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(54) Title: INDOLYLMETHYL-MORPHOLINE DERIVATIVES AS KINASE INHIBITORS

(57) Abstract: A series of morpholine derivatives, substituted in the 4-position by a substituted carbonyl or sulfonyl moiety, and in the 3-position by an optionally substituted indol-3-ylmethyl group, being selective inhibitors of PI3 kinase enzymes, are accordingly of benefit in medicine, for example in the treatment of inflammatory, autoimmune, cardiovascular, neurodegenerative, metabolic, oncological, nociceptive or ophthalmic conditions.



INDOLYLMETHYL-MORPHOLINE DERIVATIVES AS KINASE INHIBITORS

The present invention relates to a class of substituted morpholine derivatives, and to their use in therapy. More particularly, the invention provides a family of morpholine derivatives, substituted in the 4-position by a substituted carbonyl or sulfonyl moiety, and in the 3-position by an optionally substituted indol-3-ylmethyl group. These compounds are selective inhibitors of phosphoinositide 3-kinase (PI3K) enzymes, and are accordingly of benefit as pharmaceutical agents, especially in the treatment of adverse inflammatory, autoimmune, cardiovascular, neurodegenerative, metabolic, oncological, nociceptive and ophthalmic conditions.

The PI3K pathway is implicated in a variety of physiological and pathological functions that are believed to be operative in a range of human diseases. Thus, PI3Ks provide a critical signal for cell proliferation, cell survival, membrane trafficking, glucose transport, neurite outgrowth, membrane ruffling, superoxide production, actin reorganization and chemotaxis (cf. S. Ward *et al.*, *Chemistry & Biology*, 2003, **10**, 207-213; and S.G. Ward & P. Finan, *Current Opinion in Pharmacology*, 2003, **3**, 426-434); and are known to be involved in the pathology of cancer, and metabolic, inflammatory and cardiovascular diseases (cf. M.P. Wymann *et al.*, *Trends in Pharmacol. Sci.*, 2003, **24**, 366-376). Aberrant upregulation of the PI3K pathway is implicated in a wide variety of human cancers (cf. S. Brader & S.A. Eccles, *Tumori*, 2004, **90**, 2-8).

The compounds in accordance with the present invention, being potent and selective PI3K inhibitors, are therefore beneficial in the treatment and/or prevention of various human ailments. These include autoimmune and inflammatory disorders such as rheumatoid arthritis, multiple sclerosis, asthma, inflammatory bowel disease, psoriasis and transplant rejection; cardiovascular disorders including thrombosis, cardiac hypertrophy, hypertension, and irregular contractility of the heart (e.g. during heart failure); neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke, amyotrophic lateral sclerosis, spinal cord injury, head trauma and seizures; metabolic disorders such as obesity and type 2 diabetes; oncological conditions including leukaemia, glioblastoma, lymphoma, melanoma, and human cancers of the liver, bone, skin, brain, pancreas, lung, breast, stomach, colon, rectum, prostate,

ovary and cervix; pain and nociceptive disorders; and ophthalmic disorders including age-related macular degeneration (ARMD).

In addition, the compounds in accordance with the present invention may be beneficial as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents. Thus, the compounds of this invention may be useful as radioligands in assays for detecting compounds capable of binding to human PI3K enzymes.

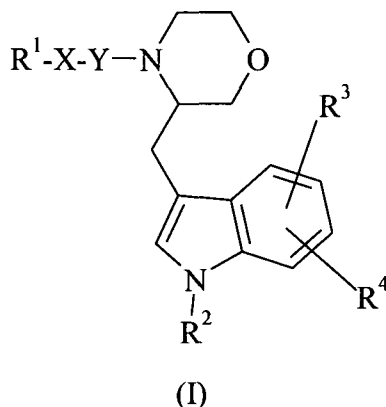
Various classes of substituted morpholine derivatives are described in WO 2006/114606, WO 2007/141504, WO 2008/001076, WO 2008/047109, WO 2009/001089, WO 2009/071888, WO 2009/071890, WO 2009/071895, and copending international patent application no. PCT/GB2009/000818, published on 8 October 2009 as WO 2009/122148. The compounds described therein are stated to be selective inhibitors of PI3 kinase enzymes which are accordingly of benefit in medicine, for example in the treatment of inflammatory, autoimmune, cardiovascular, neurodegenerative, metabolic, oncological, nociceptive and ophthalmic conditions. However, none of those publications describes compounds wherein the substituent at the 4-position of the morpholine ring is linked through a carbonyl or sulfonyl functionality.

WO 03/002561 describes a class of cyclic amine derivatives, and includes within its scope substituted morpholine derivatives. The compounds described therein are alleged to be antagonists of human orexin receptors which are of potential use in the treatment of a wide variety of medical conditions, in particular obesity. There is, however, no specific disclosure in that publication of a morpholine derivative substituted by an indol-3-yl-methyl moiety at the 3-position of the morpholine ring.

The compounds in accordance with the present invention are potent and selective PI3K inhibitors having a binding affinity (IC_{50}) for the human PI3K α and/or PI3K β and/or PI3K γ and/or PI3K δ isoform of 50 μ M or less, generally of 20 μ M or less, usually of 5 μ M or less, typically of 1 μ M or less, suitably of 500 nM or less, ideally of 100 nM or less, and preferably of 20 nM or less (the skilled person will appreciate that a *lower* IC_{50} figure denotes a *more active* compound). The compounds of the invention may possess at least a 10-fold selective affinity, typically at least a 20-fold selective affinity, suitably at least a 50-fold selective affinity, and ideally at least a 100-fold selective affinity, for the human PI3K α and/or PI3K β and/or PI3K γ and/or PI3K δ isoform relative to other human kinases.

The compounds of the invention possess notable advantages in terms of their high potency and selectivity, and valuable pharmacokinetic properties (including low clearance and high bioavailability).

The present invention provides a compound of formula (I) or an *N*-oxide thereof,
 5 or a pharmaceutically acceptable salt or solvate thereof:



wherein

10 X represents oxygen, N-R⁵ or a covalent bond;

Y represents C=O or S(O)₂;

R¹ represents C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more
 15 substituents;

R² represents hydrogen; or optionally substituted C₁₋₆ alkyl;

R³ and R⁴ independently represent hydrogen, halogen, cyano, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, -OR^a, -SR^a, -SOR^a, -SO₂R^a, -NR^bR^c, -CH₂NR^bR^c, -NR^cCOR^d, -CH₂NR^cCOR^d, -NR^cCO₂R^d, -NHCONR^bR^c, -NR^cSO₂R^e, -N(SO₂R^e)₂,
 20 -NHSO₂NR^bR^c, -COR^d, -CO₂R^d, -CONR^bR^c, -CON(OR^a)R^b or -SO₂NR^bR^c; or C₁₋₆ alkyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents;

R⁵ represents hydrogen or C₁₋₆ alkyl;

R^a represents C₁₋₆ alkyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl,
 25 any of which groups may be optionally substituted by one or more substituents;

R^b and R^c independently represent hydrogen or trifluoromethyl; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents; or

5 R^b and R^c, when taken together with the nitrogen atom to which they are both attached, represent azetidin-1-yl, pyrrolidin-1-yl, oxazolidin-3-yl, isoxazolidin-2-yl, thiazolidin-3-yl, isothiazolidin-2-yl, piperidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperazin-1-yl, homopiperidin-1-yl, homomorpholin-4-yl or homopiperazin-1-yl, any of which groups may be optionally substituted by one or more substituents;

10 R^d represents hydrogen; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, C₃₋₇ heterocycloalkyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents; and

R^e represents C₁₋₆ alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

15 The present invention also provides a compound of formula (I) or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, wherein

Y represents C=O;

R³ and R⁴ independently represent hydrogen, halogen, trifluoromethyl, -OR^a, -SR^a, -SOR^a, -SO₂R^a, -NR^bR^c, -NR^cCOR^d, -NR^cCO₂R^d, -NR^cSO₂R^e, -COR^d, -CO₂R^d,
20 -CONR^bR^c or -SO₂NR^bR^c; or C₁₋₆ alkyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl or heteroaryl-(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents;

R^b represents hydrogen or trifluoromethyl; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl-(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally
25 substituted by one or more substituents; and

R^c represents hydrogen, C₁₋₆ alkyl or C₃₋₇ cycloalkyl; or

R^b and R^c, when taken together with the nitrogen atom to which they are both attached, represent azetidin-1-yl, pyrrolidin-1-yl, isoxazolidin-2-yl, piperidin-1-yl,
30 morpholin-4-yl, thiomorpholin-4-yl, piperazin-1-yl, homopiperidin-1-yl, homomorpholin-4-yl or homopiperazin-1-yl, any of which groups may be optionally substituted by one or more substituents;

R^d represents hydrogen; or C_{1-6} alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents; and

X , R^1 , R^2 , R^a and R^e are as defined above.

Where any of the groups in the compounds of formula (I) above is stated to be optionally substituted, this group may be unsubstituted, or substituted by one or more substituents. Typically, such groups will be unsubstituted, or substituted by one or two substituents. Suitably, such groups will be unsubstituted or monosubstituted.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound of the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, e.g. carboxy, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The present invention includes within its scope solvates of the compounds of formula (I) above. Such solvates may be formed with common organic solvents, e.g. hydrocarbon solvents such as benzene or toluene; chlorinated solvents such as chloroform or dichloromethane; alcoholic solvents such as methanol, ethanol or isopropanol; ethereal solvents such as diethyl ether or tetrahydrofuran; or ester solvents such as ethyl acetate. Alternatively, the solvates of the compounds of formula (I) may be formed with water, in which case they will be hydrates.

Suitable alkyl groups which may be present on the compounds of the invention include straight-chained and branched C_{1-6} alkyl groups, for example C_{1-4} alkyl groups. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl, butyl and pentyl groups. Particular alkyl groups include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, 2,2-dimethylpropyl and 3-methylbutyl. Derived expressions such as " C_{1-6} alkoxy", " C_{1-6} alkylthio", " C_{1-6} alkylsulphonyl" and " C_{1-6} alkylamino" are to be construed accordingly.

Specific C₃₋₇ cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Suitable aryl groups include phenyl and naphthyl, preferably phenyl.

Suitable aryl(C₁₋₆)alkyl groups include benzyl, phenylethyl, phenylpropyl and
5 naphthylmethyl.

Suitable heterocycloalkyl groups, which may comprise benzo-fused analogues thereof, include oxetanyl, azetidiny, tetrahydrofuranyl, dihydrobenzofuranyl, pyrrolidiny, indoliny, oxazolidiny, isoxazolidiny, thiazolidiny, isothiazolidiny, imidazolidiny, tetrahydropyranyl, chromanyl, piperidiny, 1,2,3,4-tetrahydroquinoliny, 1,2,3,4-
10 tetrahydroisoquinoliny, piperaziny, 1,2,3,4-tetrahydroquinoxaliny, homopiperaziny, morpholiny, benzoxaziny and thiomorpholiny.

Suitable heteroaryl groups include furyl, benzofuryl, dibenzofuryl, thienyl, benzothieryl, thieno[2,3-*b*]pyridiny, pyrroly, indolyl, isoindolyl, pyrrolo[2,3-*b*]pyridiny, pyrrolo[3,2-*c*]pyridiny, pyrazolyl, pyrazolo[1,5-*a*]pyridiny, indazolyl, oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, imidazo[1,2-*a*]pyridiny, imidazo[4,5-*b*]pyridiny, imidazo[1,2-*a*]pyrimidiny, imidazo[1,2-*a*]pyraziny, oxadiazolyl, thiadiazolyl, triazolyl, benzotriazolyl, tetrazolyl, pyridiny, quinoliny, isoquinoliny, 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxaziny, pyridaziny, cinnoliny, pyrimidiny, pyraziny, quinoxaliny and
15 20 chromenyl groups.

The term "halogen" as used herein is intended to include fluorine, chlorine, bromine and iodine atoms, especially fluoro or chloro.

Where the compounds of formula (I) have one or more asymmetric centres, they may accordingly exist as enantiomers. Where the compounds of the invention possess two
25 or more asymmetric centres, they may additionally exist as diastereomers. The invention is to be understood to extend to all such enantiomers and diastereomers, and to mixtures thereof in any proportion, including racemates. Formula (I) and the formulae depicted hereinafter are intended to represent all individual stereoisomers and all possible mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (I) may
30 exist as tautomers, for example keto (CH₂C=O)↔enol (CH=CHOH) tautomers or amide (NHC=O)↔hydroxyimine (N=COH) tautomers. Formula (I) and the formulae depicted hereinafter are intended to represent all individual tautomers and all possible mixtures thereof, unless stated or shown otherwise.

It is to be understood that each individual atom present in formula (I), or in the formulae depicted hereinafter, may in fact be present in the form of any of its naturally occurring isotopes, with the most abundant isotope(s) being preferred. Thus, by way of example, each individual hydrogen atom present in formula (I), or in the formulae depicted hereinafter, may be present as a ^1H , ^2H (deuterium) or ^3H (tritium) atom, preferably ^1H . Similarly, by way of example, each individual carbon atom present in formula (I), or in the formulae depicted hereinafter, may be present as a ^{12}C , ^{13}C or ^{14}C atom, preferably ^{12}C .

In one aspect, the present invention provides a compound of formula (I) as depicted above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, wherein

Y represents $\text{C}=\text{O}$;

X represents oxygen or $\text{N}-\text{R}^5$; and

R^1 , R^2 , R^3 , R^4 and R^5 are as defined above.

In another aspect, the present invention provides a compound of formula (I) as depicted above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, wherein

Y represents $\text{C}=\text{O}$;

X represents a covalent bond;

R^1 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; and

R^2 , R^3 and R^4 are as defined above.

In a further aspect, the present invention provides a compound of formula (I) as depicted above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, wherein

Y represents $\text{S}(\text{O})_2$; and

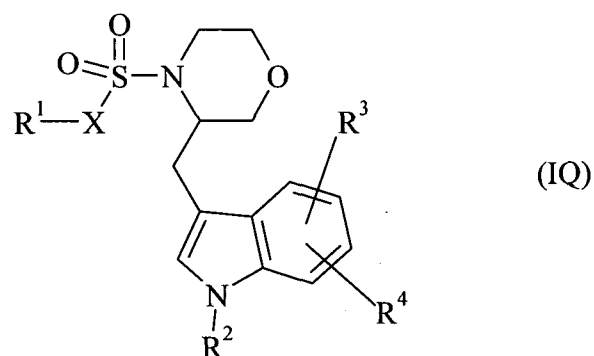
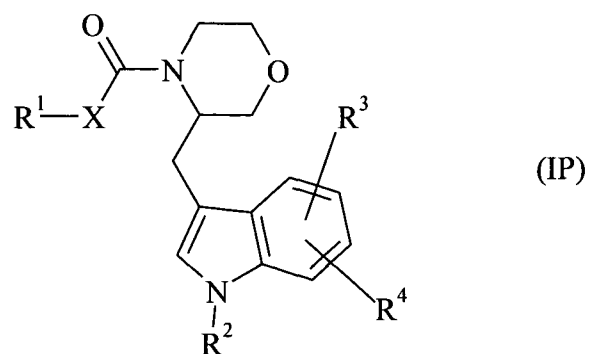
X, R^1 , R^2 , R^3 and R^4 are as defined above.

Typically, X represents oxygen or a covalent bond.

In one embodiment, X represents oxygen. In another embodiment, X represents $\text{N}-\text{R}^5$, in which R^5 is as defined above. In a further embodiment, X represents a covalent bond.

In a particular embodiment, Y represents $\text{C}=\text{O}$. In another embodiment, Y represents $\text{S}(\text{O})_2$.

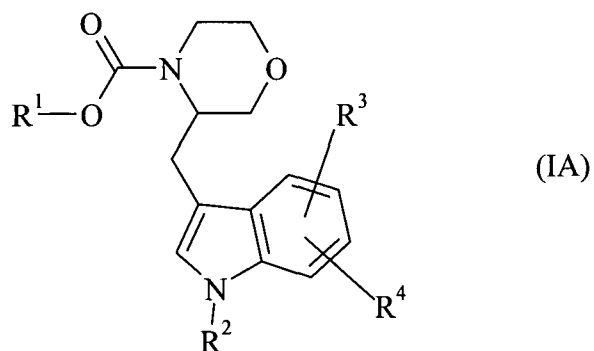
Specific sub-classes of compounds in accordance with the present invention are represented by the compounds of formula (IP) and (IQ):



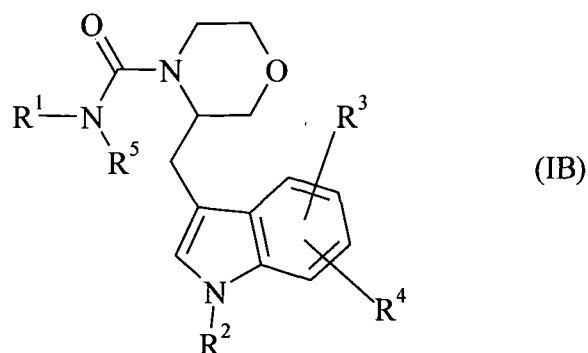
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wherein X, R¹, R², R³ and R⁴ are as defined above.

Illustrative sub-classes of the compounds of formula (IP) above are represented by the compounds of formula (IA) and (IB):

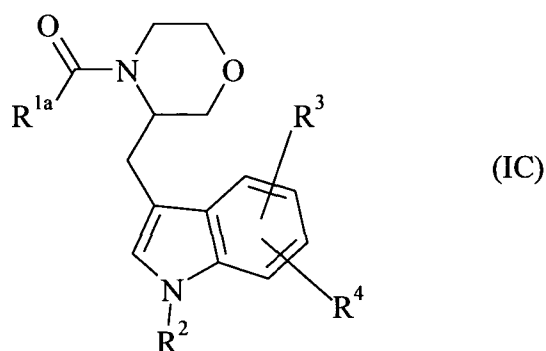


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wherein R^1 , R^2 , R^3 , R^4 and R^5 are as defined above.

