (940mg, 4.75mmol), and 10% palladium on charcoal (200mg) in ethanol (100ml) was hydrogenated at 50°C and 50psi for 18 hours. The cooled mixture was filtered through Arbocel®, and the filtrate evaporated under reduced pressure to afford the title compound (786mg, 98%) as a clear oil.

δ ($CDCl_3$) : 1.23 (3H, t), 2.59 (2H, q), 2.82 (2H, s), 4.12 (3H, s).

LRMS : m/z 169 $(M+1)^+$

PREPARATION 144

3-Bromo-2-chloro-5-(4-methylpiperazin-1-ylsulphonyl)pyridine

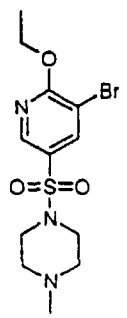


N-Methylpiperazine (7.65ml, 69.0mmol) was added dropwise to a solution of the title compound of Preparation 12 (10.0g, 34.5mmol) in ethanol (200ml), and the reaction stirred at room temperature for 3 hours. The mixture was concentrated under reduced pressure and the residue partitioned between dichloromethane (200ml) and water (100ml) and the layers separated. The organic phase was dried (Na_2SO_4), and evaporated under reduced pressure to afford the title compound (10.53g, 87%) as a yellow solid.

δ ($CDCl_3$) : 2.28 (3H, s), 2.51 (4H, m), 3.14 (4H, m), 8.24 (1H, s), 8.67 (1H, s).

PREPARATION 145

3-Bromo-2-ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)pyridine



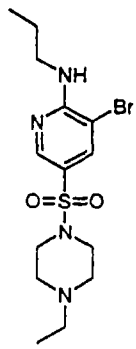
A mixture of the title compound of Preparation 144 (10.0g, 39.1mmol), potassium bis(trimethylsilyl)amide (5.92g, 29.7mmol) and ethanol (3.5ml) in tetrahydrofuran (150ml) was stirred at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate (150ml) and brine (50ml). The layers were separated, and the organic phase dried (Na_2SO_4), filtered and evaporated under reduced pressure, to afford the title compound, (9.1g, 88%).

δ ($CDCl_3$) : 1.44 (3H, t), 2.29 (3H, s), 2.51 (4H, m), 3.08 (4H, m), 4.54 (2H, q), 8.10 (1H, s), 8.44 (1H, s).

LRMS : m/z 365 $(M+1)^+$

PREPARATION 146

3-Bromo-5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propylaminopyridine



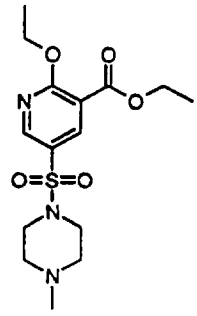
A mixture of the title compound of Preparation 13 (1.11g, 3.0mmol) and n-propylamine (590mg, 10.0mmol) in toluene (20ml) was stirred under reflux for 90 minutes. The cooled mixture was partitioned between ethyl acetate (50ml) and water (20ml), and the layers separated. The organic phase was washed with brine (20ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 96:4) to afford the title compound (1.15g, 98%) as a yellow crystalline solid.

δ ($CDCl_3$) : 1.02 (6H, m), 1.68 (2H, m), 2.41 (2H, q), 2.54 (4H, m), 3.06 (4H, m), 3.47 (2H, q), 5.57 (1H, m), 7.86 (1H, s), 8.40 (1H, s).

LRMS : m/z 393 $(M+2)^+$

PREPARATION 147

2-Ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)pyridine-3-carboxylic acid ethyl ester

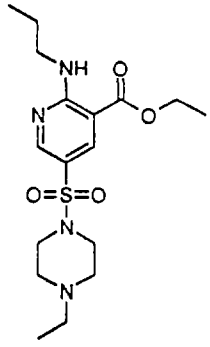


Obtained (85%) as an orange solid, from the title compound of Preparation 145 using a similar procedure to that described in Preparation 21.

δ ($CDCl_3$) : 1.40 (3H, t), 1.46 (3H, t), 2.28 (3H, s), 2.50 (4H, m), 3.09 (4H, m), 4.40 (2H, q), 4.57 (2H, q), 8.40 (1H, s), 8.63 (1H, s). LRMS : m/z 358 $(M+1)^+$

PREPARATION 148

5-(4-Ethylpiperazin-1-ylsulphonyl)-2-n-propylaminopyridine-3-carboxylic acid ethyl ester



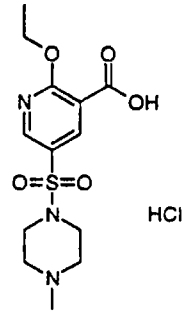
A mixture of the title compound of Preparation 146 (1.10g, 2.81mmol), triethylamine (5ml), and tetrakis(triphenylphosphine)palladium (0) (250mg, 0.216mmol) in ethanol (25ml) was stirred under an atmosphere of carbon monoxide at 100°C and 100psi for 16 hours. The cooled solution was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 96:4) to afford the title compound (1.07g, 99%) as a yellow oil.

δ ($CDCl_3$) : 1.02 (6H, t), 1.40 (3H, t), 1.69 (2H, m), 2.40 (2H, q), 2.55 (4H, m), 3.05 (4H, m), 3.54 (2H, q), 4.37 (2H, q), 8.37 (1H, s), 8.57 (2H, m).

LRMS : m/z 385 $(M+1)^+$

PREPARATION 149

2-Ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)pyridine-3-carboxylic acid hydrochloride



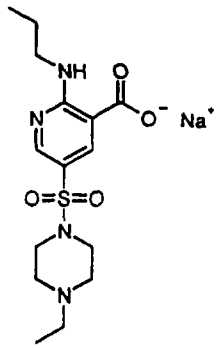
Sodium hydroxide solution (21ml, 2M, 42.0mmol) was added to a solution of the title compound of Preparation 147 (7.57g, 21.0mmol) in dioxan (150ml) and the reaction stirred at room temperature for 18 hours. The mixture was neutralised using hydrochloric acid, the dioxan removed under reduced pressure and the remaining aqueous solution acidified to pH 2, using hydrochloric acid. The solution was evaporated under reduced pressure, the residue re-suspended in hot ethanol, filtered, and the filtrate re-evaporated to afford the title compound (5.46g, 71%).