Another sub-class of the compounds of formula (IP) above is represented by the
 5 compounds of formula (IC):



wherein

10 R^{1a} represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; and

R^2 , R^3 and R^4 are as defined above.

In one aspect of the present invention, R^1 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7}
 15 cycloalkyl(C_{1-6})alkyl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

In one embodiment of that aspect, R^1 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7}
 cycloalkylmethyl, arylmethyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkylmethyl, C_{3-7}
 20 heterocycloalkylethyl or heteroarylmethyl, any of which groups may be optionally substituted by one or more substituents.

In a first embodiment, R¹ represents optionally substituted C₁₋₆ alkyl. In a second embodiment, R¹ represents optionally substituted C₃₋₇ cycloalkyl. In a third embodiment, R¹ represents optionally substituted C₃₋₇ cycloalkyl(C₁₋₆)alkyl. In one aspect of that embodiment, R¹ represents optionally substituted C₃₋₇ cycloalkylmethyl. In a fourth embodiment, R¹ represents optionally substituted aryl. In a fifth embodiment, R¹ represents optionally substituted aryl(C₁₋₆)alkyl. In one aspect of that embodiment, R¹ represents optionally substituted arylmethyl. In a sixth embodiment, R¹ represents optionally substituted C₃₋₇ heterocycloalkyl. In a seventh embodiment, R¹ represents optionally substituted C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl. In one aspect of that embodiment, R¹ represents optionally substituted C₃₋₇ heterocycloalkylmethyl. In another aspect of that embodiment, R¹ represents optionally substituted C₃₋₇ heterocycloalkylethyl. In an eighth embodiment, R¹ represents optionally substituted heteroaryl. In a ninth embodiment, R¹ represents optionally substituted heteroaryl(C₁₋₆)alkyl. In one aspect of that embodiment, R¹ represents optionally substituted heteroaryl-methyl.

Selected values of R¹ include methyl, ethyl, propyl, *tert*-butyl, cyclopropyl, cyclohexylmethyl, phenyl, naphthyl, benzyl, tetrahydrofuryl, oxetanylmethyl, pyrrolidinylethyl, furyl, thienyl, thieno[2,3-*b*]pyridinyl, indolyl, pyrrolo[2,3-*b*]pyridinyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, benzimidazolyl, imidazo[1,2-*a*]pyridinyl, oxadiazolyl, triazolyl, pyridinyl, quinoliny, 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl, pyrimidinyl, pyrazinyl, furylmethyl, indolylmethyl, thiazolylmethyl, imidazolylmethyl, imidazo[1,2-*a*]pyridinylmethyl, triazolylmethyl, benzotriazolylmethyl, tetrazolylmethyl and pyridinylmethyl, any of which groups may be optionally substituted by one or more substituents.

Typical values of R¹ include methyl, ethyl, propyl, *tert*-butyl, cyclopropyl, cyclohexylmethyl, phenyl, naphthyl, benzyl, tetrahydrofuryl, oxetanylmethyl, pyrrolidinylethyl, furyl, thienyl, pyrrolo[2,3-*b*]pyridinyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, benzimidazolyl, imidazo[1,2-*a*]pyridinyl, oxadiazolyl, triazolyl, pyridinyl, quinoliny, furylmethyl, indolylmethyl, thiazolylmethyl, imidazolylmethyl, imidazo[1,2-*a*]pyridinylmethyl, triazolylmethyl, benzotriazolylmethyl, tetrazolylmethyl and pyridinylmethyl, any of which groups may be optionally substituted by one or more substituents.

Suitably, R¹ represents phenyl or pyridinyl, either of which groups may be optionally substituted by one or more substituents.

Examples of selected substituents on R¹ include halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl, aryl(C₁₋₆)alkyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, aryloxy, hydroxybenzoyloxy, (hydroxy)(methyl)benzoyloxy, C₁₋₄ alkylenedioxy, C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, oxo, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxycarbonylamino, aryl(C₁₋₆)alkoxycarbonylamino, C₁₋₆ alkylaminocarbonylamino, arylaminocarbonylamino, C₁₋₆ alkylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxycarbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl and di(C₁₋₆)alkylaminosulphonyl.

Examples of typical substituents on R¹ include halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl, aryl(C₁₋₆)alkyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, C₁₋₄ alkylenedioxy, C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, oxo, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxycarbonylamino, aryl(C₁₋₆)alkoxycarbonylamino, C₁₋₆ alkylaminocarbonylamino, arylaminocarbonylamino, C₁₋₆ alkylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxycarbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl and di(C₁₋₆)alkylaminosulphonyl.

Definitive examples of selected substituents on R¹ include halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl, aryl(C₁₋₆)alkyl, hydroxy, C₁₋₆ alkoxy, trifluoromethoxy, trifluoroethoxy, hydroxybenzoyloxy, (hydroxy)(methyl)benzoyloxy, C₁₋₄ alkylenedioxy, C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, oxo, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxycarbonylamino, aryl(C₁₋₆)-alkoxycarbonylamino, C₁₋₆ alkylaminocarbonylamino, arylaminocarbonylamino, C₁₋₆ alkylsulphonylamino, C₂₋₆ alkoxycarbonyl and C₁₋₆ alkylaminosulphonyl.

Examples of apposite substituents on R¹ include halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl, aryl(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₁₋₄ alkylenedioxy, C₁₋₆ alkoxy(C₁₋₆)alkyl, oxo, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxycarbonylamino, aryl(C₁₋₆)alkoxycarbonylamino, C₁₋₆ alkylaminocarbonylamino, arylaminocarbonylamino and C₂₋₆ alkoxycarbonyl.

Examples of specific substituents on R¹ include fluoro, chloro, bromo, cyano, nitro, methyl, ethyl, *tert*-butyl, trifluoromethyl, benzyl, hydroxy, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, phenoxy, hydroxybenzoyloxy, (hydroxy)(methyl)benzoyloxy, methylenedioxy, ethylenedioxy, methoxymethyl,

methylthio, methylsulphonyl, oxo, amino, methylamino, dimethylamino, acetamino, methoxycarbonylamino, ethoxycarbonylamino, benzyloxycarbonylamino, ethylamino-carbonylamino, butylaminocarbonylamino, phenylaminocarbonylamino, methylsulphonyl-amino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylamino-sulphonyl.

Examples of suitable substituents on R¹ include fluoro, chloro, bromo, cyano, nitro, methyl, ethyl, *tert*-butyl, trifluoromethyl, benzyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, phenoxy, ethylenedioxy, methoxymethyl, methylthio, methylsulphonyl, oxo, amino, methylamino, dimethylamino, acetamino, methoxycarbonylamino, ethoxy-carbonylamino, benzyloxycarbonylamino, ethylaminocarbonylamino, butylamino-carbonylamino, phenylaminocarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylamino-carbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl.

Definitive examples of specific substituents on R¹ include fluoro, chloro, bromo, cyano, nitro, methyl, ethyl, *tert*-butyl, trifluoromethyl, benzyl, hydroxy, methoxy, ethoxy, isopropoxy, trifluoromethoxy, trifluoroethoxy, hydroxybenzoyloxy, (hydroxy)(methyl)-benzoyloxy, methylenedioxy, ethylenedioxy, methoxymethyl, methylthio, methylsulphonyl, oxo, amino, methylamino, dimethylamino, acetamino, methoxycarbonyl-amino, ethoxycarbonylamino, benzyloxycarbonylamino, ethylaminocarbonylamino, butylaminocarbonylamino, phenylaminocarbonylamino, methylsulphonylamino, methoxycarbonyl and methylaminosulphonyl.

Examples of detailed substituents on R¹ include fluoro, chloro, cyano, nitro, methyl, ethyl, *tert*-butyl, trifluoromethyl, benzyl, methoxy, ethylenedioxy, methoxy-methyl, oxo, amino, methylamino, dimethylamino, acetamino, ethoxycarbonylamino, benzyloxycarbonylamino, ethylaminocarbonylamino, butylaminocarbonylamino, phenylaminocarbonylamino and methoxycarbonyl.

Selected values of R¹ include methyl, ethyl, cyanoethyl, oxopropyl, *tert*-butyl, cyclopropyl, oxocyclohexylmethyl, phenyl, fluorophenyl, difluorophenyl, chlorophenyl, dichlorophenyl, cyanophenyl, (fluoro)(nitro)phenyl, methylphenyl, (fluoro)(methyl)-phenyl, (chloro)(methyl)phenyl, trifluoromethylphenyl, (fluoro)(trifluoromethyl)phenyl, (chloro)(trifluoromethyl)phenyl, (methyl)(trifluoromethyl)phenyl, hydroxyphenyl, (fluoro)(hydroxy)phenyl, (difluoro)(hydroxy)phenyl, (chloro)(hydroxy)phenyl, (bromo)-

(hydroxy)phenyl, (hydroxy)(nitro)phenyl, (hydroxy)(methyl)phenyl, (hydroxy)-(trifluoromethyl)phenyl, methoxyphenyl, (fluoro)(methoxy)phenyl, (difluoro)(methoxy)-phenyl, (chloro)(methoxy)phenyl, (chloro)(fluoro)(methoxy)phenyl, (dichloro)(methoxy)-phenyl, (methoxy)(methyl)phenyl, (methoxy)(trifluoromethyl)phenyl, (hydroxy)-

5 (methoxy)phenyl, dimethoxyphenyl, trifluoromethoxyphenyl, hydroxybenzoyloxyphenyl, (hydroxy)(methyl)benzoyloxyphenyl, methylenedioxyphenyl, ethylenedioxyphenyl, methylthiophenyl, methylsulphonylphenyl, aminophenyl, (dimethylamino)(fluoro)phenyl, (dimethylamino)(trifluoromethyl)phenyl, methylaminosulphonylphenyl, naphthyl, trifluoromethylbenzyl, (dimethyl)(oxo)tetrahydrofuryl, methyloxetanylmethyl,

10 oxopyrrolidinylethyl, dioxopyrrolidinylethyl, furyl, nitrofuryl, methoxymethylthienyl, thieno[2,3-*b*]pyridinyl, indolyl, pyrrolo[2,3-*b*]pyridinyl, pyrazolyl, methylpyrazolyl, (ethyl)(methyl)pyrazolyl, oxazolyl, dimethylisoxazolyl, methoxycarbonylisoxazolyl, chlorothiazolyl, methylthiazolyl, methoxythiazolyl, aminothiazolyl, (amino)(methyl)-thiazolyl, acetaminothiazolyl, ethylaminocarbonylaminothiazolyl, imidazolyl,

15 methylimidazolyl, (bromo)(methyl)imidazolyl, benzylimidazolyl, dimethylbenzimidazolyl, imidazo[1,2-*a*]pyridinyl, oxadiazolyl, dimethyltriazolyl, pyridinyl, fluoropyridinyl, chloropyridinyl, (fluoro)(chloro)pyridinyl, dichloropyridinyl, (bromo)(chloro)pyridinyl, cyanopyridinyl, methylpyridinyl, (chloro)(methyl)pyridinyl, (chloro)(cyano)(methyl)-pyridinyl, *tert*-butylpyridinyl, trifluoromethylpyridinyl, (chloro)(trifluoromethyl)pyridinyl,

20 hydroxypyridinyl, methoxypyridinyl, (fluoro)(methoxy)pyridinyl, (chloro)(methoxy)-pyridinyl, (chloro)(fluoro)(methoxy)pyridinyl, (bromo)(methoxy)pyridinyl, (cyano)-(methoxy)pyridinyl, (methoxy)(nitro)pyridinyl, (methoxy)(methyl)pyridinyl, (cyano)-(methoxy)(methyl)pyridinyl, (methoxy)(trifluoromethyl)pyridinyl, (hydroxy)(methoxy)-pyridinyl, dimethoxypyridinyl, ethoxypyridinyl, (chloro)(ethoxy)pyridinyl, isopropoxy-pyridinyl, trifluoroethoxypyridinyl, methylthiopyridinyl, (chloro)(methylthio)pyridinyl,

25 oxopyridinyl, (chloro)(oxo)pyridinyl, (methyl)(oxo)pyridinyl, (dimethyl)(oxo)pyridinyl, aminopyridinyl, (amino)(chloro)pyridinyl, (amino)(methoxy)pyridinyl, methylamino-pyridinyl, (chloro)(methylamino)pyridinyl, dimethylaminopyridinyl, acetaminopyridinyl, (acetylamino)(methoxy)pyridinyl, methoxycarbonylaminopyridinyl,

30 ethoxycarbonylaminopyridinyl, benzyloxycarbonylaminopyridinyl, ethylaminocarbonylaminopyridinyl, butylaminocarbonylaminopyridinyl, phenylaminocarbonylamino-pyridinyl, methylsulphonylaminopyridinyl, (chloro)(methylsulphonylamino)pyridinyl, quinolinyl, methyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl, pyrimidinyl, dimethyl-

pyrimidinyl, hydroxypyrimidinyl, methoxypyrimidinyl, (methoxy)(methyl)pyrimidinyl, dimethoxypyrimidinyl, aminopyrimidinyl, chloropyrazinyl, methoxypyrazinyl, furylmethyl, indolylmethyl, aminothiazolylmethyl, imidazolylmethyl, imidazo[1,2-*a*]pyridinylmethyl, methyltriazolylmethyl, benzotriazolylmethyl, tetrazolylmethyl, pyridinylmethyl, oxopyridinylmethyl and aminopyridinylmethyl.

Suitable values of R¹ include methyl, ethyl, cyanoethyl, oxopropyl, *tert*-butyl, cyclopropyl, oxocyclohexylmethyl, phenyl, chlorophenyl, methylphenyl, (fluoro)-(trifluoromethyl)phenyl, (methyl)(trifluoromethyl)phenyl, methoxyphenyl, (methoxy)-(trifluoromethyl)phenyl, ethylenedioxyphenyl, aminophenyl, naphthyl, trifluoromethylbenzyl, (dimethyl)(oxo)tetrahydrofuryl, methyloxetanylmethyl, oxopyrrolidinylethyl, dioxopyrrolidinylethyl, furyl, nitrofuryl, methoxymethylthienyl, pyrrolo[2,3-*b*]pyridinyl, pyrazolyl, (ethyl)(methyl)pyrazolyl, oxazolyl, dimethylisoxazolyl, methoxycarbonylisoxazolyl, methylthiazolyl, aminothiazolyl, (amino)(methyl)thiazolyl, acetylaminothiazolyl, ethylaminocarbonylaminothiazolyl, methylimidazolyl, benzylimidazolyl, dimethylbenzimidazolyl, imidazo[1,2-*a*]pyridinyl, oxadiazolyl, dimethyltriazolyl, pyridinyl, chloropyridinyl, cyanopyridinyl, methylpyridinyl, *tert*-butylpyridinyl, trifluoromethylpyridinyl, methoxypyridinyl, oxopyridinyl, aminopyridinyl, methylaminopyridinyl, dimethylaminopyridinyl, acetylaminopyridinyl, ethoxycarbonylaminopyridinyl, benzyloxycarbonylaminopyridinyl, ethylaminocarbonylaminopyridinyl, butylaminocarbonylaminopyridinyl, phenylaminocarbonylaminopyridinyl, quinolinyl, furylmethyl, indolylmethyl, aminothiazolylmethyl, imidazolylmethyl, imidazo[1,2-*a*]pyridinylmethyl, methyltriazolylmethyl, benzotriazolylmethyl, tetrazolylmethyl, pyridinylmethyl, oxopyridinylmethyl and aminopyridinylmethyl.

A particular value of R¹ is chloropyridinyl, especially 6-chloropyridin-3-yl.

A particular value of R¹ is methylpyridinyl, especially 6-methylpyridin-3-yl.

A particular value of R¹ is methoxypyridinyl, especially 6-methoxypyridin-3-yl.

A particular value of R¹ is (chloro)(methoxy)pyridinyl, especially 5-chloro-6-methoxypyridin-3-yl.

A particular value of R¹ is (chloro)(fluoro)(methoxy)pyridinyl, especially 2-chloro-5-fluoro-6-methoxypyridin-3-yl.

Selected values of R² include hydrogen, optionally substituted methyl and optionally substituted ethyl.

Examples of suitable substituents on R^2 include hydroxy, C_{1-6} alkoxy, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, aminocarbonyl, C_{1-6} alkylaminocarbonyl and di(C_{1-6})alkylaminocarbonyl.

5 Examples of typical substituents on R^2 include hydroxy, C_{1-6} alkoxy, aminocarbonyl, C_{1-6} alkylaminocarbonyl and di(C_{1-6})alkylaminocarbonyl.

Examples of selected substituents on R^2 include hydroxy, di(C_{1-6})alkylamino, aminocarbonyl and C_{1-6} alkylaminocarbonyl.

10 Suitable examples of specific substituents on R^2 include hydroxy, methoxy, amino, methylamino, dimethylamino, aminocarbonyl, methylaminocarbonyl and dimethylaminocarbonyl.

Typical examples of specific substituents on R^2 include hydroxy, methoxy, aminocarbonyl, methylaminocarbonyl and dimethylaminocarbonyl.

Selected examples of specific substituents on R^2 include hydroxy, dimethylamino, aminocarbonyl and methylaminocarbonyl.

15 In one embodiment, R^2 represents hydrogen. In another embodiment, R^2 represents optionally substituted C_{1-6} alkyl. In one aspect of that embodiment, R^2 represents unsubstituted C_{1-6} alkyl, especially methyl. In another aspect of that embodiment, R^2 represents substituted C_{1-6} alkyl, especially substituted methyl or substituted ethyl.

20 Specific values of R^2 include hydrogen, methyl, aminocarbonylmethyl, methylaminocarbonylmethyl, hydroxyethyl and dimethylaminoethyl.

Particular values of R^2 include hydrogen and methyl.

25 In a particular aspect, R^3 and R^4 independently represent hydrogen, halogen, trifluoromethyl, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-NR^bR^c$, $-NR^cCOR^d$, $-NR^cCO_2R^d$, $-NR^cSO_2R^e$, $-COR^d$, $-CO_2R^d$, $-CONR^bR^c$ or $-SO_2NR^bR^c$; or C_{1-6} alkyl, aryl, aryl- (C_{1-6}) alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

30 Selected values of R^3 include hydrogen, halogen, cyano, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, $-OR^a$, $-SO_2R^a$, $-NR^bR^c$, $-CH_2NR^bR^c$, $-NR^cCOR^d$, $-CH_2NR^cCOR^d$, $-NR^cCO_2R^d$, $-NHCONR^bR^c$, $-NR^cSO_2R^e$, $-N(SO_2R^e)_2$, $-NHSO_2NR^bR^c$, $-COR^d$, $-CO_2R^d$, $-CONR^bR^c$, $-CON(OR^a)R^b$ or $-SO_2NR^bR^c$; or C_{1-6} alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

Typical values of R^3 include hydrogen, $-OR^a$, $-CO_2R^d$ or $-CONR^bR^c$; or aryl or heteroaryl, either of which groups may be optionally substituted by one or more substituents.

In a first embodiment, R^3 represents hydrogen. In a second embodiment, R^3 represents $-OR^a$, wherein R^a is as defined above. In a third embodiment, R^3 represents $-CO_2R^d$, wherein R^d is as defined above. In a fourth embodiment, R^3 represents $-CONR^bR^c$, wherein R^b and R^c are as defined above. In a fifth embodiment, R^3 represents optionally substituted aryl. In a sixth embodiment, R^3 represents optionally substituted heteroaryl. In a seventh embodiment, R^3 represents halogen. In one aspect of that embodiment, R^3 represents fluoro. In another aspect of that embodiment, R^3 represents chloro. In an eighth embodiment, R^3 represents cyano. In a ninth embodiment, R^3 represents nitro. In a tenth embodiment, R^3 represents hydroxy. In an eleventh embodiment, R^3 represents trifluoromethyl. In a twelfth embodiment, R^3 represents trifluoromethoxy. In a thirteenth embodiment, R^3 represents $-SO_2R^a$, wherein R^a is as defined above. In a fourteenth embodiment, R^3 represents $-NR^bR^c$, wherein R^b and R^c are as defined above. In a fifteenth embodiment, R^3 represents $-CH_2NR^bR^c$, wherein R^b and R^c are as defined above. In a sixteenth embodiment, R^3 represents $-NR^cCOR^d$, wherein R^c and R^d are as defined above. In a seventeenth embodiment, R^3 represents $-CH_2NR^cCOR^d$, wherein R^c and R^d are as defined above. In an eighteenth embodiment, R^3 represents $-NR^cCO_2R^d$, wherein R^c and R^d are as defined above. In a nineteenth embodiment, R^3 represents $-NHCONR^bR^c$, wherein R^b and R^c are as defined above. In a twentieth embodiment, R^3 represents $-NR^cSO_2R^e$, wherein R^c and R^e are as defined above. In a twenty-first embodiment, R^3 represents $-N(SO_2R^e)_2$, wherein R^e is as defined above. In a twenty-second embodiment, R^3 represents $-NHSO_2NR^bR^c$, wherein R^b and R^c are as defined above. In a twenty-third embodiment, R^3 represents $-COR^d$, wherein R^d is as defined above. In a twenty-fourth embodiment, R^3 represents $-CON(OR^a)R^b$, wherein R^a and R^b are as defined above. In a twenty-fifth embodiment, R^3 represents $-SO_2NR^bR^c$; wherein R^b and R^c are as defined above. In a twenty-sixth embodiment, R^3 represents optionally substituted C_{1-6} alkyl.

Examples of typical substituents on R^3 and/or R^4 include halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, aryl(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, C_{1-4} alkylenedioxy, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, oxo, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino,

C₂₋₆ alkoxy-carbonylamino, aryl(C₁₋₆)alkoxy-carbonylamino, C₁₋₆ alkylaminocarbonyl-amino, arylaminocarbonylamino, C₁₋₆ alkylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxy-carbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl and di(C₁₋₆)alkylamino-sulphonyl.

Selected examples of typical substituents on R³ and/or R⁴ include halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy and C₁₋₄ alkylenedioxy.

Examples of apposite substituents on R³ and/or R⁴ include halogen and C₁₋₆ alkyl.

Examples of suitable substituents on R³ and/or R⁴ include fluoro, chloro, bromo, cyano, nitro, methyl, ethyl, *tert*-butyl, trifluoromethyl, benzyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, phenoxy, ethylenedioxy, methoxymethyl, methylthio, methylsulphonyl, oxo, amino, methylamino, dimethylamino, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, benzyloxycarbonylamino, ethylaminocarbonylamino, butylaminocarbonylamino, phenylaminocarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl. An additional example is methylenedioxy.

Selected examples of suitable substituents on R³ and/or R⁴ include fluoro, methyl, methoxy and methylenedioxy.

Examples of detailed substituents on R³ and/or R⁴ include fluoro and methyl.

Definitive values of R³ include hydrogen, fluoro, chloro, cyano, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, -OR^a, -SO₂R^a, -NR^bR^c, -CH₂NR^bR^c, -NR^cCOR^d, -CH₂NR^cCOR^d, -NR^cCO₂R^d, -NHCONR^bR^c, -NR^cSO₂R^e, -N(SO₂R^e)₂, -NHSO₂NR^bR^c, -COR^d, -CO₂R^d, -CONR^bR^c, -CON(OR^a)R^b, -SO₂NR^bR^c, methyl, phenyl, fluorophenyl, methylphenyl, methoxyphenyl, methylenedioxyphenyl, thiazolyl, imidazolyl, methylimidazolyl, pyridinyl and methylpyridinyl.

Suitable values of R³ include hydrogen, -OR^a, -CO₂R^d, -CONR^bR^c, phenyl, fluorophenyl, methylphenyl and methylimidazolyl.

Typical values of R⁴ include hydrogen, halogen, -COR^d, -CO₂R^d, -CONR^bR^c and C₁₋₆ alkyl, wherein R^b, R^c and R^d are as defined above.

Selected values of R⁴ include hydrogen, halogen, -COR^d, -CO₂R^d and -CONR^bR^c, wherein R^b, R^c and R^d are as defined above.

Suitable values of R⁴ include hydrogen and C₁₋₆ alkyl.

In one embodiment, R⁴ represents hydrogen. In another embodiment, R⁴ represents halogen, especially chloro. In another embodiment, R⁴ represents -COR^d, wherein R^d is as defined above. In another embodiment, R⁴ represents -CO₂R^d, wherein R^d is as defined above. In another embodiment, R⁴ represents -CONR^bR^c, wherein R^b and R^c are as defined above. In another embodiment, R⁴ represents C₁₋₆ alkyl, especially methyl.

Suitably, R⁵ represents hydrogen or methyl.

In one embodiment, R⁵ represents hydrogen. In another embodiment, R⁵ represents C₁₋₆ alkyl, especially methyl.

Typical examples of suitable substituents on R^a, R^b, R^c, R^d or R^e, or on the heterocyclic moiety -NR^bR^c, include halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, hydroxy, hydroxy(C₁₋₆)alkyl, amino(C₁₋₆)alkyl, cyano, trifluoromethyl, oxo, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxycarbonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, phenylamino, pyridinylamino, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxycarbonylamino, aminocarbonyl, C₁₋₆ alkylaminocarbonyl and di(C₁₋₆)alkylaminocarbonyl. Additional examples include C₁₋₆ alkylsulphinyl, C₂₋₆ alkylcarbonyloxy, C₂₋₆ alkylcarbonylamino(C₁₋₆)alkyl and C₁₋₆ alkylsulphonylamino.

Selected examples of suitable substituents on R^a, R^b, R^c, R^d or R^e, or on the heterocyclic moiety -NR^bR^c, include halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkylsulphonyl, hydroxy, hydroxy(C₁₋₆)alkyl, amino(C₁₋₆)alkyl, cyano, oxo, C₂₋₆ alkylcarbonyl, C₂₋₆ alkylcarbonyloxy, carboxy, C₂₋₆ alkoxycarbonyl, amino, di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkylcarbonylamino(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonylamino, C₁₋₆ alkylsulphonylamino and aminocarbonyl.

Typical examples of specific substituents on R^a, R^b, R^c, R^d or R^e, or on the heterocyclic moiety -NR^bR^c, include fluoro, chloro, bromo, methyl, ethyl, isopropyl, methoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, methoxymethyl, methylthio, ethylthio, methylsulphonyl, hydroxy, hydroxymethyl, hydroxyethyl, aminomethyl, cyano, trifluoromethyl, oxo, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, amino, methylamino, ethylamino, dimethylamino, phenylamino, pyridinylamino, acetylamino, *tert*-butoxycarbonylamino, aminocarbonyl, methylaminocarbonyl and dimethylaminocarbonyl. Additional examples include methylsulphinyl, acetoxymethyl, acetylaminomethyl and methylsulphonylamino.

Selected examples of specific substituents on R^a, R^b, R^c, R^d or R^e, or on the heterocyclic moiety -NR^bR^c, include fluoro, chloro, methyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, hydroxy, hydroxymethyl, aminomethyl, cyano, oxo, acetyl, acetoxymethyl, carboxy, ethoxycarbonyl, *tert*-butoxycarbonyl, amino, dimethylamino, acetylamino, acetylaminomethyl, *tert*-butoxycarbonylamino, methylsulphonylamino and aminocarbonyl.

Suitably, R^a represents C₁₋₆ alkyl, aryl(C₁₋₆)alkyl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents.

Selected values of R^a include methyl, ethyl, benzyl and isoindolylpropyl, any of which groups may be optionally substituted by one or more substituents.

Selected examples of suitable substituents on R^a include C₁₋₆ alkoxy and oxo.

Selected examples of specific substituents on R^a include methoxy and oxo.

In one embodiment, R^a represents optionally substituted C₁₋₆ alkyl. In one aspect of that embodiment, R^a ideally represents unsubstituted C₁₋₆ alkyl, especially methyl. In another aspect of that embodiment, R^a ideally represents substituted C₁₋₆ alkyl, e.g. methoxyethyl. In another embodiment, R^a represents optionally substituted aryl. In one aspect of that embodiment, R^a represents unsubstituted aryl, especially phenyl. In another aspect of that embodiment, R^a represents monosubstituted aryl, especially methylphenyl. In another embodiment, R^a represents optionally substituted aryl(C₁₋₆)alkyl, ideally unsubstituted aryl(C₁₋₆)alkyl, especially benzyl. In a further embodiment, R^a represents optionally substituted heteroaryl. In a further embodiment, R^a represents optionally substituted heteroaryl(C₁₋₆)alkyl, e.g. dioxoisindolylpropyl.

Specific values of R^a include methyl, methoxyethyl, benzyl and dioxoisindolylpropyl.

In a particular aspect, R^b represents hydrogen or trifluoromethyl; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents.

Selected values of R^b include hydrogen; or C₁₋₆ alkyl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl or C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents.

Typical values of R^b include hydrogen and C₁₋₆ alkyl.

Illustratively, R^b represents hydrogen or trifluoromethyl; or methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, 2-methylpropyl, *tert*-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, phenyl, benzyl, phenylethyl, azetidiny, tetrahydrofuryl, tetrahydrothienyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, azetidinylmethyl, tetrahydrofurylmethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl, thiazolidinylmethyl, imidazolidinylethyl, piperidinylmethyl, piperidinylethyl, tetrahydroquinolinylmethyl, piperazinylpropyl, morpholinylmethyl, morpholinylethyl, morpholinylpropyl, pyridinyl, indolylmethyl, pyrazolylmethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl, benzimidazolylmethyl, triazolylmethyl, pyridinylmethyl or pyridinylethyl, any of which groups may be optionally substituted by one or more substituents.

Representative values of R^b include hydrogen; or methyl, ethyl, *n*-propyl, benzyl, pyrrolidinyl or morpholinylpropyl, any of which groups may be optionally substituted by one or more substituents.

Selected examples of suitable substituents on R^b include C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkylsulphonyl, hydroxy, cyano, C₂₋₆ alkoxycarbonyl, di-(C₁₋₆)alkylamino and C₂₋₆ alkoxycarbonylamino.

Selected examples of specific substituents on R^b include methoxy, methylthio, methylsulphinyl, methylsulphonyl, hydroxy, cyano, *tert*-butoxycarbonyl, dimethylamino and *tert*-butoxycarbonylamino.

Specific values of R^b include hydrogen, methyl, methoxyethyl, methylthioethyl, methylsulphinylethyl, methylsulphonylethyl, hydroxyethyl, cyanoethyl, dimethylaminoethyl, *tert*-butoxycarbonylaminoethyl, dihydroxypropyl, benzyl, pyrrolidinyl, *tert*-butoxycarbonylpyrrolidinyl and morpholinylpropyl.

In one embodiment, R^b represents hydrogen. In another embodiment, R^b represents C₁₋₆ alkyl, especially methyl.

Selected values of R^c include hydrogen; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl or C₃₋₇ heterocycloalkyl, any of which groups may be optionally substituted by one or more substituents.

In a particular aspect, R^c represents hydrogen, C₁₋₆ alkyl or C₃₋₇ cycloalkyl.

Representative values of R^c include hydrogen; or methyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydropyranyl and piperidinyl, any of which groups may be optionally substituted by one or more substituents.

Selected examples of suitable substituents on R^c include C₂₋₆ alkylcarbonyl and
5 C₂₋₆ alkoxy carbonyl.

Selected examples of specific substituents on R^c include acetyl and *tert*-butoxycarbonyl.

Specific values of R^c include hydrogen, methyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydropyranyl, acetylpiperidinyl and *tert*-butoxycarbonylpiperidinyl,

10 Suitably, R^c represents hydrogen or C₁₋₆ alkyl. In one embodiment, R^c is hydrogen. In another embodiment, R^c represents C₁₋₆ alkyl, especially methyl or ethyl, particularly methyl. In a further embodiment, R^c represents C₃₋₇ cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Alternatively, the moiety -NR^bR^c may suitably represent azetidin-1-yl, pyrrolidin-
15 1-yl, oxazolidin-3-yl, isoxazolidin-2-yl, thiazolidin-3-yl, isothiazolidin-2-yl, piperidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperazin-1-yl, homopiperidin-1-yl, homomorpholin-4-yl or homopiperazin-1-yl, any of which groups may be optionally substituted by one or more substituents.

In a particular aspect, the moiety -NR^bR^c may suitably represent azetidin-1-yl,
20 pyrrolidin-1-yl, isoxazolidin-2-yl, piperidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperazin-1-yl, homopiperidin-1-yl, homomorpholin-4-yl or homopiperazin-1-yl, any of which groups may be optionally substituted by one or more substituents.

Selected values for the moiety -NR^bR^c suitably include azetidin-1-yl, pyrrolidin-1-yl, oxazolidin-3-yl, isoxazolidin-2-yl, thiazolidin-3-yl, isothiazolidin-2-yl, piperidin-1-yl,
25 morpholin-4-yl, piperazin-1-yl and homopiperazin-1-yl, any of which groups may be optionally substituted by one or more substituents.

Selected examples of suitable substituents on the heterocyclic moiety -NR^bR^c include C₁₋₆ alkyl, C₁₋₆ alkylsulphonyl, hydroxy, hydroxy(C₁₋₆)alkyl, amino(C₁₋₆)alkyl, cyano, oxo, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxy carbonyl, amino, C₂₋₆ alkylcarbonyl-
30 amino, C₂₋₆ alkylcarbonylamino(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonylamino, C₁₋₆ alkylsulphonylamino and aminocarbonyl.

Selected examples of specific substituents on the heterocyclic moiety -NR^bR^c include methyl, methylsulphonyl, hydroxy, hydroxymethyl, aminomethyl, cyano, oxo,

acetyl, carboxy, ethoxycarbonyl, amino, acetylamino, acetylaminomethyl, *tert*-butoxycarbonylamino, methylsulphonylamino and aminocarbonyl.

Specific values of the moiety $-NR^bR^c$ include azetidin-1-yl, hydroxyazetidin-1-yl, hydroxymethylazetidin-1-yl, (hydroxy)(hydroxymethyl)azetidin-1-yl, aminomethyl-
 5 azetidin-1-yl, cyanoazetidin-1-yl, carboxyazetidin-1-yl, aminoazetidin-1-yl, aminocarbonylazetidin-1-yl, pyrrolidin-1-yl, aminomethylpyrrolidin-1-yl, oxopyrrolidin-1-yl, acetylaminomethylpyrrolidin-1-yl, *tert*-butoxycarbonylaminopyrrolidin-1-yl, oxo-oxazolidin-3-yl, hydroxyisoxazolidin-2-yl, thiazolidin-3-yl, oxothiazolidin-3-yl, dioxo-isothiazolidin-2-yl, piperidin-1-yl, hydroxypiperidin-1-yl, hydroxymethylpiperidin-1-yl,
 10 aminopiperidin-1-yl, acetylaminopiperidin-1-yl, *tert*-butoxycarbonylaminopiperidin-1-yl, methylsulphonylaminopiperidin-1-yl, morpholin-4-yl, piperazin-1-yl, methylpiperazin-1-yl, methylsulphonylpiperazin-1-yl, oxopiperazin-1-yl, acetypiperazin-1-yl, ethoxycarbonylpiperazin-1-yl and oxohomopiperazin-1-yl.

Suitably, R^d represents hydrogen; or C_{1-6} alkyl, aryl or heteroaryl, any of which
 15 groups may be optionally substituted by one or more substituents.

Selected examples of suitable values for R^d include hydrogen, methyl, ethyl, isopropyl, 2-methylpropyl, *tert*-butyl, cyclopropyl, cyclobutyl, phenyl, thiazolidinyl, thienyl, imidazolyl and thiazolyl, any of which groups may be optionally substituted by one or more substituents.

20 Selected examples of suitable substituents on R^d include halogen, C_{1-6} alkyl, C_{1-6} alkoxy, oxo, C_{2-6} alkylcarbonyloxy and $di(C_{1-6})$ alkylamino.