δ ($DMSOd_6$) : 1.37 (3H, t), 2.50 (4H, m), 2.72 (3H, s), 3.13-3.39 (4H, m), 4.53 (2H, q), 8.30 (1H, s), 8.75 (1H, s).

LRMS : m/z 330 $(M+1)^+$

PREPARATION 150

5-(4-Ethylpiperazin-1-ylsulphonyl)-2-n-propylaminopyridine-3-carboxylic acid sodium salt

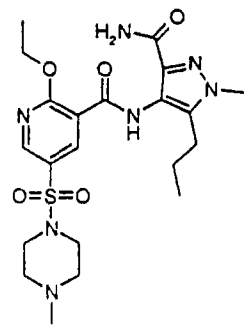


A mixture of the title compound of Preparation 148 (1.06g, 2.76mmol) in sodium hydroxide solution (1.5ml, 2N, 3.0mmol) and ethanol (10ml) was stirred at room temperature for 4 hours. The reaction was evaporated under reduced pressure, the solid triturated with ether, and the suspension filtered and dried to afford the title compound (950mg).

δ ($DMSOd_6$) : 0.87 (6H, t), 1.50 (2H, m), 2.43 (2H, q), 2.56 (4H, m), 2.78 (4H, m), 3.34 (2H, t), 8.08 (1H, s), 8.16 (1H, s).

PREPARATION 151

4-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-2-methyl-3-n-propylpyrazole-5-carboxamide



The title compound of Preparation 136 (525mg, 2.88mmol) was added to a mixture of the title compound of Preparation 149 (1.04g, 3.2mmol), 1-

hydroxybenzotriazole hydrate (470mg, 3.5mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (670mg, 3.5mmol) and N-ethyldiisopropylamine (2.4ml, 14.0mmol) in tetrahydrofuran (50ml), and the reaction stirred at room temperature for 36 hours. The reaction mixture was concentrated under reduced pressure and the residue suspended in sodium carbonate solution (20ml) and extracted with dichloromethane (3x20ml). The combined organic extracts were washed with brine (3x20ml), dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was triturated with ether to give a yellow solid which was then purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 96:4) to give the title compound (720mg, 51%) as a white solid.

A sample (50mg) of this product was recrystallised from ethyl acetate to give colourless crystals (32mg) of the title compound.

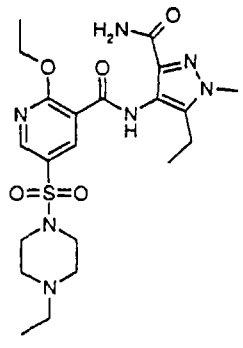
m.p. 242-244°C

δ ($CDCl_3$) : 0.95 (3H, t), 1.59 (5H, m), 2.27 (3H, s), 2.48 (4H, m), 2.89 (2H, t), 3.10 (4H, m), 3.86 (3H, s), 4.79 (2H, q), 5.27 (1H, s), 6.63 (1H, s), 8.65 (1H, s), 8.84 (1H, s), 10.53 (1H, s).

LRMS : m/z 494 $(M+1)^+$

PREPARATION 152

4-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-3-ethyl-2-methylpyrazole-5-carboxamide



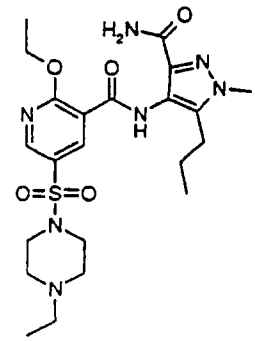
Obtained as a solid (65%) from the title compounds of Preparations 23 and 138, following the procedure described in Preparation 151.

δ ($CDCl_3$) : 1.02 (3H, t), 1.21 (3H, t), 1.58 (3H, t), 2.39 (2H, q), 2.54 (4H, m), 2.90 (2H, q), 3.10 (4H, m), 3.84 (3H, s), 4.78 (2H, q), 5.30 (1H, s), 6.63 (1H, s), 8.64 (1H, s), 8.83 (1H, s), 10.54 (1H, s).

LRMS : m/z 494 $(M+1)^+$

PREPARATION 153

4-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-2-methyl-3-n-propylpyrazole-5-carboxamide



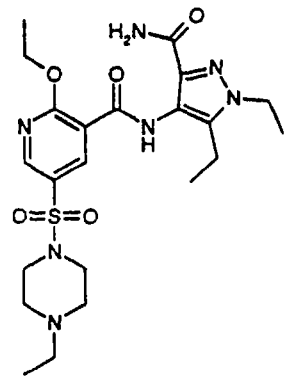
Obtained as a solid (64%) from the title compounds of Preparations 23 and 136, following a similar procedure to that described in Preparation 151, except an elution gradient of methanol: ethyl acetate (7:93 to 10:90) was used as the chromatographic eluant.

δ ($CDCl_3$) : 0.94 (3H, t), 1.02 (3H, t), 1.60 (5H, m), 2.40 (2H, q), 2.54 (4H, m), 2.89 (2H, t), 3.10 (4H, m), 3.84 (3H, s), 4.78 (2H, q), 5.25 (1H, s), 6.63 (1H, s), 8.65 (1H, s), 8.83 (1H, s), 10.52 (1H, s).

LRMS : m/z 508 $(M+1)^+$

PREPARATION 154

4-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-2,3-diethylpyrazole-5-carboxamide



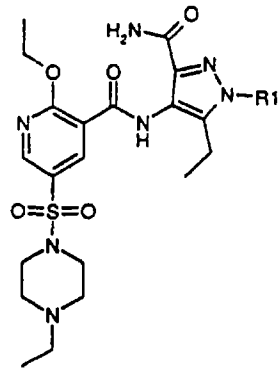
The title compound of Preparation 137 (3.3g, 16.8mmol) and triethylamine (7.5ml, 54.0mmol) were added to an ice-cooled solution of the title compound of Preparation 28 (6.51g, 18.0mmol) in dichloromethane (100ml), and the reaction was stirred at room temperature for 18 hours. The mixture was washed consecutively with brine (50ml), aqueous sodium bicarbonate solution (2x50ml), then dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 90:10) to afford the title compound as a solid.

δ ($CDCl_3$) : 1.04 (3H, t), 1.22 (3H, t), 1.50 (3H, t), 1.59 (3H, t), 2.40 (2H, q), 2.54 (4H, m), 2.91 (2H, q), 3.10 (4H, m), 4.16 (2H, q), 4.78 (2H, q), 5.30 (1H, s), 6.68 (1H, s), 8.65 (1H, s), 8.84 (1H, s), 10.55 (1H, s).