Selected examples of particular substituents on R^d include fluoro, methyl, methoxy, oxo, acetoxy and dimethylamino.

In one embodiment, R^d represents hydrogen. In another embodiment, R^d
 25 represents optionally substituted C_{1-6} alkyl. In one aspect of that embodiment, R^d ideally represents unsubstituted C_{1-6} alkyl, e.g. methyl, ethyl, isopropyl, 2-methylpropyl or *tert*-butyl, especially methyl. In another aspect of that embodiment, R^d ideally represents substituted C_{1-6} alkyl, e.g. substituted methyl or substituted ethyl, including acetoxymethyl, dimethylaminomethyl and trifluoroethyl. In another embodiment, R^d
 30 represents optionally substituted aryl. In one aspect of that embodiment, R^d represents unsubstituted aryl, especially phenyl. In another aspect of that embodiment, R^d represents monosubstituted aryl, especially methylphenyl. In a further aspect of that embodiment, R^d represents disubstituted aryl, e.g. dimethoxyphenyl. In a further embodiment, R^d

represents optionally substituted heteroaryl, e.g. thienyl, chlorothienyl, methylthienyl, methylimidazolyl or thiazolyl. In another embodiment, R^d represents optionally substituted C₃₋₇ cycloalkyl, e.g. cyclopropyl or cyclobutyl. In a further embodiment, R^d represents optionally substituted C₃₋₇ heterocycloalkyl, e.g. thiazolidinyl or oxo-thiazolidinyl.

Selected examples of specific values for R^d include hydrogen, methyl, acetoxy-methyl, dimethylaminomethyl, ethyl, trifluoroethyl, isopropyl, 2-methylpropyl, *tert*-butyl, cyclopropyl, cyclobutyl, phenyl, dimethoxyphenyl, thiazolidinyl, oxothiazolidinyl, thienyl, chlorothienyl, methylthienyl, methylimidazolyl and thiazolyl.

Suitably, R^e represents C₁₋₆ alkyl or aryl, either of which groups may be optionally substituted by one or more substituents.

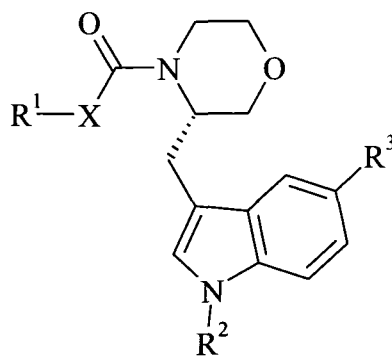
Selected examples of suitable substituents on R^e include C₁₋₆ alkyl, especially methyl.

In one embodiment, R^e represents optionally substituted C₁₋₆ alkyl, ideally unsubstituted C₁₋₆ alkyl, e.g. methyl or propyl, especially methyl. In another embodiment, R^e represents optionally substituted aryl. In one aspect of that embodiment, R^e represents unsubstituted aryl, especially phenyl. In another aspect of that embodiment, R^e represents monosubstituted aryl, especially methylphenyl. In a further embodiment, R^e represents optionally substituted heteroaryl.

Selected values of R^e include methyl, propyl and methylphenyl.

Suitably, the substituent at the 3-position of the morpholine ring in the compounds of formula (I) as depicted above is in the (*S*) configuration.

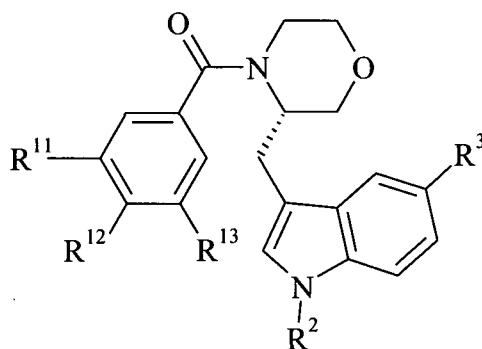
One sub-class of compounds according to the invention is represented by the compounds of formula (IIA) and *N*-oxides thereof, and pharmaceutically acceptable salts and solvates thereof:



(IIA)

wherein X, R¹, R² and R³ are as defined above.

One subset of the compounds of formula (IIA) above is represented by the
 5 compounds of formula (IIB) and *N*-oxides thereof, and pharmaceutically acceptable salts and solvates thereof:



(IIB)

10 wherein

R² and R³ are as defined above;

R¹¹ represents hydrogen, halogen, C₁₋₆ alkyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, trifluoromethoxy or C₁₋₆ alkylaminosulphonyl;

R¹² represents hydrogen, halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl,
 15 hydroxy, C₁₋₆ alkoxy, trifluoromethoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, amino or di(C₁₋₆)alkylamino; and

R¹³ represents hydrogen, halogen, trifluoromethyl or C₁₋₆ alkoxy.

Suitable values of R¹¹ include hydrogen, fluoro, chloro, methyl, trifluoromethyl, hydroxy, methoxy, trifluoromethoxy and methylaminosulphonyl.

20 A particular value of R¹¹ is hydroxy.

Suitable values of R^{12} include hydrogen, fluoro, chloro, bromo, cyano, nitro, methyl, trifluoromethyl, hydroxy, methoxy, trifluoromethoxy, methylthio, methylsulphonyl, amino and dimethylamino.

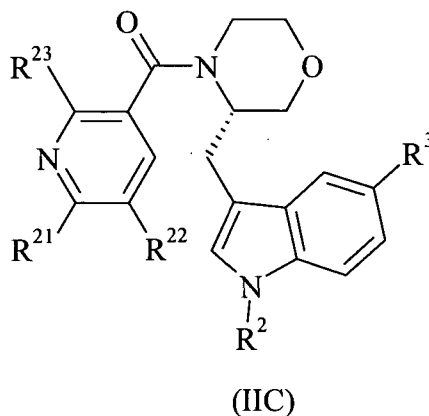
A particular value of R^{12} is methoxy.

5 Suitable values of R^{13} include hydrogen, fluoro, chloro, bromo, trifluoromethyl and methoxy.

In a particular embodiment, R^{13} represents hydrogen. In another embodiment, R^{13} represents halogen. In one aspect of that embodiment, R^{13} represents fluoro. In another aspect of that embodiment, R^{13} represents chloro. In a further aspect of that embodiment, R^{13} represents bromo. In another embodiment, R^{13} represents trifluoromethyl. In a further
10 embodiment, R^{13} represents C_{1-6} alkoxy, especially methoxy.

Another subset of the compounds of formula (IIA) above is represented by the compounds of formula (IIC) and *N*-oxides thereof, and pharmaceutically acceptable salts and solvates thereof:

15



wherein

R^2 and R^3 are as defined above;

20 R^{21} represents hydrogen, halogen, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, trifluoroethoxy, C_{1-6} alkylthio, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxy carbonylamino, aryl(C_{1-6})alkoxy carbonylamino, C_{1-6} alkylaminocarbonylamino, arylaminocarbonylamino or C_{1-6} alkylsulphonylamino;

R^{22} represents hydrogen, halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, amino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxy carbonylamino or C_{1-6}
25 alkylsulphonylamino; and

R²³ represents hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy or amino.

Suitable values of R²¹ include hydrogen, chloro, cyano, methyl, *tert*-butyl, methoxy, ethoxy, isopropoxy, trifluoroethoxy, methylthio, amino, methylamino, dimethylamino, acetylamino, ethoxycarbonylamino, benzyloxycarbonylamino, ethylaminocarbonylamino, butylaminocarbonylamino, phenylaminocarbonylamino and methylsulphonylamino.

Particular values of R²¹ include halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy and amino.

In one embodiment, R²¹ represents hydrogen. In another embodiment, R²¹ represents halogen, especially chloro. In another embodiment, R²¹ represents C₁₋₆ alkyl, especially methyl. In a particular embodiment, R²¹ represents C₁₋₆ alkoxy, especially methoxy. In a further embodiment, R²¹ represents amino.

Suitable values of R²² include hydrogen, fluoro, chloro, bromo, cyano, nitro, methyl, trifluoromethyl, hydroxy, methoxy, amino, acetylamino, methoxycarbonylamino and methylsulphonylamino.

Particular values of R²² include hydrogen, halogen, cyano and C₁₋₆ alkyl.

In one embodiment, R²² represents hydrogen. In another embodiment, R²² represents halogen, especially fluoro or chloro. In one aspect of that embodiment, R²² represents fluoro. In one aspect of that embodiment, R²² represents chloro. In a further embodiment, R²² represents cyano. In another embodiment, R²² represents C₁₋₆ alkyl, especially methyl.

Suitable values of R²³ include hydrogen, chloro, cyano, methyl, methoxy and amino.

Particular values of R²³ include hydrogen and halogen.

In one embodiment, R²³ represents hydrogen. In another embodiment, R²³ represents halogen, especially chloro.

Suitably, R²¹ is chloro, and R²² and R²³ are both hydrogen.

Suitably, R²¹ is methyl, and R²² and R²³ are both hydrogen.

Suitably, R²¹ is methoxy, and R²² and R²³ are both hydrogen.

Suitably, R²¹ is methoxy, R²² is chloro and R²³ is hydrogen.

Suitably, R²¹ is methoxy, R²² is fluoro and R²³ is chloro.

Specific novel compounds in accordance with the present invention include each of the compounds whose preparation is described in the accompanying Examples, and pharmaceutically acceptable salts and solvates thereof.

The present invention also provides a pharmaceutical composition which comprises a compound in accordance with the invention as described above, or a pharmaceutically acceptable salt or solvate thereof, in association with one or more pharmaceutically acceptable carriers.

5 Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, ophthalmic or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with
10 pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methyl cellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogenphosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in
15 the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles or preservatives. The preparations may
20 also contain buffer salts, flavouring agents, colouring agents or sweetening agents, as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration, the compositions may take the form of tablets or
25 lozenges formulated in conventional manner.

The compounds of formula (I) may be formulated for parenteral administration by injection, e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoules or multi-dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in
30 oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (I) may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds according to the present invention may be conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, fluorotrichloromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

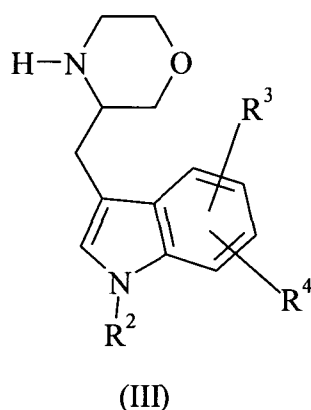
For topical administration the compounds according to the present invention may be conveniently formulated in a suitable ointment containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, liquid petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively, the compounds according to the present invention may be formulated in a suitable lotion containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, benzyl alcohol, 2-octyldodecanol and water.

For ophthalmic administration the compounds according to the present invention may be conveniently formulated as microionized suspensions in isotonic, pH-adjusted sterile saline, either with or without a preservative such as a bactericidal or fungicidal agent, for example phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively, for ophthalmic administration compounds may be formulated in an ointment such as petrolatum.

For rectal administration the compounds according to the present invention may be conveniently formulated as suppositories. These can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and so will melt in the rectum to release the active component. Such materials include, for example, cocoa butter, beeswax and polyethylene glycols.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen and the condition of the patient to be treated. In general, however, daily dosages may range from around 10 ng/kg to 1000 mg/kg, typically from 100 ng/kg to 100 mg/kg, e.g. around 0.01 mg/kg to 40 mg/kg body weight, for oral or buccal administration, from around 10 ng/kg to 50 mg/kg body weight for parenteral administration, and from around 0.05 mg to around 1000 mg, e.g. from around 0.5 mg to around 1000 mg, for nasal administration or administration by inhalation or insufflation.

The compounds of formula (I) above wherein X represents a covalent bond may be prepared by a process which comprises reacting a compound of formula R^1-Y-Cl with a compound of formula (III):



wherein Y, R^1 , R^2 , R^3 and R^4 are as defined above.

The reaction is conveniently effected in a suitable solvent, typically under basic conditions, e.g. in the presence of an organic base such as triethylamine or *N,N*-diisopropylethylamine. Suitable solvents include chlorinated solvents such as dichloromethane, cyclic ether solvents such as tetrahydrofuran, and dipolar aprotic solvents such as *N,N*-dimethylformamide.

Alternatively, the compounds of formula (I) above wherein X represents a covalent bond and Y represents C=O may be prepared by a process which comprises reacting a compound of formula R^1-CO_2H , wherein R^1 is as defined above, with a compound of formula (III) as defined above; in the presence of a coupling reagent.

The coupling agent of use in the above reaction is suitably 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide (EDC), in which case the reaction is conveniently effected in

the presence of an additive such as 1-hydroxybenzotriazole hydrate (HOBT), typically under basic conditions, e.g. in the presence of an organic base such as *N,N*-diisopropylethylamine.

Alternatively, the coupling agent employed may be polymer-supported Mukaiyama resin, in which case the reaction is conveniently effected under basic conditions, e.g. in the presence of an organic base such as *N,N*-diisopropylethylamine.

In another alternative, the coupling agent employed may be polymer-supported carbodiimide (PS-CDI), in which case the reactants may be brought together in the presence of the coupling agent and the material thereby obtained may then be treated with polymer-supported isocyanate (PS-NCO) in the presence of a base, typically an organic base such as triethylamine.

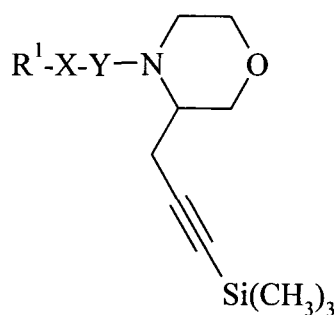
The compounds of formula (I) above wherein X represents oxygen and Y represents C=O may be prepared by a two-stage process which comprises (i) reacting a compound of formula R^1-OH , wherein R^1 is as defined above, with a condensing agent such as 4-nitrophenyl chloroformate; then (ii) reacting the resulting product with a compound of formula (III) as defined above.

Both stages of the above process may conveniently be performed in a suitable solvent, e.g. a chlorinated solvent such as dichloromethane, typically under basic conditions, e.g. in the presence of an organic base such as *N,N*-diisopropylethylamine.

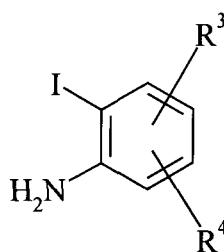
The compounds of formula (I) above wherein X represents N-H and Y represents C=O may be prepared by a process which comprises reacting an isocyanate derivative of formula $R^1-N=C=O$, wherein R^1 is as defined above, with a compound of formula (III) as defined above.

The reaction may conveniently be performed in a suitable solvent, e.g. a cyclic ether solvent such as tetrahydrofuran, typically in the presence of *N,N*-dimethylacetamide.

In an additional procedure, the compounds of formula (I) wherein R^2 is hydrogen may be prepared by a process which comprises reacting a compound of formula (IV) with a compound of formula (V):



(IV)



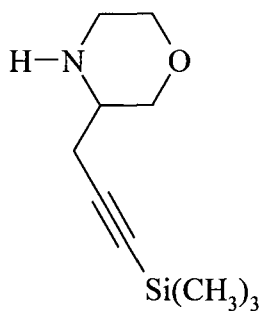
(V)

wherein X, Y, R¹, R³ and R⁴ are as defined above; in the presence of a transition metal catalyst; followed by removal of the trimethylsilyl moiety from the 2-position of the
 5 resulting cycloaddition product.

The transition metal catalyst of use in the reaction between compounds (IV) and (V) is suitably palladium(II) acetate, in which case the reaction may conveniently be effected at an elevated temperature in a suitable solvent, e.g. a dipolar aprotic solvent such as *N,N*-dimethylformamide, in the presence of lithium chloride and a base, typically an
 10 inorganic base, e.g. an alkaline earth metal carbonate such as sodium carbonate.

Removal of the trimethylsilyl moiety from the resulting cycloaddition product may be effected by treatment with an acid, e.g. a mineral acid such as hydrochloric acid.

The intermediates of formula (IV) above wherein X represents a covalent bond may be prepared by reacting a compound of formula R¹-Y-Cl with the compound of
 15 formula (VI):



(VI)

wherein Y and R¹ are as defined above; under conditions analogous to those described
 20 above for the reaction between a compound of formula R¹-Y-Cl and compound (III).

The intermediates of formula (III) above may be prepared by the methods described in prior art publications, including WO 2006/114606, WO 2007/141504, WO 2008/001076, WO 2008/047109, WO 2009/001089, WO 2009/071888, WO 2009/071890, WO 2009/071895, and copending international patent application no. 5 PCT/GB2009/000818, published on 8 October 2009 as WO 2009/122148.

Where they are not commercially available, the starting materials of formula R^1-Y-Cl , R^1-CO_2H , R^1-OH , $R^1-N=C=O$, (V) and (VI) may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

10 It will be understood that any compound of formula (I) initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula (I) by techniques known from the art. By way of example, a compound of formula (I) wherein R^1 contains an amino ($-NH_2$) group may be converted into the corresponding compound wherein R^1 contains a C_{2-6} alkoxycarbonylamino or 15 aryl(C_{1-6})alkoxycarbonylamino moiety by treatment with the appropriate alkyl or aryl- (C_{1-6})alkyl chloroformate respectively. Moreover, a compound of formula (I) wherein R^1 contains an amino ($-NH_2$) group may be converted into the corresponding compound wherein R^1 contains a C_{1-6} alkylaminocarbonylamino or arylaminocarbonylamino moiety by treatment with the appropriate alkyl or aryl isocyanate respectively. A compound of 20 formula (I) wherein R^1 contains an amino ($-NH_2$) group may be converted into the corresponding compound wherein R^1 contains a C_{1-6} alkylsulphonylamino moiety by treatment with the appropriate alkyl sulphonyl chloride, typically in the presence of a base, e.g. an organic base such as triethylamine.

A compound of formula (I) wherein R^1 contains a halogen atom, e.g. chloro, may 25 be converted into the corresponding compound wherein R^1 contains a C_{1-6} alkoxy moiety, e.g. methoxy or ethoxy, by treatment with an alkali metal alkoxide, e.g. sodium methoxide; or by treatment with a C_{1-6} alkanol, e.g. methanol or ethanol, in the presence of a base, e.g. an alkali metal hydroxide such as sodium hydroxide or lithium hydroxide. Moreover, a compound of formula (I) wherein R^1 contains a halogen atom, e.g. fluoro or 30 chloro, may be converted into the corresponding compound wherein R^1 contains a C_{1-6} alkylamino or di(C_{1-6})alkylamino moiety, e.g. methylamino or dimethylamino, by treatment with the appropriate alkylamine or dialkylamine, e.g. methylamine or dimethylamine respectively, optionally in the presence of a base, typically an inorganic base, e.g.

an alkali metal carbonate such as potassium carbonate. A compound of formula (I) wherein R^1 contains a halogen atom, e.g. chloro, may be converted into the corresponding compound wherein R^1 contains a C_{1-6} alkylthio moiety, e.g. methylthio, by treatment with an alkali metal thioalkoxide, e.g. sodium thiomethoxide.

- 5 A compound of formula (I) wherein R^1 contains a halogen atom, e.g. chloro, may be converted into the corresponding compound wherein R^1 contains a C_{1-6} alkylsulphonyl-amino moiety, e.g. methylsulphonylamino, by treatment with the appropriate alkyl sulphonamide, e.g. methanesulphonamide, generally in the presence of a transition metal catalyst. A suitable transition metal catalyst is tris(dibenzylideneacetone)dipalladium(0),
10 in which case the reaction is conveniently effected in the presence of 4,5-bis(diphenyl-phosphino)-9,9-dimethylxanthene (Xantphos) and a base, typically an inorganic base, e.g. an alkali metal carbonate such as caesium carbonate.

- A compound of formula (I) wherein R^1 contains a halogen atom, e.g. bromo, may be converted into the corresponding compound wherein R^1 contains a hydroxy (-OH)
15 group by treatment with a hydroxide salt, e.g. an alkali metal hydroxide such as potassium hydroxide, generally in the presence of a transition metal catalyst. A suitable transition metal catalyst is tris(dibenzylideneacetone)dipalladium(0), in which case the reaction is conveniently effected in the presence of a reagent such as 2-di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl.

- 20 A compound of formula (I) wherein R^1 contains a nitro (-NO₂) group may be converted into the corresponding compound wherein R^1 contains an amino (-NH₂) group by treatment with a reducing agent, which may typically be elemental zinc in the presence of an acid, e.g. an organic acid such as acetic acid, or a mineral acid such as hydrochloric acid.

- 25 A compound of formula (I) wherein R^1 contains a N-H moiety may be converted into the corresponding compound wherein R^1 contains a N-methyl moiety by treatment with a methylating agent, e.g. iodomethane, typically under basic conditions, e.g. in the presence of sodium hydride.

- A compound of formula (I) wherein R^2 represents hydrogen may be converted into
30 the corresponding compound wherein R^2 represents optionally substituted C_{1-6} alkyl, e.g. methyl or 2-(dimethylamino)ethyl, by treatment with an appropriate alkylating agent, e.g. iodomethane, methyl carbonate or *N*-(2-chloroethyl)dimethylamine, typically under basic

conditions, e.g. in the presence of sodium hydride, 1,4-diazabicyclo[2.2.2]octane (DABCO) or lithium bis(trimethylsilyl)amide.

A compound of formula (I) wherein R^3 represents nitro ($-\text{NO}_2$) may be converted into the corresponding compound wherein R^3 represents amino ($-\text{NH}_2$) by treatment with a reducing agent, which may typically be elemental zinc in the presence of an acid, e.g. a mineral acid such as hydrochloric acid, or an organic acid such as acetic acid.

A compound of formula (I) wherein R^3 represents amino ($-\text{NH}_2$) may be converted into the corresponding compound wherein R^3 represents $-\text{NHCOR}^d$ by treatment with the appropriate compound of formula Cl-COR^d , typically in the presence of a base, e.g. an organic base such as triethylamine, or an alkali metal carbonate such as potassium carbonate. A compound of formula (I) wherein R^3 represents $-\text{NHCO}(\text{CH}_2)_3\text{Cl}$ may be cyclised to the corresponding compound wherein R^3 represents 2-oxopyrrolidin-1-yl by treatment with a base such as lithium bis(trimethylsilyl)amide or potassium carbonate.

A compound of formula (I) wherein R^3 represents amino ($-\text{NH}_2$) may be converted into the corresponding compound wherein R^3 represents $-\text{NHCO}_2\text{R}^d$ by treatment with the appropriate compound of formula $\text{Cl-CO}_2\text{R}^d$, typically in the presence of a base, e.g. an organic base such as triethylamine. A compound of formula (I) wherein R^3 represents $-\text{NHCO}_2(\text{CH}_2)_2\text{Cl}$ may be cyclised to the corresponding compound wherein R^3 represents 2-oxooxazolidin-3-yl by treatment with a base, e.g. an alkali metal carbonate such as potassium carbonate.

A compound of formula (I) wherein R^3 contains an amino ($-\text{NH}_2$) group may be converted into the corresponding compound wherein R^3 contains a $-\text{NHSO}_2\text{R}^e$ or $-\text{N}(\text{SO}_2\text{R}^e)_2$ moiety by treatment with the appropriate compound of formula $\text{Cl-SO}_2\text{R}^e$, typically in the presence of a base, e.g. an organic base such as triethylamine. A compound of formula (I) wherein R^3 represents $-\text{NHSO}_2(\text{CH}_2)_3\text{Cl}$ may be cyclised to the corresponding compound wherein R^3 represents 1,1-dioxoiso-thiazolidin-2-yl by treatment with a base, e.g. an alkali metal carbonate such as potassium carbonate.

A compound of formula (I) wherein R^3 represents $-\text{NHCO}_2\text{R}^d$ or $-\text{NHSO}_2\text{R}^e$ may be converted into the corresponding compound wherein R^3 represents $-\text{NR}^c\text{CO}_2\text{R}^d$ or $-\text{NR}^c\text{SO}_2\text{R}^e$ in which R^c is C_{1-6} alkyl, e.g. methyl, by treatment with an appropriate alkylating agent, e.g. iodomethane, typically under basic conditions, e.g. in the presence of sodium hydride.

A compound of formula (I) wherein R^3 contains a N-H moiety may be converted into the corresponding compound wherein R^3 contains a N-COCH₃ moiety by treatment with an acetylating agent, which may suitably be acetic anhydride and optionally acetic acid, typically under basic conditions, e.g. in the presence of an organic base such as triethylamine or 4-(dimethylamino)pyridine.

A compound of formula (I) wherein R^3 represents an ester moiety -CO₂R^d (wherein R^d is other than hydrogen) may be converted into the corresponding compound wherein R^3 represents a carboxy moiety -CO₂H by standard saponification methodology, generally by treatment with a base, typically an inorganic base, e.g. an alkali metal hydroxide such as sodium hydroxide or lithium hydroxide.

A compound of formula (I) wherein R^3 represents a carboxy moiety -CO₂H may be converted into the corresponding compound wherein R^3 represents an ester moiety -CO₂R^d (wherein R^d is other than hydrogen) by treatment with the appropriate compound of formula R^d-OH in the presence of a coupling reagent, which will suitably be 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), and an additive such as 1-hydroxybenzotriazole hydrate (HOBT), typically under basic conditions, e.g. in the presence of an organic base such as *N,N*-diisopropylethylamine. A compound of formula (I) wherein R^3 represents -CO₂H may be converted into the corresponding compound wherein R^3 represents *tert*-butoxycarbonyl by treatment with *N,N*-dimethylformamide di-*tert*-butyl acetal.

A compound of formula (I) wherein R^3 represents -CO₂H may be converted into the corresponding compound wherein R^3 represents -CONR^bR^c by treatment with the appropriate compound of formula H-NR^bR^c in the presence of a coupling reagent, which will suitably be 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), and an additive such as 1-hydroxybenzotriazole hydrate (HOBT), typically under basic conditions, e.g. in the presence of an organic base such as *N,N*-diisopropylethylamine or triethylamine. Alternatively, the coupling agent may be 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate (HATU), in which case the reaction will conveniently be performed in the presence of an organic base such as *N,N*-diisopropylethylamine.

A compound of formula (I) wherein R^3 represents pentafluorophenoxycarbonyl may be converted into the corresponding compound wherein R^3 represents -CONR^bR^c by

treatment with the appropriate compound of formula $\text{H-NR}^b\text{R}^c$, typically under basic conditions, e.g. in the presence of an organic base such as *N,N*-diisopropylethylamine.

A compound of formula (I) wherein R^3 represents $-\text{CO}_2\text{H}$ may be converted into the corresponding compound wherein R^3 represents $-\text{CON}(\text{OR}^a)\text{R}^b$ by treatment with the appropriate compound of formula $\text{H-N}(\text{OR}^a)\text{R}^b$, typically in the presence of 2-chloro-4,6-dimethoxy [1,3,5]triazine and an organic base such as *N,N*-diisopropylethylamine.

A compound of formula (I) wherein R^3 represents $-\text{CON}(\text{OR}^a)\text{R}^b$ may be converted into the corresponding compound wherein R^3 represents $-\text{COR}^d$, in which R^d is optionally substituted aryl or optionally substituted heteroaryl, by treatment with the appropriate arylmagnesium bromide or heteroarylmagnesium bromide. Moreover, a compound of formula (I) wherein R^3 represents $-\text{CON}(\text{OR}^a)\text{R}^b$ may be converted into the corresponding compound wherein R^3 represents $-\text{COR}^d$, in which R^d is optionally substituted heteroaryl, by treatment with the appropriate heteroaromatic compound, e.g. thiazole or 1-methyl-1*H*-imidazole, in the presence of a base such as *n*-butyllithium.

A compound of formula (I) wherein R^3 represents halogen, e.g. chloro, may be converted into the corresponding compound wherein R^3 represents hydrogen by treatment with a hydrogenation catalyst, e.g. 10% palladium on charcoal, ideally under transfer hydrogenation conditions, e.g. in the presence of ammonium formate.

A compound of formula (I) wherein R^3 represents halogen, e.g. chloro, may be converted into the corresponding compound wherein R^3 represents optionally substituted aryl or optionally substituted heteroaryl by treatment with the appropriate arylboronic acid or heteroarylboronic acid, in the presence of a transition metal catalyst. A suitable transition metal catalyst is tris(dibenzylideneacetone)dipalladium(0), in which case the reaction is conveniently effected in the presence of 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos) and a base, typically an inorganic base, e.g. an alkali metal phosphate such as potassium phosphate.

Moreover, a compound of formula (I) wherein R^3 represents halogen, e.g. bromo, may be converted into the corresponding compound wherein R^3 represents optionally substituted heteroaryl by treatment with the appropriate tri-*n*-butyltin(IV)-substituted heteroaromatic compound, e.g. 2-(tributylstannanyl)thiazole, in the presence of a transition metal catalyst. A suitable transition metal catalyst is tetrakis(triphenylphosphine)-palladium(0), in which case the reaction is conveniently effected in the presence of lithium chloride.

A compound of formula (I) wherein R^3 represents benzyloxy may be converted into the corresponding compound wherein R^3 represents hydroxy by treatment with a hydrogenation catalyst, e.g. 10% palladium on charcoal, ideally under transfer hydrogenation conditions, e.g. in the presence of ammonium formate.

5 A compound of formula (I) wherein R^3 represents hydroxy may be converted into the corresponding compound wherein R^3 represents an optionally substituted C_{1-6} alkoxy, aryl(C_{1-6})alkoxy or heteroaryl(C_{1-6})alkoxy moiety, e.g. 2-methoxyethoxy or 3-(1,3-dioxo-isoindol-2-yl)propoxy, by treatment with the appropriate alkylating agent, e.g. an alkyl halide, typically an alkyl bromide, such as 1-bromo-2-methoxyethane or 2-(3-bromo-propyl)isoindole-1,3-dione, typically in the presence of a base, e.g. an alkali metal carbonate such as caesium carbonate.

A compound of formula (I) wherein R^3 represents hydroxymethyl may be converted into the corresponding compound wherein R^3 represents formyl (-CHO) by treatment with an oxidising agent, which may suitably be manganese dioxide. A
15 compound of formula (I) wherein R^3 represents -CHO may be converted into the corresponding compound wherein R^3 represents $-CH_2NR^bR^c$ by treatment with the appropriate compound of formula $H-NR^bR^c$ in the presence of a reducing agent, which may suitably be polymer-supported cyanoborohydride (PS-BH₃CN). A compound of formula (I) wherein R^3 represents -CHO may be converted into the corresponding
20 compound wherein R^3 represents 1*H*-imidazol-2-yl by treatment with glyoxal and ammonia.

A compound of formula (I) wherein R^3 represents -COCH₃ may be converted into the corresponding compound wherein R^3 represents isopropylcarbonyl or *tert*-butylcarbonyl by treatment with iodomethane in the presence of lithium bis(trimethylsilyl)-
25 amide.

A compound of formula (I) wherein R^3 contains a -S- moiety may be converted into the corresponding compound wherein R^3 contains a -S(O)- (sulfinyl) moiety by treatment with 3-chloroperoxybenzoic acid (MCPBA). In the appropriate circumstances, prolonged treatment with MCPBA may give rise to the corresponding compound wherein
30 R^3 contains a -S(O)₂- (sulfonyl) moiety.

A compound of formula (I) wherein R^3 contains a cyano moiety may be converted into the corresponding compound wherein R^3 contains an aminocarbonyl or carboxy

moiety by treatment with hydrogen peroxide and a base, e.g. an inorganic base which may suitably be an alkali metal hydroxide, e.g. sodium hydroxide.

A compound of formula (I) wherein R⁵ represents hydrogen may be converted into the corresponding compound wherein R⁵ represents C₁₋₆ alkyl, e.g. methyl, by standard alkylation procedures, e.g. by treatment with an alkylating agent such as iodomethane in the presence of a base such as sodium hydride; or by treatment with a carbonyl compound such as formaldehyde in the presence of a reducing agent such as sodium cyanoborohydride.

Where a mixture of products is obtained from any of the processes described above for the preparation of compounds according to the invention, the desired product can be separated therefrom at an appropriate stage by conventional methods such as preparative HPLC; or column chromatography utilising, for example, silica and/or alumina in conjunction with an appropriate solvent system.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques. In particular, where it is desired to obtain a particular enantiomer of a compound of formula (I) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers. Thus, for example, diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (I), e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation, and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt. In another resolution process a racemate of formula (I) may be separated using chiral HPLC. Moreover, if desired, a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above. Alternatively, a particular enantiomer may be obtained by performing an enantiomer-specific enzymatic biotransformation, e.g. an ester hydrolysis using an esterase, and then purifying only the enantiomerically pure hydrolysed acid from the unreacted ester antipode. Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 3rd edition, 1999. The protecting groups may be removed at any convenient subsequent stage utilising methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds in accordance with this invention potently inhibit the activity of human PI3K α and/or PI3K β and/or PI3K γ and/or PI3K δ .

Enzyme Inhibition Assays

Measurement of the ability of compounds to inhibit the lipid kinase activity of the four class 1 PI3 kinase isoforms (α , β , γ and δ) was performed using a commercially available homogeneous time-resolved fluorescence assay as described by Gray *et al.*, *Anal. Biochem.*, 2003, **313**, 234-245, according to the manufacturer's instructions (Upstate). All assays were performed at 2 μ M ATP and a concentration of purified class 1 PI3 kinase known to generate product within the linear range of the assay. Dilutions of inhibitor in DMSO were added to the assay and compared with assays run in the presence of 2% (v/v) DMSO alone (100% activity). The concentration of inhibitor required to inhibit the enzyme activity by 50% is quoted as the IC₅₀.

When tested in the above assay, the compounds of the accompanying Examples were all found to possess IC₅₀ values for inhibition of activity of human PI3K α and/or PI3K β and/or PI3K γ and/or PI3K δ of 50 μ M or better.

EXAMPLES

Abbreviations

DCM: dichloromethane

DMF: *N,N*-dimethylformamide

DMSO: dimethylsulphoxide

EtOAc: ethyl acetate

Et₂O: diethyl ether

MeOH: methanol

- THF: tetrahydrofuran MeCN: acetonitrile
DMAP: 4-(dimethylamino)pyridine TEA: triethylamine
DABCO: 1,4-diazabicyclo[2.2.2]octane Pd(OAc)₂: palladium(II) acetate
DIPEA: *N,N*-diisopropylethylamine EtOH: ethanol
5 *n*-BuOH: *n*-butanol AcOH: acetic acid
HOBT: 1-hydroxybenzotriazole hydrate LiHMDS: lithium bis(trimethylsilyl)amide
TBME: *tert*-butyl methyl ether TBAF: tetrabutylammonium fluoride
PS-CDI: polymer-supported carbodiimide PS-NCO: polymer-supported isocyanate
SiO₂: silica r.t.: room temperature
10 br: broad h: hour
M: mass
brine: saturated aqueous sodium chloride solution
DMF.DBA: *N,N*-dimethylformamide di-*tert*-butyl acetal
EDC: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
15 HATU: 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate
XPhos: 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
Pd₂(dba)₃: tris(dibenzylideneacetone)dipalladium(0)
PS-BH₃CN: polymer-supported cyanoborohydride
20 HPLC: High Performance Liquid Chromatography
LCMS: Liquid Chromatography Mass Spectrometry
ES+: Electrospray Positive Ionisation

Analytical Conditions

- 25 All NMRs were obtained either at 300 MHz or 400 MHz.
Compounds were named with the aid of MDL ISIS™/Draw version 2.5 SP 2.
All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen atmosphere using dried solvents and glassware.
Compound purities were determined by LCMS using *Method 1 or 2* below.
30 Preparative HPLC for compounds that required it was performed using *Method 3 or 4* below.

Method 1: Waters XBridge, C18, 2.1 x 20 mm, 2.5 µm column.