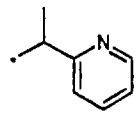
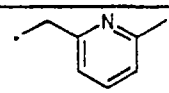
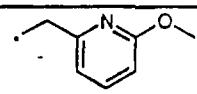
LRMS : m/z 508 $(M+1)^+$

PREPARATIONS 155 TO 157

The compounds of the following tabulated Preparations of the general formula:



were prepared, from the title compound of Preparation 28 and the appropriate amines, following similar procedures to that described in Preparation 154.

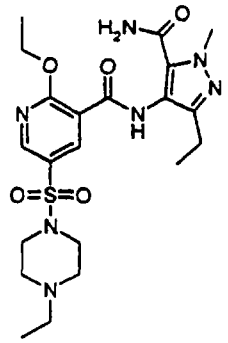
Prep.	R1	Data
155[1]		δ ($CDCl_3$) : 1.02 (6H, m), 1.59 (3H, t), 1.98 (3H, d), 2.40 (2H, q), 2.54 (4H, m), 2.86 (2H, q), 3.09 (4H, m), 4.79 (2H, q), 5.32 (1H, s), 5.67 (1H, q), 6.77 (1H, s), 6.94 (1H, d), 7.20 (1H, m), 7.63 (1H, m), 8.58 (1H, d), 8.65 (1H, s), 8.82 (1H, s), 10.55 (1H, s). LRMS : m/z 585 $(M+1)^+$
156[2]		δ ($CDCl_3$) : 1.04 (6H, m), 1.59 (3H, t), 2.40 (2H, q), 2.52 (4H, m), 2.59 (3H, s), 2.89 (2H, q), 3.09 (4H, m), 4.80 (2H, q), 5.30 (1H, s), 5.42 (2H, s), 6.62 (1H, d), 6.70 (1H, s), 7.08 (1H, d), 7.54 (1H, m), 8.64 (1H, s), 8.82 (1H, s), 10.61 (1H, s).
157[2]		δ($CDCl_3$) : 1.04 (3H, t), 1.23 (3H, t), 1.59 (3H, t), 2.41 (2H, q), 2.54 (4H, m), 2.70 (2H, q), 3.10 (4H, m), 3.86 (3H, s), 4.78 (2H, q), 5.52 (2H, s), 5.66 (1H, s), 6.70 (1H, d), 6.93 (1H, d), 7.59 (1H, m), 8.68 (1H, s), 8.83 (1H, s), 9.02 (1H, s), 9.90 (1H, s). LRMS : m/z 601 $(M+1)^+$

1 = the title compound was isolated by trituration with ether.

2 = ethyl acetate: methanol (94:6) was used as the chromatographic eluant.

PREPARATION 158

4-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-3-ethyl-1-methylpyrazole-5-carboxamide



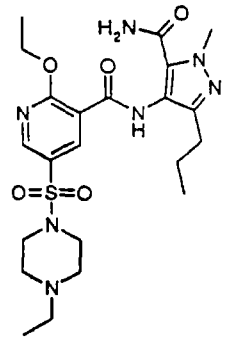
Obtained (51%) as a white solid from the title compounds of Preparations 23 and 143, using a similar procedure to that described in Preparation 151.

δ ($CDCl_3$) : 1.03 (3H, t), 1.25 (3H, t), 1.57 (3H, t), 2.42 (2H, q), 2.58 (6H, m), 3.10 (4H, m), 4.06 (3H, s), 4.76 (2H, q), 5.57 (1H, br s), 7.55 (1H, br s), 8.70 (1H, s), 8.83 (1H, s), 9.24 (1H, s).

LRMS : m/z 494 $(M+1)^+$

PREPARATION 159

4-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-1-methyl-3-n-propylpyrazole-5-carboxamide



A mixture of the title compounds of Preparation 24 (2.0g, 5.48mmol), the hydrochloride salt of 4-amino-1-methyl-3-n-propylpyrazole-5-carboxamide, EP-A-0463756; (1.08g, 4.94mmol), 1-hydroxybenzotriazole hydrate (920mg, 6.87mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.15g, 6.0mmol) and N-ethyldiisopropylamine (2.86ml, 16.5mmol) in tetrahydrofuran (20ml) was stirred at room temperature for 18 hours. The

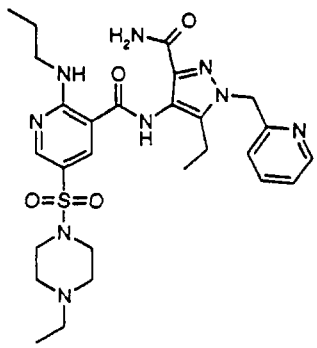
reaction mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate (100ml) and water (50ml). The layers were separated and the organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using dichloromethane: methanol (95:5) as eluant to afford the title compound (940mg, 38%), as a white solid.

δ ($CDCl_3$) : 0.95 (3H, t), 1.02 (3H, t), 1.52 (3H, t), 1.63 (2H, m), 2.40 (2H, q), 2.54 (6H, m), 3.09 (4H, m), 4.05 (3H, s), 4.75 (2H, q), 5.81 (1H, s), 7.58 (1H, s), 8.67 (1H, s), 8.80 (1H, s), 9.25 (1H, s).

LRMS : m/z 509 $(M+2)^+$

PREPARATION 160

3-Ethyl-4-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propylaminopyridin-3-ylcarboxamido]-2-(pyridin-2-yl)methylpyrazole-5-carboxamide



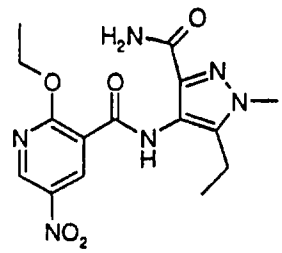
1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (250mg, 1.3mmol) was added to a solution of the title compounds of Preparations 40 (245mg, 1.0mmol) and 150 (456mg, 1.2mmol), N-ethyldiisopropylamine (194mg, 1.5mmol) and 1-hydroxybenzotriazole hydrate (203mg, 1.5mmol) in dichloromethane (10ml), and the reaction stirred at room temperature for 16 hours. The reaction was poured into ethyl acetate (30ml), washed with water (10ml) and brine (10ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol (100:0 to 94:6), and triturated with ether, to afford the title compound (242mg, 41%) as a white solid.

δ ($CDCl_3$) : 0.95 (3H, t), 1.01 (6H, m), 1.62 (2H, m), 2.39 (2H, q), 2.52 (4H, m), 2.86 (2H, q), 3.09 (4H, m), 3.46 (2H, q), 5.39 (1H, s), 5.43 (2H, s), 6.64 (1H, s), 6.87 (1H, d), 7.20 (1H, m), 7.63 (1H, m), 8.17 (1H, s), 8.53 (1H, s), 8.58 (1H, d), 8.64 (1H, m), 9.58 (1H, s).

LRMS : m/z 584 $(M+1)^+$

PREPARATION 161

4-(2-Ethoxy-5-nitropyridin-3-ylcarboxamido)-3-ethyl-2-methylpyrazole-5-carboxamide



Oxalyl chloride (2.6ml, 30.2mmol) was added dropwise to an ice-cooled solution of the title compound of Preparation 8 (1.6g, 7.55mmol) and N,N-dimethylformamide (1 drop) in dichloromethane (40ml), and the reaction stirred at room temperature for 3 hours. The mixture was concentrated under reduced pressure and azeotroped with dichloromethane several times.

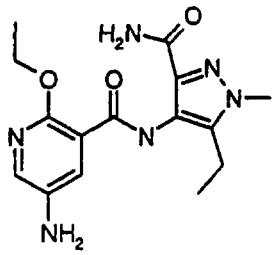
This intermediate acid chloride was added to an ice-cooled solution of the title compound of Preparation 138 (960mg, 5.74mmol) and triethylamine (2.6ml, 18.7mmol) in dichloromethane (40ml), and the reaction stirred at room temperature for 2 hours. The mixture was washed with water (20ml), brine (20ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 90:10) to afford the title compound (2.06g, 99%).

δ ($CDCl_3$) : 1.24 (3H, t), 1.61 (3H, t), 2.92 (2H, q), 3.88 (3H, s), 4.84 (2H, q), 5.27 (1H, s), 6.66 (1H, s), 9.17 (1H, s), 9.33 (1H, s), 10.57 (1H, s).

LRMS : m/z 363 $(M+1)^+$

PREPARATION 162

4-(5-Amino-2-ethoxypyridin-3-ylcarboxamido)-3-ethyl-2-methylpyrazole-5-carboxamide



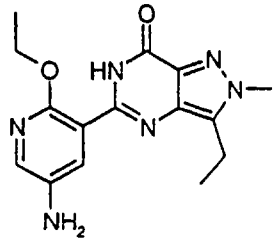
A mixture of the title compound of Preparation 161 (2.06g, 5.7mmol) and 10% palladium on charcoal (200mg) in ethanol (70ml) was hydrogenated at room temperature and 50psi, for 6 hours. The reaction mixture was filtered through Arbocel®, the filter pad washed with further ethanol, and the combined filtrates evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 95:5) to afford the title compound (760mg, 40%) as a solid.

δ ($CDCl_3$) : 1.23 (3H, t), 1.54 (3H, t), 2.87 (2H, q), 3.50 (2H, s), 3.87 (3H, s), 4.60 (2H, q), 5.24 (1H, s), 6.62 (1H, s), 7.78 (1H, s), 7.96 (1H, s), 10.54 (1H, s).

LRMS : m/z 333 $(M+1)^+$

PREPARATION 163

5-(5-Amino-2-ethoxypyridin-3-yl)-3-ethyl-2-methylpyrazole-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



A mixture of the title compound of Preparation 162 (760mg, 2.29mmol) and potassium bis(trimethylsilyl)amide (685mg, 3.43mmol) in ethanol (50ml) was heated at 100°C in a sealed vessel for 20 hours. The cooled mixture was

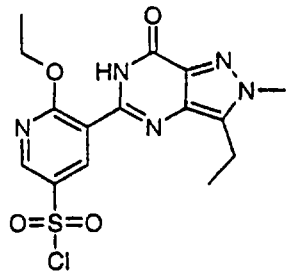
evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 95:5) to afford the title compound (550mg, 76%) as a solid.

δ ($CDCl_3$) : 1.41 (3H, t), 1.53 (3H, t), 3.03 (2H, q), 3.58 (2H, s), 4.09 (3H, s), 4.58 (2H, q), 4.78 (1H, s), 8.20 (1H, s), 11.17 (1H, s).

LRMS : m/z 315 $(M+1)^+$

PREPARATION 164

5-(5-Chlorosulphonyl-2-ethoxypyridin-3-yl)-3-ethyl-2-methylpyrazole-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

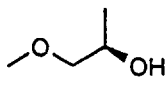


Obtained (72%) from the title compound of Preparation 163 following a similar procedure to that described in Preparation 63.

δ ($CDCl_3$) : 1.42 (3H, t), 1.60 (3H, t), 3.07 (2H, q), 4.14 (3H, s), 4.82 (2H, q), 8.92 (1H, s), 9.36 (1H, s), 10.58 (1H, s).

PREPARATION 165

(R)-1-Methoxy-2-propanol



Sodium methoxide (54g, 1.0mol) was added portionwise to ice-cooled methanol (1000ml), and the resulting solution stirred for 20 minutes in an ice-bath. (R)-Propylene oxide (58g, 1mol) was added dropwise over 30 minutes, and once addition was complete, the reaction was stirred at room temperature for 18

hours. The mixture was concentrated under reduced pressure, and acidified, with ice-cooling, using (1M) ethereal hydrochloric acid, and the resulting mixture stirred for an hour, then filtered. The filtrate was dried (K_2CO_3), filtered and evaporated under reduced pressure. The residue was heated to 70°C over dried calcium oxide for 30 minutes, then distilled at atmospheric pressure to afford the title compound (25.4g, 28%) as an oil.

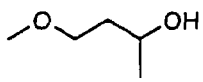
b.p. 118-120°C

δ ($CDCl_3$) : 1.16 (3H, d), 2.28 (1H, d), 3.20 (1H, m), 3.36 (1H, m), 3.40 (3H, s), 3.97 (1H, m).