Mobile phase A: 10 mM ammonium formate in water + 0.1% formic acid

Mobile phase B: acetonitrile + 5% mobile phase A + 0.1% formic acid

Gradient program (flow rate 1.0 mL/min, column temperature 40°C):

	Time	A%	B%
5	0.00	95.0	5.0
	4.00	5.0	95.0
	5.00	5.0	95.0
	5.10	95.0	5.0

10 *Method 2:* Waters XBridge, C18, 2.1 x 20 mm, 2.5 µm column.

Mobile phase A: 10 mM ammonium formate in water + 0.1% ammonia solution

Mobile phase B: acetonitrile + 5% solvent A2 + 0.1% ammonia solution

Gradient Program (flow rate 1.0 mL/min, column temperature 40°C):

	Time	A%	B%
15	0.00	95.0	4.9
	4.00	5.0	95.0
	5.00	5.0	95.0
	5.10	95.0	4.9

20 *Method 3:* Luna C18, 21.2 mm, 5 mm column, pH 2.5. Mobile phase A: 99.92% water and 0.08% formic acid. Mobile phase B: 99.92% MeCN and 0.08% formic acid.

Gradient program (flow rate 25 mL/min, column temperature ambient): variable gradient.

Method 4: Waters XBridge Prep MS C18 ODB, 30 x 50 mm, 5 µm column.

25 Mobile phase A: water. Mobile phase B: MeCN. Mobile Phase C: NH₄HCO₃ in water (40g/5L). Gradient program (flow rate 35 mL/min → 60 mL/min):

	Time	A%	B%	C%	flow rate
30	0.00	85.0	5.0	10.0	35
	1.00	85.0	5.0	10.0	35
	7.00	80.0	20.0	0.0	35
	7.50	5.0	95.0	0.0	35
	9.00	5.0	95.0	0.0	35
	9.10	5.0	95.0	0.0	60

12.00	5.0	95.0	0.0	60
12.50	90.0	10.0	0.0	35
13.00	85.0	5.0	10.0	35
16.00	85.0	5.0	10.0	35

5

INTERMEDIATE 1

(S)-3-[5-(Dimethylcarbamoyl)-2-(trimethylsilyl)-1H-indol-3-ylmethyl]morpholine-4-carboxylic acid *tert*-butyl ester

- 10 To a stirred solution of 4-amino-3-iodo-*N,N*-dimethylbenzamide (6.70 g, 23.10 mmol) in DMF (100 mL) was added (S)-3-[3-(trimethylsilyl)prop-2-ynyl]morpholine-4-carboxylic acid *tert*-butyl ester (6.86 g, 23.10 mmol), LiCl (0.97 g, 23.10 mmol) and Na₂CO₃ (4.90 g, 46.21 mmol). The reaction mixture was then degassed before Pd(OAc)₂ (0.26 g, 2.31 mmol) was added and the mixture further degassed. The solution was
- 15 heated to 100°C for 16 h. After cooling to room temperature, the solids were removed by filtration through celite and the remaining solution was diluted with DCM (250 mL), washed with brine (2 x 250 mL), dried (sodium sulphate), filtered and concentrated *in vacuo* to give a crude oil. Purification by column chromatography (SiO₂, 20-60% EtOAc/hexanes) gave the *title compound* (7.53 g, 71%) as an orange solid. δ_{H} (CDCl₃)
- 20 8.02 (s, 1H), 7.92 (s, 1H), 7.35 (d, *J* 8.3 Hz, 1H), 7.32-7.27 (m, 1H), 4.33-4.23 (m, 1H), 3.99-3.79 (m, 2H), 3.69-3.60 (m, 1H), 3.52-3.39 (m, 2H), 3.38-3.26 (m, 2H), 3.07 (s, 6H), 2.96 (s, 1H), 1.45 (s, 9H), 0.43 (s, 9H). LCMS (ES+) 460 (M+H)⁺.

INTERMEDIATE 2

25

(S)-3-[5-(Dimethylcarbamoyl)-1-methyl-2-(trimethylsilyl)-1H-indol-3-ylmethyl]-morpholine-4-carboxylic acid *tert*-butyl ester

- Intermediate 1* (7.53 g, 16.41 mmol) was dissolved in THF (100 mL), cooled to -78°C and treated with methyl iodide (3.49 g, 24.62 mmol). LiHMDS (1M in THF, 18 mL, 18.00 mmol) was added and the reaction mixture was stirred at -78°C for 30 minutes.
- 30 After warming to room temperature the mixture was diluted with ethyl acetate (100 mL), washed with saturated ammonium chloride solution (2 x 100 mL), the organic phase dried (sodium sulphate) and concentrated *in vacuo*. Purification by column chromatography

(SiO₂, 20-60% EtOAc/hexanes) yielded the *title compound* (5.60 g, 72%) as a pale brown foam. δ_{H} (CDCl₃) 8.01-7.96 (m, 1H), 7.44-7.38 (m, 1H), 7.32 (s, 1H), 4.28-4.21 (m, 1H), 3.97 (dd, *J* 10.9, 2.0 Hz, 1H), 3.90 (s, 3H), 3.69-3.46 (m, 2H), 3.40-3.31 (m, 2H), 3.15 (s, 6H), 3.00 (dd, *J* 13.6, 3.3 Hz, 2H), 1.86 (s, 1H), 1.52 (s, 9H), 0.56 (s, 9H). LCMS (ES+) 474 (M+H)⁺.

INTERMEDIATE 3

1-Methyl-3-[(*S*)-morpholin-3-ylmethyl]-1*H*-indole-5-carboxylic acid dimethylamide

Intermediate 2 (5.60 g, 11.84 mmol) was dissolved in MeOH (20 mL) and treated with 4M HCl in 1,4-dioxane (50 mL). The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated *in vacuo* and then partitioned between ethyl acetate (100 mL) and sodium hydrogencarbonate solution (100 mL). The aqueous layer was washed with DCM (3 x 100 mL). The combined organic layers were dried (sodium sulphate) and concentrated *in vacuo* yielding the *title compound* (3.58 g, 100%) as a brown oil. δ_{H} (CDCl₃) 7.74 (s, 1H), 7.33 (m, 2H), 6.97 (s, 1H), 4.15-4.07 (m, 1H), 3.89 (dd, *J* 10.9, 2.5 Hz, 1H), 3.85-3.77 (m, 4H), 3.55 (td, *J* 10.6, 3.5 Hz, 1H), 3.30 (t, *J* 9.9 Hz, 1H), 3.12 (s, 6H), 2.90-2.79 (m, 3H), 2.63 (dd, *J* 14.1, 9.1 Hz, 1H). LCMS (ES+) 302 (M+H)⁺.

INTERMEDIATE 4

6-(Acetylamino)nicotinic acid

6-Aminonicotinic acid (1 g, 7.24 mmol) was dissolved in pyridine (30 mL) and treated with acetic anhydride (0.81 mL, 7.96 mmol). The reaction mixture was heated at 130°C for 16 h. After cooling, the mixture was stirred at room temperature for 2 h. A precipitate was formed, which was filtered and dried on a freeze drier, yielding the *title compound* (641 mg, 49%) as a white solid. δ_{H} (d₆-DMSO) 13.08 (br s, 1H), 10.82 (s, 1H), 8.82-8.80 (m, 1H), 8.24 (dd, *J* 8.6, 2.3 Hz, 1H), 8.17 (d, *J* 8.6 Hz, 1H), 2.13 (s, 3H). LCMS (ES+) 181 (M+H)⁺.

INTERMEDIATE 5**2-(Acetylamino)thiazole-5-carboxylic acid**

2-Amino-1,3-thiazole-5-carboxylic acid (1 g, 6.94 mmol) was dissolved in pyridine (30 mL) and treated with acetic anhydride (722 mg, 7.63 mmol). The reaction mixture was heated at 130°C for 16 h. After cooling, the mixture was stirred at room temperature for 2 h. A precipitate was formed, which was filtered and dried on a freeze drier, yielding the *title compound* (920 mg, 71%) as a white solid. δ_{H} (d_6 -DMSO) 13.04 (br s, 1H), 12.45 (s, 1H), 8.04 (s, 1H), 2.19 (s, 3H). LCMS (ES+) 187 (M+H)⁺.

INTERMEDIATE 6**(S)-3-[5-Chloro-2-(trimethylsilanyl)-1H-indol-3-ylmethyl]morpholine-4-carboxylic acid tert-butyl ester**

Prepared from 4-chloro-2-iodoaniline and (S)-3-[3-(trimethylsilanyl)prop-2-ynyl]morpholine-4-carboxylic acid *tert*-butyl ester using the procedure described for *Intermediate 1* and the method described in WO 2008/001076.

INTERMEDIATE 7**(S)-3-[5-(*o*-Tolyl)-2-(trimethylsilanyl)-1H-indol-3-ylmethyl]morpholine-4-carboxylic acid tert-butyl ester**

To a stirred solution of *Intermediate 6* (224 mg, 530 μmol) in *n*-butanol (4 mL) were added *o*-tolylboronic acid (108 mg, 795 μmol), potassium phosphate (225 mg, 1.06 mmol), XPhos (10 mg, 21 μmol) and tris(dibenzylideneacetone)dipalladium(0) (5 mg, 5.3 μmol). The reaction mixture was degassed, heated at reflux overnight, cooled and partitioned between DCM and water. The organic layer was separated, dried (magnesium sulphate), and concentrated *in vacuo* to afford a yellow oil which was chromatographed on silica gel to afford the *title compound* (223 mg, 88%) as a colourless oil. δ_{H} (CDCl_3) 8.16-7.95 (m, 1H), 7.97-7.57 (m, 1H), 7.52-6.98 (m, 6H), 4.48-4.28 (m, 1H), 4.27-4.05 (m, 1H), 4.05-3.85 (m, 2H), 3.84-3.64 (m, 1H), 3.61-3.24 (m, 4H), 3.13-2.91 (m, 1H), 2.31 (m, 2H), 1.35-1.25 (m, 9H), 0.47 (m, 9H). LCMS (ES+) 479.2 (M+H)⁺.

INTERMEDIATE 8

(S)-3-[1-Methyl-5-(*o*-tolyl)-2-(trimethylsilyl)-1*H*-indol-3-ylmethyl]morpholine-4-carboxylic acid *tert*-butyl ester

- 5 To a stirred solution of *Intermediate 7* (223 mg, 466 μ mol) in THF (5 mL) at -78°C were added iodomethane (87 μ L, 1.40 mmol) and LiHMDS (1.0M, 700 μ L). The reaction mixture was stirred at r.t. for 1 h and partitioned between brine and Et₂O. The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*, to afford the *title compound* (265 mg, 100%) as a colourless oil which was used without
10 further purification in the next reaction. LCMS (ES+) 493.2 (M+H)⁺.

INTERMEDIATE 9

(S)-3-[5-(4-Fluorophenyl)-2-(trimethylsilyl)-1*H*-indol-3-ylmethyl]morpholine-4-carboxylic acid *tert*-butyl ester

- 15 To a stirred solution of *Intermediate 6* (322 mg, 762 μ mol) in *n*-butanol (6 mL) were added 4-fluoroboronic acid (160 mg, 1.14 mmol), potassium phosphate (323 mg, 1.52 mmol), XPhos (14.5 mg, 30 μ mol) and tris(dibenzylideneacetone)dipalladium(0) (7 mg, 7.6 μ mol). The reaction mixture was degassed, heated at reflux for 4 h, cooled and
20 partitioned between diisopropyl ether and water. The organic layer was separated, washed with brine, dried (magnesium sulphate) and concentrated *in vacuo* to afford the *title compound* (574 mg, 100%) as a yellow oil which was used without further purification in the next reaction. LCMS (ES+) 479.2 (M+H)⁺.

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INTERMEDIATE 10

5-(4-Fluorophenyl)-3-[(*S*)-morpholin-3-ylmethyl]-1*H*-indole

- Intermediate 9* (574 mg, 760 μ mol) was dissolved in HCl (4M solution in 1,4-dioxane). After 3 h the solution was concentrated *in vacuo*, the residue dissolved in DCM
30 (5 mL) and shaken with aqueous sodium carbonate. The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo* to afford the *title compound* (275 mg, 100%) as a yellow oil which was used without further purification in the next reaction. LCMS (ES+) 311.2 (M+H)⁺.

INTERMEDIATES 11 TO 13

Prepared using the procedures described for *Intermediates 1 to 3* and the methods described in WO 2008/001076.

Intermediate 11: 1-Methyl-3-[(*S*)-morpholin-3-ylmethyl]-5-phenyl-1*H*-indole

Intermediate 12: 1-Methyl-5-(2-methylimidazol-1-yl)-3-[(*S*)-morpholin-3-ylmethyl]-1*H*-indole

Intermediate 13: (*S*)-3-(5-Benzyloxy-1-methyl-1*H*-indol-3-ylmethyl)morpholine-4-carboxylic acid *tert*-butyl ester

INTERMEDIATE 14

(6-Chloropyridin-3-yl)-{(S)-3-[3-(trimethylsilyl)prop-2-ynyl]morpholin-4-yl}-methanone

To a stirred solution of (*S*)-3-[3-(trimethylsilyl)prop-2-ynyl]morpholine (2.9 g, 12.4 mmol) and 6-chloronicotinoyl chloride (2.18 g, 12.4 mmol) in DCM (30 mL) at 0-5°C was added triethylamine (1.8 mL, 24.8 mmol). The reaction was stirred at r.t. for 2 h and then partitioned between ethyl acetate (50 mL) and brine (50 mL). The organic layer was separated, dried (MgSO₄) and concentrated *in vacuo*. The resulting oil was chromatographed (SiO₂, 0-50% EtOAc/hexanes), yielding the *title compound* (830 mg, 100%) as a colourless oil. LCMS (ES⁺) 337 (M+H)⁺.

INTERMEDIATE 15

(6-Methoxypyridin-3-yl)-{(S)-3-[3-(trimethylsilyl)prop-2-ynyl]morpholin-4-yl}-methanone

To a stirred solution of (*S*)-3-[3-(trimethylsilyl)prop-2-ynyl]morpholine (500 mg, 2.5 mmol) and 6-methoxynicotinoyl chloride (572 mg, 2.75 mmol) in DCM (10 mL) at 0-5°C was added triethylamine (1.1 mL, 7.5 mmol). The reaction was stirred at r.t. for 1 h and then partitioned between ethyl acetate (20 mL) and brine (20 mL). The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The

resulting oil was chromatographed (SiO₂, 0-50% EtOAc/hexanes), yielding the *title compound* (755 mg, 91%) as a yellow oil. LCMS (ES⁺) 333 (M+H)⁺.

INTERMEDIATE 16

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(S)-3-[5-(Dimethylaminomethyl)-1-methyl-1*H*-indol-3-ylmethyl]morpholine-4-carboxylic acid *tert*-butyl ester

To a stirred solution of (S)-3-[5-(dimethylcarbamoyl)-1-methyl-1*H*-indol-3-ylmethyl]morpholine-4-carboxylic acid *tert*-butyl ester (250 mg, 0.63 mmol) in THF (10 mL) at 0°C was added lithium aluminium hydride (125 mg, 3.1 mmol). The reaction mixture was stirred at r.t. for 3 h, then quenched with water (625 µL) and stirred for 15 minutes. The reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to afford the *title compound* (402 mg) as a brown oil. LCMS (ES⁺) 388 (M+H)⁺.

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INTERMEDIATE 17

{1-Methyl-3-[(3*S*)-morpholin-3-ylmethyl]-1*H*-indol-5-yl}methanol

To a stirred solution of methyl 1-methyl-3-[(3*S*)-morpholin-3-ylmethyl]-1*H*-indole-5-carboxylate (WO 2008/001076, *Intermediate 77*; 200 mg, 0.69 mmol) in THF (10 mL) at 0°C was added lithium aluminium hydride (130 mg, 3.45 mmol). The reaction mixture was stirred at r.t. for 16 h, then quenched with water (600 µL) and stirred for 30 minutes. The reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to afford the *title compound* (260 mg) as a colourless oil. LCMS (ES⁺) 261 (M+H)⁺.

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INTERMEDIATE 18

[(S)-3-(5-Hydroxymethyl-1-methyl-1*H*-indol-3-ylmethyl)morpholin-4-yl]-(6-methoxy-pyridin-3-yl)-methanone

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To a stirred solution of *Intermediate 17* (260 mg, 1.0 mmol) in DCM (5 mL) at 0°C were added triethylamine (285 µL, 2.0 mmol) and 6-methoxynicotinoyl chloride (120 mg, 0.7 mmol). The reaction mixture was stirred at r.t. for 1 h. The mixture was

partitioned between ethyl acetate (10 mL) and water (10 mL). The organic layer was dried (phase separator), concentrated *in vacuo* and chromatographed (SiO₂, 2:1 EtOAc: hexanes), yielding the *title compound* (210 mg, 76%) as a colourless oil. LCMS (ES⁺) 396 (M+H)⁺.

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INTERMEDIATE 19

3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carbaldehyde

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To a stirred solution of *Intermediate 18* (1.03 g, 2.6 mmol) in DCM (20 mL) was added activated MnO₂ (2.26 g, 26 mmol). The reaction mixture was stirred for 18 h. More MnO₂ (226 mg, 2.6 mmol) was added and the reaction stirred for 1 h. The reaction mixture was filtered through celite and concentrated *in vacuo* to give the *title compound* (919 mg, 90%) as a colourless oil. LCMS (ES⁺) 394 (M+H)⁺.

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INTERMEDIATE 20

1-Methyl-3-[(3S)-morpholin-3-ylmethyl]-5-nitro-1H-indole

Prepared using the method described in WO2008/001076.

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INTERMEDIATE 21

[(S)-3-(5-Amino-1-methyl-1H-indol-3-ylmethyl)morpholin-4-yl]-(6-methoxypyridin-3-yl)-methanone

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To a stirred solution of *Example 306* (3.1 g, 7.56 mmol) in MeOH (200 mL) was added zinc (3.0 g, 4.59 mol) and conc. HCl (3 mL). The reaction mixture was heated at 50°C for 30 minutes until a clear solution was obtained. The excess zinc was removed by filtration and the solution was concentrated *in vacuo*. The residue was partitioned between saturated sodium carbonate solution (200 mL) and DCM (200 mL). The aqueous layer was washed with DCM (2 x 100 mL). The organic layers were combined, dried (sodium sulphate), filtered and concentrated *in vacuo* to yield the *title compound* (3.0 g, 100%) as a pale pink foam. δ_H (d₆-DMSO at 110°C) 8.05 (d, *J* 2.3 Hz, 1H), 7.43 (dd, *J* 8.6, 2.3 Hz, 1H), 7.05 (d, *J* 8.6 Hz, 1H), 6.82 (s, 1H), 6.71 (d, *J* 8.6 Hz, 1H), 6.57

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(dd, J 8.6, 2.0 Hz, 1H), 6.51 (s, 1H), 4.25-4.18 (m, 1H), 4.12-4.03 (m, 2H), 3.95-3.89 (m, 4H), 3.85-3.75 (m, 2H), 3.63 (s, 3H), 3.57 (dd, J 11.4, 3.0 Hz, 1H), 3.50-3.43 (m, 2H), 3.10 (dd, J 14.4, 8.3 Hz, 1H), 2.99-2.93 (m, 1H). LCMS (ES^+) 381 ($M+H$)⁺.

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INTERMEDIATE 22

1-{3-[(*S*)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-2-(trimethylsilyl)-1*H*-indol-5-yl}ethanone

To a stirred degassed solution of *Intermediate 15* (2.0 g, 6.0 mmol) in DMF (25 mL) were added 1-(4-amino-3-iodophenyl)ethanone (1.6 g, 6.0 mmol), Pd(OAc)₂ (67 mg, 0.3 mmol), LiCl (253 mg, 6.0 mmol) and sodium carbonate (1.28 g, 12.0 mmol). The reaction mixture was heated at 90°C for 21 h, then filtered and partitioned between water (50 mL) and ethyl acetate (150 mL). The organic layer was washed with water (5 x 40 mL) and brine (40 mL), dried (sodium sulphate), concentrated *in vacuo* and chromatographed (SiO₂, 0-25% ethyl acetate/hexanes) to give the *title compound* (1.15 g, 41%) as a white solid. δ_H (d_6 -DMSO at 110°C) 10.41 (d, J 0.8 Hz, 1H), 8.08 (d, J 0.8 Hz, 1H), 7.76 (m, 1H), 7.48 (dd, J 8.6, 1.5 Hz, 1H), 7.21 (d, J 8.6 Hz, 1H), 7.19-7.15 (m, 1H), 6.46 (d, J 8.6 Hz, 1H), 4.28-4.19 (m, 1H), 3.73 (dd, J 10.9, 2.8 Hz, 1H), 3.67 (s, 3H), 3.61-3.54 (m, 1H), 3.50 (m, 1H), 3.44-3.25 (m, 3H), 3.18 (dd, J 14.1, 8.8 Hz, 1H), 2.96 (dd, J 14.1, 6.3 Hz, 1H), 2.33 (s, 3H), 0.16 (m, 9H). LCMS (ES^+) 466 ($M+H$)⁺.

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INTERMEDIATE 23

(6-Methylpyridin-3-yl)-{(*S*)-3-[3-(trimethylsilyl)prop-2-ynyl]morpholin-4-yl}-methanone

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To a stirred solution of (*S*)-3-[3-(trimethylsilyl)prop-2-ynyl]morpholine (6.11 g, 31 mmol), 6-methylnicotinic acid (4.25 g, 31 mmol), HOBt (4.74 g, 31 mmol) and 4-methylmorpholine (6.8 mL, 62 mmol) in DMF (50 mL) was added EDC (5.95 g, 31 mmol). The reaction mixture was stirred at r.t. for 16 h and then concentrated *in vacuo*. The residue was partitioned between ethyl acetate (100 mL) and brine (100 mL). The organic layer was washed with brine (3 x 100 mL), separated, dried (sodium sulphate) and concentrated *in vacuo*. The residue was chromatographed (SiO₂, 50-100% EtOAc/hexanes), yielding a mixture of product and HOBt. This was dissolved in EtOAc (50

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mL), washed with 2M sodium carbonate solution (3 x 50 mL) and brine (50mL), dried (sodium sulphate) and concentrated *in vacuo* to yield the *title compound* (9.16 g, 93%) as a brown oil. δ_{H} (CDCl_3) 8.46 (d, J 1.9 Hz, 1H), 7.57 (dd, J 7.9, 1.9 Hz, 1H), 7.09 (d, J 7.9 Hz, 1H), 3.77 (m, 3H), 3.48 (dd, J 11.7, 2.8 Hz, 1H), 3.40-3.32 (1H, m), 3.21 (br s, 2H), 2.70 (dd, J 17.0, 7.9 Hz, 1H), 2.57 (dd, J 16.8, 7.9 Hz, 1H), 2.47 (s, 3H), 0.00 (m, 9H). LCMS (ES^+) 317 ($\text{M}+\text{H}$)⁺.

INTERMEDIATE 24

10 3-Chloropropanesulfonic acid {3-[(*S*)-4-(6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indol-5-yl} amide

To a stirred solution of *Intermediate 21* (150 mg, 0.395 mmol) in DCM (5 mL) was added TEA (83 μL , 0.593 mmol) followed by 3-chloropropanesulfonyl chloride (48 μL , 0.395 mmol). The reaction mixture was stirred at r.t. for 2 h, then diluted with DCM (5 mL) and washed with brine (2 x 10mL). The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried (phase separator) and concentrated *in vacuo*. The residue was chromatographed (SiO_2 , 60-100% EtOAc/hexanes), yielding the *title compound* (142 mg, 69%) as a white solid. δ_{H} (d_6 -DMSO at 110°C) 9.03 (s, 1H), 7.94-7.91 (m, 1H), 7.41-7.38 (m, 1H), 7.37-7.30 (m, 2H), 7.08 (dd, J 8.6, 1.5 Hz, 1H), 7.03 (s, 1H), 6.68 (d, J 8.3 Hz, 1H), 4.34-4.26 (m, 1H), 3.94-3.87 (m, 4H), 3.84-3.74 (m, 2H), 3.73 (s, 3H), 3.72-3.68 (m, 2H), 3.61 (dd, J 11.6, 3.3 Hz, 1H), 3.56-3.47 (m, 2H), 3.19-3.10 (m, 4H), 2.24-2.16 (m, 2H). LCMS (ES^+) 521 ($\text{M}+\text{H}$)⁺.

INTERMEDIATE 25

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7-Acetyl-3-[(*S*)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-2-(trimethylsilyl)-1*H*-indole-5-carboxylic acid methyl ester

To a stirred degassed solution of *Intermediate 23* (500 mg, 1.58 mmol), 3-acetyl-4-amino-5-iodobenzoic acid methyl ester (506 mg, 1.58 mmol), LiCl (67 mg, 1.58 mmol) and sodium carbonate (335 mg, 3.16 mmol) in DMF (20 mL) was added $\text{Pd}(\text{OAc})_2$ (18 mg, 0.08 mmol). The reaction mixture was further degassed, then heated at 90°C for 16 h. The reaction mixture was cooled and partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was washed with water (3 x 50 mL), dried (sodium

sulphate), concentrated *in vacuo* and chromatographed (SiO₂, 60-100% ethyl acetate/hexanes), to give the *title compound* (130 mg, 30%) as an off-white solid. LCMS (ES⁺) 505 (M+H)⁺.

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INTERMEDIATE 26

7-Acetyl-3-[(S)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid methyl ester

To a stirred solution of *Intermediate 25* (130 mg, 0.299 mmol) in MeOH (5 mL) was added HCl (4M in 1,4-dioxane, 5 mL). The reaction mixture was stirred at r.t. for 4 h, then concentrated *in vacuo*. The residue was partitioned between 2M sodium carbonate solution (10 mL) and DCM (10 mL). The organic layer was dried (phase separator) and concentrated *in vacuo*, yielding the *title compound* (100 mg, 77%) as a brown foam. LCMS (ES⁺) 436 (M+H)⁺.

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INTERMEDIATE 27

7-Acetyl-3-[(S)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid

To a stirred solution of *Intermediate 26* (100 mg, 0.229 mmol) in MeOH (5 mL) and THF (5 mL) was added 2M NaOH solution (5 mL). The reaction mixture was heated at 50°C for 30 minutes, then concentrated *in vacuo* and passed down a Biotage 103 resin to remove any inorganic salts. The resin was washed with MeOH (25 mL). The resulting filtrate was concentrated *in vacuo*, yielding the *title compound* (~100 mg, 100%) as a colourless oil. LCMS (ES⁺) 422 (M+H)⁺.

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INTERMEDIATE 28

(4-Amino-3-iodophenyl)-phenyl-methanone

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To a stirred solution of (4-aminophenyl)-phenyl-methanone (3 g, 15 mmol) and calcium carbonate (2.4 g, 15 mmol) in methanol (50 mL) and water (10 mL) was added ICl (3.4 g, 15 mmol). The reaction mixture was stirred at r.t. for 16 h, then concentrated *in vacuo*. The brown residue was partitioned between EtOAc (100 mL) and saturated

sodium bisulphite solution (100 mL). The organic layer was dried (sodium sulphate), filtered and concentrated *in vacuo*. The residue was washed with DCM (50 mL), yielding the *title compound* (1.1 g, 23%) as a pale grey solid. δ_{H} (d_6 -DMSO) 7.99 (d, J 2.1 Hz, 1H), 7.67-7.58 (m, 4H), 7.57-7.44 (m, 3H), 6.80 (d, J 8.7 Hz, 1H), 6.24-6.16 (m, 2H).

5 LCMS (ES^+) 324 ($\text{M}+\text{H}$)⁺.

INTERMEDIATE 29

10 {(S)-3-[5-Benzoyl-2-(trimethylsilanyl)-1H-indol-3-ylmethyl]morpholin-4-yl}-(6-methoxypyridin-3-yl)-methanone

To a stirred solution of *Intermediate 28* (179 mg, 0.5 mmol) in DMF (3 mL) were added *Intermediate 15* (170 mg, 0.5 mmol), LiCl (20 mg, 0.5 mmol) and sodium carbonate (150 mg, 1.0 mmol). The reaction mixture was then degassed before $\text{Pd}(\text{OAc})_2$ (7 mg, 0.025 mmol) was added and the mixture further degassed. The solution was
15 heated to 90°C for 16 h. After cooling to r.t., the reaction mixture was partitioned between DCM (50 mL) and water (20 mL). The organic layer was separated and washed with water (4 x 20 mL), dried (sodium sulphate), filtered and concentrated *in vacuo*. The dark oil was purified by column chromatography (SiO_2 , 0-100% EtOAc/hexanes) to give the *title compound* (208 mg, 78%) as a colourless oil. LCMS (ES^+) 528 ($\text{M}+\text{H}$)⁺.

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INTERMEDIATE 30

[(S)-3-(5-Benzoyloxy-1-methyl-1H-indol-3-ylmethyl)morpholin-4-yl]-(6-methylpyridin-3-yl)-methanone

25 *Intermediate 13* (975 mg, 2.24 mmol) was dissolved in 4M HCl in 1,4-dioxane (15 mL). After 1 h the solution was concentrated *in vacuo* and the residue partitioned between DCM (10 mL) and sodium carbonate solution (20 mL). The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. To the brown oil in DCM (10 mL) were added 6-methylnicotinic acid (337 mg, 2.46 mmol), HOBT (342 mg, 2.24 mmol), DIPEA (795 μL , 4.5 mmol) and EDC (688 mg, 3.6 mmol). The reaction
30 mixture was stirred at r.t. for 16 h, then shaken with water (20 mL). The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*, yielding the *title*

compound (1.0 g, 98%) as a brown oil. The crude product was elaborated further without additional purification. LCMS (ES^+) 456 ($\text{M}+\text{H}$) $^+$.

INTERMEDIATE 31

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{(S)-3-[5-(Methanesulfonyl)-2-(trimethylsilyl)-1H-indol-3-ylmethyl]morpholin-4-yl}-(6-methoxypyridin-3-yl)-methanone

To a stirred solution of 2-iodo-4-(methanesulfonyl)phenylamine (158 mg, 0.53 mmol) in DMF (3 mL) were added *Intermediate 15* (175 mg, 0.53 mmol), LiCl (22 mg, 0.53 mmol) and sodium carbonate (112 mg, 1.6 mmol). The reaction mixture was then degassed before $\text{Pd}(\text{OAc})_2$ (6 mg, 0.025 mmol) was added and the mixture further degassed. The solution was heated to 100°C for 2 h. After cooling to r.t., the reaction mixture was partitioned between DCM (10 mL) and water (10 mL). The organic layer was separated and washed with water (4 x 10 mL), dried (sodium sulphate), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , 0-100% EtOAc/hexanes) to give the *title compound* (107 mg, 40%) as a white solid. LCMS (ES^+) 502 ($\text{M}+\text{H}$) $^+$.

INTERMEDIATE 32

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3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-2-(trimethylsilyl)-1H-indole-5-sulfonic acid dimethylamide

To a stirred solution of 4-amino-*N,N*-dimethyl-3-iodobenzenesulfonamide (173 mg, 0.53 mmol) in DMF (3 mL) were added *Intermediate 15* (175 mg, 0.53 mmol), LiCl (22 mg, 0.53 mmol) and sodium carbonate (112 mg, 1.6 mmol). The reaction mixture was then degassed before $\text{Pd}(\text{OAc})_2$ (6 mg, 0.025 mmol) was added and the mixture further degassed. The solution was heated to 100°C for 2 h. After cooling to r.t., the reaction mixture was partitioned between DCM (10 mL) and water (10 mL). The organic layer was separated and washed with water (4 x 10 mL), dried (sodium sulphate), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , 0-100% EtOAc/hexanes) to give the *title compound* (142 mg, 51%) as a white solid. LCMS (ES^+) 530 ($\text{M}+\text{H}$) $^+$.

INTERMEDIATE 33**1-Methyl-3-[(S)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid**

5 To a stirred solution of *Example 280* (2.86 g, 7.04 mmol) in MeOH (50 mL) was added 10% NaOH solution (2.5M, 10 mL). The reaction mixture was heated to reflux and stirred for 5 h. The reaction mixture was cooled to r.t., acidified with 1M HCl and then concentrated *in vacuo*. The residue was washed with DCM to give a precipitate, which was washed with water and filtered. The resulting solid was washed with DCM (3
10 x 50 mL) and the combined organic layers were dried (sodium sulphate) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-20% MeOH/EtOAc) to give the *title compound* (2.52 mg, 91%) as a white solid. δ_H (d₆-DMSO at 110°C) 8.18-8.13 (m, 1H), 8.09-8.05 (m, 1H), 7.77 (dd, *J* 8.8, 1.5 Hz, 1H), 7.40 (d, *J* 8.6 Hz, 1H), 7.27-7.21 (m, 1H), 7.13 (s, 1H), 7.07-7.01 (m, 1H), 4.35-4.27 (m, 1H), 3.97-3.91
15 (m, 1H), 3.87-3.81 (m, 2H), 3.81-3.75 (m, 3H), 3.64 (dd, *J* 11.4, 3.0 Hz, 1H), 3.50 (m, 2H), 3.19 (d, *J* 7.6 Hz, 2H), 2.43 (s, 3H). LCMS (ES⁺) 394 (M+H)⁺.

INTERMEDIATE 34**{(S)-3-[5-Bromo-2-(trimethylsilanyl)-1H-indol-3-ylmethyl]morpholin-4-yl}-(6-methoxy-pyridin-3-yl)-methanone**

To a stirred degassed solution of *Intermediate 15* (332 mg, 1.0 mmol) in DMF (5 mL) were added 4-bromo-2-iodoaniline (298 mg, 1.0 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), LiCl (42 mg, 1.0 mmol) and sodium carbonate (212 mg, 2.0 mmol). The reaction
25 mixture was heated at 100°C for 2 h, then filtered and partitioned between water (25 mL) and ethyl acetate (25 mL). The organic layer was washed with water (5 x 40 mL) and brine (40 mL), dried (sodium sulphate) and concentrated *in vacuo* to give the *title compound* (282 mg, 56%) as a brown solid. LCMS (ES⁺) 503 (M+H)⁺.

INTERMEDIATE 35

[(S)-3-(5-Bromo-1H-indol-3-ylmethyl)morpholin-4-yl]-(6-methoxypyridin-3-yl)-methanone

- 5 To a stirred solution of *Intermediate 34* (282 mg, 0.56 mmol) in MeOH (5 mL) was added HCl (4M in 1,4-dioxane, 5 mL). The reaction mixture was stirred at r.t. for 4 h, then concentrated *in vacuo*. The residue was partitioned between 2M sodium carbonate solution (10 mL) and DCM (10 mL). The organic layer was dried (phase separator) and concentrated *in vacuo*, yielding the *title compound* (104 mg, 43%) as an off-white foam.
- 10 LCMS (ES⁺) 431 (M+H)⁺.

INTERMEDIATE 36

[(S)-3-(5-Hydroxymethyl-1-methyl-1H-indol-3-ylmethyl)morpholin-4-yl]-(6-methylpyridin-3-yl)-methanone

- 15 To a stirred solution of *Intermediate 17* (3.33 g, 12.8 mmol) in DCM (50 mL) at 0°C were added triethylamine (7.4 mL, 51.2 mmol) and 6-methylnicotinoyl chloride (3.07 mg, 12.8 mmol). The reaction mixture was stirred at r.t. for 30 minutes. The mixture was partitioned between DCM (50 mL) and water (100 mL). The organic layer was dried
- 20 (phase separator), concentrated *in vacuo* and chromatographed (SiO₂, 5% MeOH/EtOAc), yielding the *title compound* (2.78 g, 57%) as a yellow solid. LCMS (ES⁺) 380 (M+H)⁺.