$[\alpha]_D$ -20.83° (c=1.02, dichloromethane)

PREPARATION 166

4-Methoxy-2-butanol

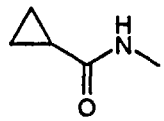


Lithium aluminium hydride (220ml, 1.0M solution in tetrahydrofuran, 220mmol) was added dropwise over 15 minutes, to an ice-cooled solution of 4-methoxybut-3-en-2-one (20.0g, 200mmol) in tetrahydrofuran (200ml), and the reaction stirred at room temperature for 16 hours. The solution was re-cooled in an ice-bath, water (8ml) was added dropwise, followed by 15% aqueous sodium hydroxide solution (8ml), and after a further 10 minutes, additional water (24ml). The mixture was stirred for 20 minutes, filtered, and the filtrate concentrated under reduced pressure to a volume of 100ml. 10% Palladium on charcoal (500mg) was added and the mixture hydrogenated at 60 psi for 16 hours. The reaction was filtered through Arbocel®, and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane: ether (99:1 to 50:50) to afford the title compound (4.0g, 19%).

δ ($CDCl_3$) : 1.20 (3H, d), 1.67-1.78 (2H, m), 2.80 (1H, s), 3.38 (3H, s), 3.55-3.65 (2H, m), 4.00 (1H, m).

PREPARATION 167

N-Methylcyclopropylcarboxamide



Cyclopropane carboxylic acid (15.83ml, 200mmol) was added dropwise to a warm (40°C) solution of thionyl chloride (16.71ml, 213mmol) in toluene (80ml), and once addition was complete, the reaction was stirred at 80°C for 2 hours. The mixture was cooled in an ice-bath, a solution of methylamine in tetrahydrofuran (300ml, 2M, 600mmol) was added, the mixture allowed to warm to room temperature and concentrated under reduced pressure. The residue was suspended in dichloromethane (200ml), washed with saturated aqueous sodium bicarbonate solution (200ml), brine (200ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residual white solid was recrystallised from hexane/ether, to afford the title compound (11.3g, 57%) as a white crystalline solid.

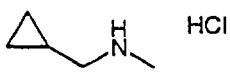
Found : C, 58.73; H, 9.30; N, 13.70. $C_5H_9NO;0.2H_2O$ requires C, 58.46; H, 9.22; N, 13.63%

δ ($CDCl_3$) : 0.70 (2H, m), 0.95 (2H, m), 1.32 (1H, m), 2.81 (3H, d), 5.73 (1H, s).

LRMS : m/z 199 $(M+1)^+$

PREPARATION 168

N-Cyclopropylmethyl-N-methylamine hydrochloride



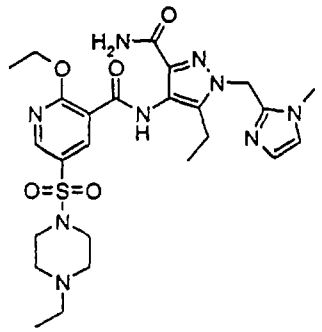
A solution of the title compound of Preparation 167 (7.90g, 79.7mmol) in ether (75ml) was added dropwise over 5 minutes to a suspension of lithium

aluminium hydride (3.03g, 96.0mmol) in ether (100ml), and the reaction stirred under reflux for 4 hours. The cooled mixture was quenched by the consecutive addition of water (3ml), 10% aqueous sodium hydroxide solution (9ml) and water (3ml). The resulting suspension was stirred for 5 minutes, filtered and the solids washed well with ether (100ml). The combined filtrate was dried ($MgSO_4$), cooled in an ice-bath, and saturated with hydrochloric acid. This solution was evaporated under reduced pressure to afford the title compound (8.7g, 90%) as a gum.

δ ($CDCl_3$) : 0.45 (2H, m), 0.72 (2H, m), 1.24 (1H, m), 2.70 (3H, t), 2.88 (3H, t), 2.88 (2H, m), 9.48 (2H, br s).

Preparation 169

4-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-ylcarboxamido]-3-ethyl-2-(1-methylimidazol-2-yl)methylpyrazole-5-carboxamide



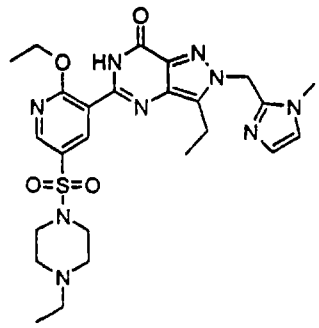
1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.2g, 6.25 mmol) was added to a solution of the preparations of 23 (1.6g, 4.66mmol) and 89 (1.2g, 4.84mmol), hydroxybenzotriazole hydrate (960mg, 6.2mmol) and N-ethyldiisopropylamine (2.5ml, 14.5mmol) in tetrahydrofuran (15ml), and N,N-dimethylformamide (3ml), and the reaction stirred at room temperature for 18 hours. The mixture was diluted with water (100ml), and extracted with dichloromethane (3x150ml). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using dichloromethane:methanol (95:5) as eluant to afford the title compound (1.42g, 2.55mmol).

δ ($CDCl_3$) : 0.98-1.16 (6H, m), 1.52-1.70 (6H, m), 2.40 (2H, q), 2.55 (4H, m), 2.99-3.16 (6H, m), 3.72 (3H, s), 4.78 (2H, q), 5.30 (1H, br s), 5.44 (2H, s), 6.60 (1H, br s), 6.86 (1H, s), 7.00 (1H, s), 8.65 (1H, s), 8.82 (1H, s), 10.48 (1H, s).

LRMS : m/z 574 $(M+18)^+$

Preparation 170

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(1-methylimidazol-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



Obtained as a cream foam (62%) from the title compound of Preparation 169 following a similar procedure to that described in Example 78.

δ ($CDCl_3$) : 1.00 (3H, t), 1.30 (3H, t), 1.57 (3H, t), 2.40 (2H, q), 2.54 (4H, m), 3.06-3.20 (6H, m), 3.78 (3H, s), 4.75 (2H, q), 5.64 (2H, s), 6.84 (1H, s), 6.99 (1H,s), 8.61 (1H, s), 8.99 (1H, s), 10.66 (1H, s).

LRMS : m/z 556 $(M+1)^+$

Biological Activity

The following Table illustrates the in vitro activities for a range of the compounds of the invention as inhibitors of cGMP PDE5.

TABLE

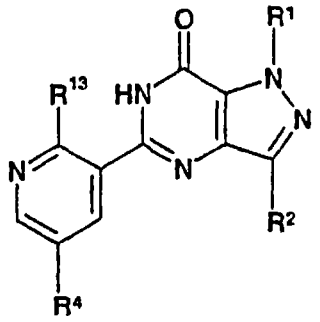
EXAMPLE	IC_{50} (nm)
10	10.1
11	10.0
18	8.9
43b	3.6
46	8.1
48	6.9
98	7.0
99	5.7
127	7.3
153	7.2

Safety Profile

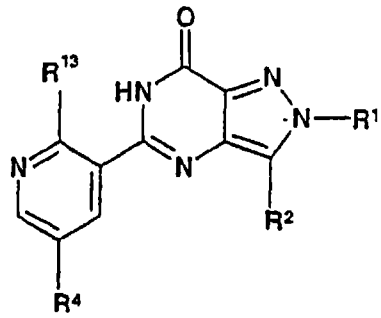
Several compounds of the invention have been tested at doses of up to 3mg/kg i.v. in mouse and at 0.5mg/kg p.o. in dog, with no untoward effects being observed.

CLAIMS

1. A compound of the formula (IA) or (IB):



(IA)



(IB)

or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of either entity, wherein R^1 is C_1 to C_3 alkyl optionally substituted with phenyl, Het or a N-linked heterocyclic group selected from piperidinyl and morpholinyl; wherein said phenyl group is optionally substituted by one or more substitutents selected from C_1 to C_4 alkoxy; halo; CN; CF_3; OCF_3 or C_1 to C_4 alkyl wherein said C_1 to C_4 alkyl group is optionally substituted by C_1 to C_4 haloalkyl or haloalkoxy either of which is substituted by one or more halo atoms;

R^2 is C_1 to C_6 alkyl;

R^{13} is OR^3 or NR^5R^6;

R^3 is C_1 to C_6 alkyl optionally substituted with one or two substituents selected from C_3 to C_5 cycloalkyl, OH, C_1 to C_4 alkoxy, benzyloxy, NR^5R^6, phenyl, furanyl and pyridinyl; C_3 to C_6 cycloalkyl; 1-(C_1 to C_4 alkyl) piperidinyl; tetrahydrofuranyl or tetrahydropyranyl; and wherein said C_1 to C_6 alkyl or said C_1 to C_4 alkoxy groups are optionally terminated by haloalkyl;

R^4 is $SO_2NR^7R^8$;

R^5 and R^6 are each independently selected from H and C_1 to C_4 alkyl optionally substituted with C_3 to C_5 cycloalkyl or C_1 to C_4 alkoxy, or, together with the nitrogen atom to which they are attached, form an azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl group;

R^7 and R^8, together with the nitrogen atom to which they are attached,

form a 4-R^{10}-piperazinyl group optionally substituted with one or two C_1 to C_4 alkyl groups and optionally in the form of its 4-N-oxide;
R^{10} is H; C_1 to C_4 alkyl optionally substituted with one or two substituents selected from OH, NR^5R^6, $CONR^5R^6$, phenyl optionally substituted with C_1 to C_4 alkoxy, benzodioxolyl and benzodioxanyl; C_3 to C_6 alkenyl; pyridinyl or pyrimidinyl; and
Het is a C-linked 6-membered heterocyclic group containing one or two nitrogen atoms, optionally in the form of its mono-N-oxide, or a C-linked 5-membered heterocyclic group containing two or three nitrogen atoms, wherein either of said heterocyclic groups is optionally substituted with C_1 to C_4 alkyl, C_1 to C_4 alkoxy or NHR^{15} wherein R^{15} is H, C_1 to C_4 alkyl or C_1 to C_4 alkanoyl and halo is Br, Cl, F or I.

2. A compound according to claim 1 wherein R^1 is C_1 to C_2 alkyl optionally substituted with Het; 2-(morpholin-4-yl)ethyl or benzyl; R^2 is C_2 to C_4 alkyl; R^{13} is OR^3 or NR^5R^6; R^3 is C_1 to C_4 alkyl optionally substituted with one or two substituents selected from cyclopropyl, cyclobutyl, OH, methoxy, ethoxy, benzyloxy, NR^5R^6, phenyl, furan-3-yl, pyridin-2-yl and pyridin-3-yl; cyclobutyl; 1-methylpiperidin-4-yl; tetrahydrofuran-3-yl or tetrahydropyran-4-yl; R^5 and R^6 are each independently selected from H and C_1 to C_2 alkyl optionally substituted with cyclopropyl or methoxy, or, together with the nitrogen atom to which they are attached, form a azetidinyl, pyrrolidinyl or morpholinyl group; R^7 and R^8, together with the nitrogen atom to which they are attached, form a 4-R^{10}-piperazinyl group optionally substituted with one or two methyl groups and optionally in the form of its 4-N-oxide; R^{10} is H, C_1 to C_3 alkyl optionally substituted with one or two substituents selected from OH, NR^5R^6, $CONR^5R^6$, phenyl optionally substituted with methoxy, benzodioxol-5-yl and benzodioxan-2-yl; allyl; pyridin-2-yl; pyridin-4-yl or pyrimidin-2-yl; and Het is selected from pyridin-2-yl; 1-oxidopyridin-2-yl; 6-methylpyridin-2-yl; 6-methoxypyridin-2-yl; pyridazin-3-yl; pyrimidin-2-yl and 1-methylimidazol-2-yl.

3. A compound according to claim 2 wherein R^1 is C_1 to C_2 alkyl optionally substituted with Het; 2-(morpholin-4-yl)ethyl or benzyl; R^2 is C_2 to C_4 alkyl; R^{13} is OR^3; R^3 is C_1 to C_4 alkyl optionally monosubstituted with cyclopropyl, cyclobutyl, OH, methoxy, ethoxy, phenyl, furan-3-yl or pyridin-2-yl; cyclobutyl; tetrahydrofuran-3-yl or tetrahydropyran-4-yl; R^7 and R^8, together with the nitrogen atom to which they are attached, form a 4-R^{10}-piperazinyl group optionally in the form of its 4-N-oxide; R^{10} is C_1 to C_3 alkyl optionally monosubstituted with OH; and Het is selected from pyridin-2-yl; 1-oxidopyridin-2-yl; 6-methylpyridin-2-yl; 6-methoxypyridin-2-yl; pyridazin-3-yl; pyrimidin-2-yl and 1-methylimidazol-2-yl.

4. A compound according to any of claims 1 to 3 selected from:
3-ethyl-5-[2-(2-methoxyethoxy)-5-(4-methylpiperazin-1-ylsulphonyl)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
3-ethyl-5-[5-(4-ethyl-4-oxidopiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-(2-methoxyethoxy)-5-(4-methylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
(+)-3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1(R)-methylethoxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1(R)-methylethoxy)pyridin-3-yl]-2-(6-methylpyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(6-methoxypyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-i-butoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-2,3-diethyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and
5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[1-(pyridin-2-yl)ethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

5. A pharmaceutical composition comprising a compound of formula (IA) or (IB) as defined in Claim 1, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, together with a pharmaceutically acceptable diluent or carrier.

6. A veterinary formulation comprising a compound of formula (IA) or (IB) as defined in Claim 1, or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, together with a veterinarily acceptable diluent or carrier.

7. A compound of formula (IA) or (IB) as defined in Claim 1, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, or a pharmaceutical composition containing any of the foregoing, for use as a human medicament.

8. A compound of formula (IA) or (IB) as defined in Claim 1, or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, or a veterinary formulation containing any of the foregoing, for use as an animal medicament.

9. The use of a compound of formula (IA) or (IB) as defined in Claim 1, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, for the manufacture of a human medicament for the curative or prophylactic treatment of a medical condition for which a cGMP PDE5 inhibitor is indicated.

10. The use of a compound of formula (IA) or (IB) as defined in Claim 1, or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, for the manufacture of an animal medicament for the curative or prophylactic treatment of a medical condition for which a cGMP PDE5 inhibitor is indicated.

11. The use of a compound of formula (IA) or (IB) as defined in Claim 1, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate containing either entity, for the manufacture of a human medicament for the curative or prophylactic treatment of male erectile dysfunction (MED), female sexual dysfunction (FSD), premature labour, dysmenorrhoea, benign prostatic hyperplasia (BPH), bladder outlet obstruction, incontinence, stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility.

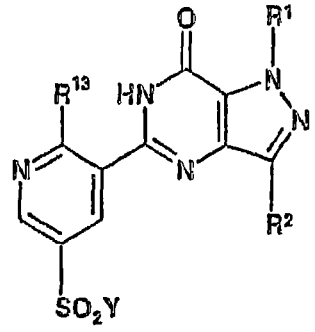
12. The use of a compound of formula (IA) or (IB) as defined in Claim 1, or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate containing either entity, for the manufacture of an animal medicament for the curative or prophylactic treatment of male erectile dysfunction (MED), female sexual dysfunction (FSD), premature labour, dysmenorrhoea, benign prostatic hyperplasia (BPH), bladder outlet obstruction,

incontinence, stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility;

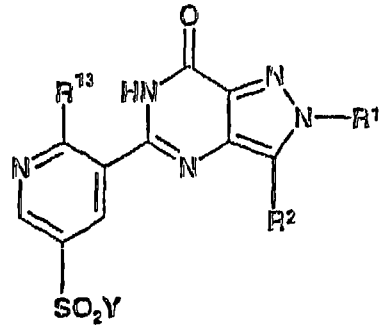
13. The use of a therapeutically effective amount of a compound of formula (IA) or (IB), or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of either entity, or a pharmaceutical composition or veterinary formulation containing any of the foregoing for the preparation of a medicament for the treatment or prevention of a medical condition for which a cGMP PDE5 inhibitor is indicated in a mammal (including a human being).

14. The use of a therapeutically effective amount of a compound of formula (IA) or (IB), or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of either entity, or a pharmaceutical composition or veterinary formulation containing any of the foregoing for the preparation of a medicament for the treatment or prevention of male erectile dysfunction (MED), female sexual dysfunction (FSD), premature labour, dysmenorrhoea, benign prostatic hyperplasia (BPH), bladder outlet obstruction, incontinence, stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility in a mammal (including a human being).

15. A compound of formula (IIA) or (IIB):



(IIA)

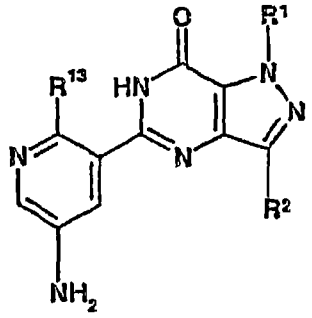


(IIB)

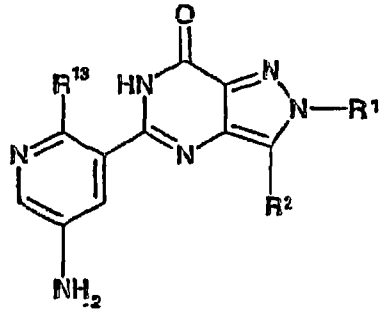
wherein Y is halo, and R^1, R^2 and R^{13} are as previously defined in claim 1.

16. A compound according to claim 15 wherein Y is chloro.

17. A compound of formula (IVA) or (IVB):



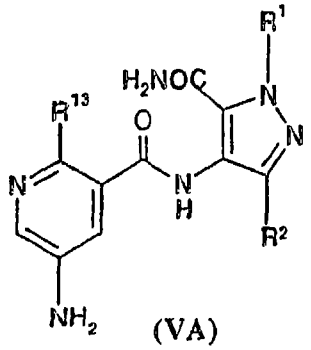
(IVA)



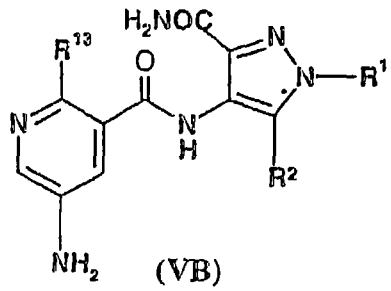
(IVB)

wherein R^1, R^2 and R^{13} are as previously defined in claim 1.

18. A compound of formula (VA) or (VB):



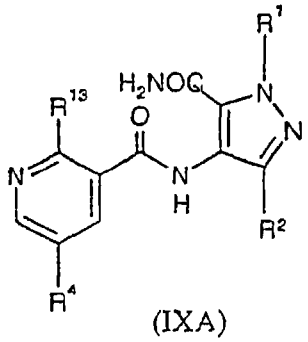
(VA)



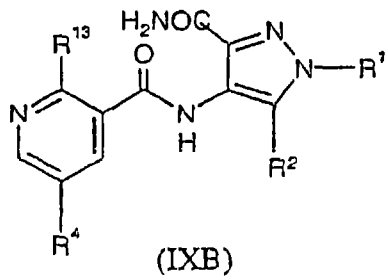
(VB)

wherein R^1, R^2 and R^{13} are as previously defined in claim 1.

19. A compound of the formula (IXA) or (IXB):



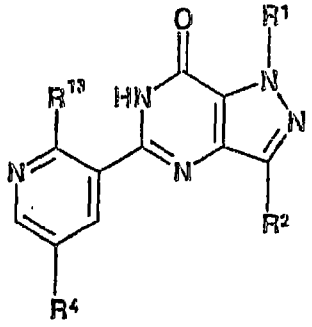
(IXA)



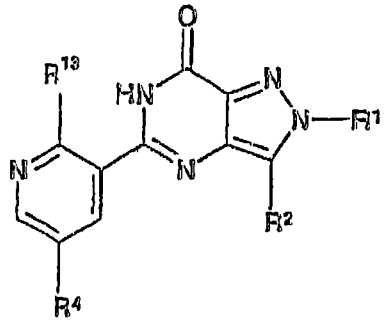
(IXB)

wherein R^1, R^2, R^4 and R^{13} are as previously defined in claim 1.

20. A process for the preparation of a compound of formula (IA) or (IB):

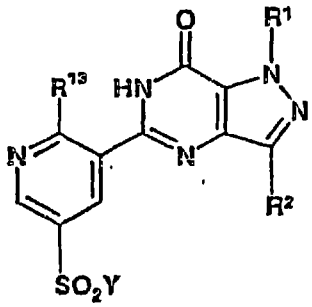


(IA)

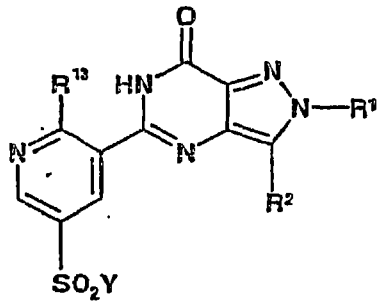


(IB)

wherein R^1, R^2, R^4 and R^{13} are as defined in claim 1, which process comprises reacting a compound of formula (IIA) or (IIB), respectively:



(IIA)



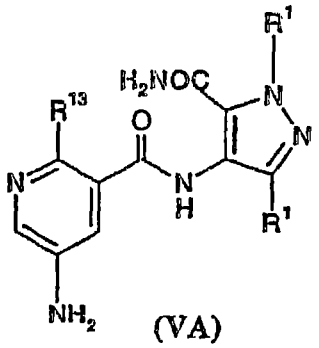
(IIB)

wherein Y is halo, and R^1, R^2 and R^{13} are as previously defined in this claim, with a compound of formula (III):

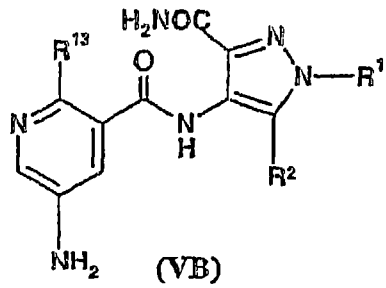
$$R^7R^8NH \qquad (III)$$

wherein R^7 and R^8 are as previously defined in this claim, optionally followed by formation of a pharmaceutically or veterinarily acceptable salt of the required product or a pharmaceutically or veterinarily acceptable solvate of either entity.

21. A process for the preparation of a compound of formula (IA) or (IB) as defined in claim 20, or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of either entity, which comprises cyclisation of a compound of formula (VA) or (VB) respectively:

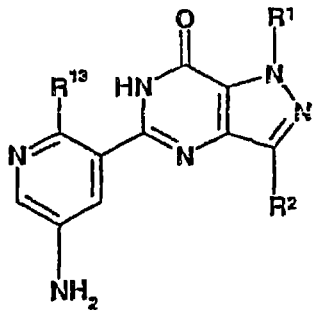


(VA)

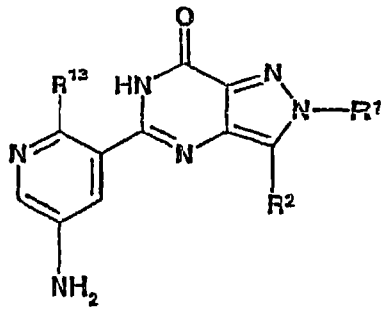


(VB)

wherein R^1, R^2 and R^{13} are as previously defined for formulae (~~I~~A) and (IB) in claim 20 to form a compound of formula (IVA) or (IVB):



(IVA)

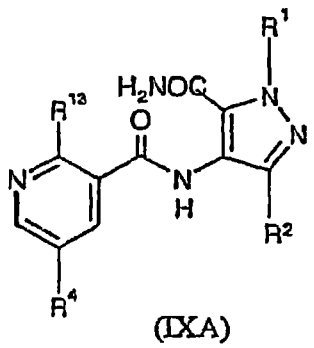


(IVB)

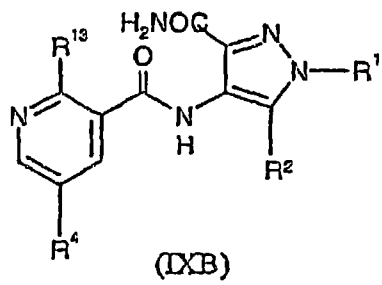
which can be converted to a compound of formula (IIA) or (IIB), by reaction with a compound of formula (III) R^7R^8NH wherein R^7 and R^8 are as defined in claim 20, said compound of formula (IIA) or (IIB) may in turn be converted by the process according to claim 20 to

form a compound of formula (IA) or (IB) which is optionally followed by formation of a pharmaceutically or veterinarily acceptable salt of the required product or a pharmaceutically or veterinarily acceptable solvate of either entity.

22. A process for the preparation of a compound of formula (IA) or (IB) as defined in claim 20, or a pharmaceutically or veterinarily acceptable salt of the required product or a pharmaceutically or veterinarily acceptable solvate of either entity which comprises cyclisation of a compounds of formula (IXA) or (IXB) respectively:



(IXA)



(IXB)

wherein R^1, R^2, R^4 and R^{13} are as defined in claim 20.