INTERMEDIATE 37

1-Methyl-3-[(S)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1H-indole-5-carbaldehyde

- 25 To a stirred solution of *Intermediate 36* (2.78 g, 7.34 mmol) in DCM (50 mL) was added activated MnO₂ (6.44 g, 73.4 mmol). The reaction mixture was stirred for 2 h, then filtered through celite and concentrated *in vacuo* to give the *title compound* (3.66 g,
- 30 100%) as a yellow oil. LCMS (ES⁺) 378 (M+H)⁺.

INTERMEDIATE 38

[(S)-3-(5-Amino-1H-indol-3-ylmethyl)morpholin-4-yl]-(6-methoxypyridin-3-yl)-methanone

To a stirred solution of *Example 372* (200 mg, 0.51 mmol) and zinc (300 mg, 4.59 mmol) in MeOH (13 mL) was added conc. hydrochloric acid (33 drops). The reaction mixture was stirred at 50°C for 10 minutes and then allowed to cool to r.t. The reaction mixture was filtered and the filtrate concentrated *in vacuo*. The residue was partitioned between DCM (25 mL) and saturated sodium carbonate solution (25 mL). A white precipitate began to form. NaOH pellets (4) were added and the reaction was stirred for 30 minutes. The aqueous layer was separated, then washed with DCM (2 x 50 mL) and 10% MeOH in DCM (2 x 50 mL). The combined organic layers were dried (sodium sulphate), filtered and concentrated *in vacuo*, yielding the *title compound* (200 mg, 100%) as a beige foam. LCMS (ES⁺) 367 (M+H)⁺.

INTERMEDIATE 39

3-Chloropropanesulfonic acid {3-[(S)-4-(6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1H-indol-5-yl}amide

To a stirred solution of *Intermediate 38* (428 mg, 1.17 mmol) in DCM (15 mL) was added triethylamine (0.25 mL, 1.76 mmol), followed by 3-chloropropanesulphonyl chloride (207 mg, 1.17 mmol). The reaction mixture was stirred at r.t. for 16 h. Additional 3-chloropropanesulphonyl chloride (62 mg, 0.35 mmol) was added and the reaction mixture stirred for 3 h. The reaction was not complete, so additional 3-chloropropanesulphonyl chloride (41 mg, 0.23 mmol) and triethylamine (0.08 mL, 0.59 mmol) were added and the reaction mixture stirred for 40 minutes. The reaction was still not complete, so additional 3-chloropropanesulphonyl chloride (31 mg, 0.18 mmol) was added and the reaction mixture stirred for 40 minutes. The reaction mixture was partitioned between DCM (25 mL) and brine (2 x 40 mL). The combined aqueous layers were extracted with DCM (2 x 40 mL). The combined organic layers were dried (sodium sulphate), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 60-100% EtOAc/hexanes), yielding the *title compound* (291 mg, 49%) as a beige foam. δ_{H} (d₆-DMSO at 110°C) 10.63-10.54 (m, 1H), 8.98 (s, 1H), 7.95

(d, J 2.3 Hz, 1H), 7.38 (s, 1H), 7.35-7.29 (m, 2H), 7.08 (d, J 2.0 Hz, 1H), 7.02 (dd, J 8.6, 2.0 Hz, 1H), 6.66 (d, J 8.3 Hz, 1H), 4.36-4.29 (m, 1H), 3.91 (d, J 7.1 Hz, 1H), 3.89 (s, 3H), 3.81 (m, 1H), 3.78-3.73 (m, 1H), 3.71 (t, J 6.8 Hz, 2H), 3.61 (dd, J 11.4, 3.0 Hz, 1H), 3.54-3.47 (m, 2H), 3.19-3.12 (m, 4H), 2.24-2.15 (m, 2H). LCMS (ES⁺) 507

5 (M+H)⁺.

INTERMEDIATE 40

10 4-Chloro-*N*-{3-[(*S*)-4-(6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indol-5-yl}butyramide

To a stirred solution of *Intermediate 21* (150 mg, 0.39 mmol) in MeCN (5 mL) was added potassium carbonate (136 mg, 0.99 mmol), followed by 4-chlorobutyryl chloride (56 mg, 0.39 mmol). The reaction mixture was stirred at r.t. for 2 h, then partitioned between DCM (15 mL) and water (15 mL). The combined aqueous layers
15 were extracted with DCM (2 x 15 mL). The combined organic layers were dried (phase separator) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-0.5% MeOH/EtOAc), yielding the *title compound* (111 mg, 58%) as a white solid. δ_{H} (d₆-DMSO at 110°C) 9.35-9.25 (m, 1H), 7.95 (d, J 2.0 Hz, 1H), 7.61 (m, 1H), 7.35-7.28 (m, 2H), 7.27-7.24 (m, 1H), 6.98 (s, 1H), 6.64 (d, J 8.3 Hz, 1H),
20 4.32-4.26 (m, 1H), 3.94-3.89 (m, 1H), 3.89 (m, 3H), 3.85-3.76 (m, 2H), 3.75-3.72 (m, 1H), 3.72-3.66 (m, 5H), 3.62 (dd, J 11.4, 3.0 Hz, 1H), 3.49 (d, J 9.1 Hz, 2H), 3.11 (d, J 7.6 Hz, 2H), 2.47 (d, J 7.3 Hz, 1H), 2.15-2.06 (m, 2H). LCMS (ES⁺) 485 (M+H)⁺.

INTERMEDIATE 41

25 6-(2,2,2-Trifluoroethoxy)nicotinic acid

To a stirred solution of 2,2,2-trifluoroethanol (1.0 mL, 14 mmol) in THF (25 mL) was added sodium hydride (60% dispersion in oil, 0.56 g, 14 mmol). The reaction mixture was stirred at r.t. for 30 minutes prior to the addition of 6-chloronicotinic acid
30 methyl ester (1.71 g, 10 mmol) in MeCN (5 mL). The reaction mixture was heated at 70°C for 1.5 h, then partitioned between EtOAc (50 mL) and saturated ammonium chloride solution (50 mL). The aqueous layer was extracted with EtOAc (30 mL). The combined organic layers were dried (sodium sulphate), filtered and concentrated *in vacuo*.

The resulting white solid was dissolved in THF (5 mL) and water (5 mL). Lithium hydroxide (200 mg) was added and the reaction mixture was stirred at r.t. for 2 h, then taken to pH 6 with HCl (2M aqueous). The reaction mixture was concentrated *in vacuo*, yielding the *title compound* (0.7 g, 32%) as a white solid. δ_{H} (d_6 -DMSO) 8.62 (d, *J* 2.0 Hz, 1H), 8.17 (dd, *J* 8.6, 2.3 Hz, 1H), 6.86 (d, *J* 8.3 Hz, 1H), 5.00 (q, *J* 9.1 Hz, 2H). LCMS (ES^+) 222 ($\text{M}+\text{H}$)⁺.

INTERMEDIATE 42

10 3-[(3*S*)-Morpholin-3-ylmethyl]-1*H*-indole-5-carboxylic acid dimethylamide

Prepared using the method described in WO2008/001076.

INTERMEDIATE 43

15 (*S*)-3-{5-[*N*-(2-Methoxyethyl)-*N*-methylcarbamoyl]-2-(trimethylsilyl)-1*H*-indol-3-ylmethyl}morpholine-4-carboxylic acid *tert*-butyl ester

Methyl 3-{[(3*S*)-4-(*tert*-butoxycarbonyl)morpholin-3-yl]methyl}-2-(trimethylsilyl)-1*H*-indole-5-carboxylate (WO 2008/001076, *Intermediate 41*; 446 mg, 1.0 mmol) was added portionwise to a solution of *N*-(2-methoxyethyl)-*N*-methylamine (356 μL , 4.0 mmol) and trimethylaluminium (1 mL, 2.0M in toluene) at 0°C. The mixture was then warmed to r.t. and heated to reflux for 18 h. The reaction mixture was quenched with water and partitioned between TBME (10 mL) and 2M NaOH (10 mL, aqueous). The aqueous layer was extracted with TBME (2 x 10 mL). The combined organic layers were dried (sodium sulphate), filtered and concentrated *in vacuo* to give the *title compound* (440 mg, 82%) as a yellow oil. LCMS (ES^+) 504 ($\text{M}+\text{H}$)⁺.

INTERMEDIATE 44

30 3-[(3*S*)-Morpholin-3-ylmethyl]-1*H*-indole-5-carboxylic acid *N*-(2-methoxyethyl)-*N*-methylamide

The *title compound* was prepared from *Intermediate 43* according to *Method J* and was isolated as a yellow oil. LCMS (ES^+) 332 ($\text{M}+\text{H}$)⁺.

INTERMEDIATE 45

(5-Chloro-6-methoxypyridin-3-yl)-[(S)-3-(5-hydroxymethyl-1-methyl-1H-indol-3-ylmethyl)morpholin-4-yl]-methanone

- 5 The *title compound* was prepared from *Intermediate 17* according to *Method F* and was isolated as a colourless oil. LCMS (ES⁺) 412.

INTERMEDIATE 46

- 10 (S)-3-[5-Amino-2-(trimethylsilyl)-1H-indol-3-ylmethyl]morpholine-4-carboxylic acid tert-butyl ester

Prepared using the method described in WO2008/001076.

INTERMEDIATE 47

- 15 (S)-3-[5-(Acetylamino)-2-(trimethylsilyl)-1H-indol-3-ylmethyl]morpholine-4-carboxylic acid tert-butyl ester

The *title compound* was prepared from *Intermediate 46* and acetyl chloride according to *Method D* and was isolated as a colourless oil. LCMS (ES⁺) 446 (M+H)⁺.

20

INTERMEDIATE 48

N-{3-[(3S)-Morpholin-3-ylmethyl]-1H-indol-5-yl}acetamide

- 25 The *title compound* was prepared from *Intermediate 47* according to *Method J* and was isolated as a colourless oil. LCMS (ES⁺) 274 (M+H)⁺.

INTERMEDIATE 49

- 30 (S)-3-[5-(Methoxycarbonylamino)-2-(trimethylsilyl)-1H-indol-3-ylmethyl]morpholine-4-carboxylic acid tert-butyl ester

The *title compound* was prepared from *Intermediate 46* and methyl chloroformate according to *Method D* and was isolated as a colourless oil. LCMS (ES⁺) 462 (M+H)⁺.

INTERMEDIATE 50

{3-[(3S)-Morpholin-3-ylmethyl]-1H-indol-5-yl}carbamic acid methyl ester

The *title compound* was prepared from *Intermediate 49* according to *Method J* and was isolated as a colourless oil. LCMS (ES⁺) 290 (M+H)⁺.

INTERMEDIATE 51

(S)-3-[5-(Cyclopropanecarbonylamino)-2-(trimethylsilanyl)-1H-indol-3-ylmethyl]-morpholine-4-carboxylic acid tert-butyl ester

The *title compound* was prepared from *Intermediate 46* and cyclopropanecarbonyl chloride according to *Method D* and was isolated as a colourless oil. LCMS (ES⁺) 472 (M+H)⁺.

INTERMEDIATE 52

Cyclopropanecarboxylic acid {3-[(3S)-morpholin-3-ylmethyl]-1H-indol-5-yl}amide

The *title compound* was prepared from *Intermediate 51* according to *Method J* and was isolated as a colourless oil. LCMS (ES⁺) 300 (M+H)⁺.

INTERMEDIATE 53

(S)-3-[5-(1,1-Dioxo-1 Λ 6-isothiazolidin-2-yl)-2-(trimethylsilanyl)-1H-indol-3-ylmethyl]-morpholine-4-carboxylic acid tert-butyl ester

To a stirred solution of *Intermediate 46* (400 mg, 1.0 mmol) in DCM (5 mL) at 0°C were added triethylamine (276 μ L, 2.0 mmol) and 3-chloropropanesulfonyl chloride (145 μ L, 1.2 mmol). The reaction mixture was stirred at r.t. for 18 h, then quenched with water. The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The resulting material was dissolved in MeCN (5 mL), potassium carbonate (350 mg, 2.5 mmol) was added and the reaction was heated at 80°C for 1.5 h. The reaction mixture was partitioned between DCM (20 mL) and water (20 mL), dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by column

chromatography (SiO₂, 0-1% MeOH/DCM), yielding a colourless oil. LCMS (ES⁺) 509 (M+H)⁺.

INTERMEDIATE 54

5

5-(1,1-Dioxo-1 Λ 6-isothiazolidin-2-yl)-3-[(3*S*)-morpholin-3-ylmethyl]-1*H*-indole

The *title compound* was prepared from *Intermediate 53* according to *Method J* and was isolated as a colourless oil. LCMS (ES⁺) 336 (M+H)⁺.

10

INTERMEDIATE 55

(5-Chloro-6-methoxypyridin-3-yl)-[(*S*)-3-(1-methyl-5-nitro-1*H*-indol-3-ylmethyl)-morpholin-4-yl]-methanone

The *title compound* was prepared from *Intermediate 20* and 5-chloro-6-methoxy-nicotinic acid at r.t. according to *Method A* and was isolated as a yellow solid. LCMS (ES⁺) 445 (M+H)⁺.

INTERMEDIATE 56

20 [(*S*)-3-(5-Amino-1-methyl-1*H*-indol-3-ylmethyl)morpholin-4-yl]-(5-chloro-6-methoxy-pyridin-3-yl)-methanone

To a stirred solution of *Intermediate 55* (1.1 g, 5.65 mmol) in AcOH (3 mL) was added zinc powder (1.1 g, 16.8 mmol). The reaction mixture was heated at 80°C for 1 h. The reaction mixture was cooled, quenched with water (50 mL) and saturated sodium carbonate solution (100 mL) and partitioned with EtOAc. The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 1% TEA/EtOAc), yielding a red oil. LCMS (ES⁺) 415 (M+H)⁺.

INTERMEDIATE 57

3-[(S)-4-(3-Hydroxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid methyl ester

5 The *title compound* was prepared from methyl 1-methyl-3-[(3S)-morpholin-3-ylmethyl]-1H-indole-5-carboxylate (WO 2008/001076, *Intermediate 77*) and 3-hydroxybenzoic acid at r.t. according to *Method A* and was isolated as a white solid. LCMS (ES⁺) 409 (M+H)⁺.

10

INTERMEDIATE 58

3-[(S)-4-(3-Hydroxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid

15 To a stirred solution of *Intermediate 57* (0.87 mg, 2.13 mmol) in MeOH (15 mL) was added aqueous sodium hydroxide solution (2M, 4.0 mL). The reaction was heated at reflux for 1 h. The reaction mixture was cooled and concentrated *in vacuo*. The aqueous residue was acidified using HCl (2M, 25 mL) to pH 2, and extracted with DCM (30 mL). The organic layer was dried (magnesium sulphate) and concentrated *in vacuo*, yielding the *title compound* (820 mg, 97%) as a white foam. LCMS (ES⁺) 395 (M+H)⁺.

20

INTERMEDIATE 59

(1-{3-[(S)-4-(3-Hydroxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carbonyl}azetidin-3-yl)carbamic acid tert-butyl ester

25 The *title compound* was prepared from *Intermediate 58* and azetidin-3-ylcarbamic acid *tert*-butyl ester at r.t. according to *Method F* and was isolated as a white solid. LCMS (ES⁺) 549 (M+H)⁺.

INTERMEDIATE 60

30

5-Chloro-6-methoxynicotinic acid

To a stirred solution of 5-chloro-6-methoxynicotinic acid methyl ester (1.0 g, 4.96 mmol) in THF (4 mL) and water (4 mL) was added lithium hydroxide (0.6 g, 14.3 mmol).

The reaction mixture was stirred at r.t. for 2.5 h, then neutralised with acetic acid and extracted with DCM. The organics were combined, dried (sodium sulphate) and concentrated *in vacuo*, yielding the *title compound* (0.4 g, 43%) as a white solid. δ_{H} (CDCl₃) 13.30 (br s, 1H), 8.65 (d, *J* 2.0 Hz, 1H), 8.22 (d, *J* 2.0 Hz, 1H), 4.02 (s, 3H).

5

INTERMEDIATE 61

3-[(*S*)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carboxylic acid methyl ester

10

The *title compound* was prepared from methyl 1-methyl-3-[(3*S*)-morpholin-3-ylmethyl]-1*H*-indole-5-carboxylate (WO 2008/001076, *Intermediate 77*) and *Intermediate 60* at r.t. according to *Method F* and was isolated as a white solid. LCMS (ES⁺) 458 (M+H)⁺.

15

INTERMEDIATE 62

3-[(*S*)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carboxylic acid

20

To a stirred solution of *Intermediate 61* (0.7 g, 1.53 mmol) in THF (5 mL) and water (5 mL) was added lithium hydroxide monohydrate (0.2 g, 4.76 mmol). The reaction mixture was heated to 75°C for 18 h, then cooled and neutralised with 2M HCl. The precipitate was filtered, washed with water and dried *in vacuo*, yielding the *title compound* (0.47 g, 69%) as a white solid. LCMS (ES⁺) 444 (M+H)⁺.

25

INTERMEDIATE 63

3-[(*S*)-4-(4-Chloro-3-hydroxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carboxylic acid methyl ester

30

The *title compound* was prepared from methyl 1-methyl-3-[(3*S*)-morpholin-3-ylmethyl]-1*H*-indole-5-carboxylate (WO 2008/001076, *Intermediate 77*) and 4-chloro-3-hydroxybenzoic acid at r.t. according to *Method F* and was isolated as a yellow solid. LCMS (ES⁺) 443 (M+H)⁺.

INTERMEDIATE 64

3-[(S)-4-(4-Chloro-3-hydroxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid

To a stirred solution of *Intermediate 63* (0.7 g, 1.58 mmol) in THF (5 mL) and water (5 mL) was added lithium hydroxide monohydrate (0.25 g, 5.95 mmol). The reaction mixture was heated to 75°C for 3 h, then cooled and neutralised with 2M HCl. The precipitate was filtered, washed with water and dried *in vacuo*, yielding the *title compound* (0.5 g, 74%) as a white solid. LCMS (ES⁺) 429 (M+H)⁺.

INTERMEDIATE 65

3-[(S)-4-(3-Fluoro-5-hydroxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid methyl ester

The *title compound* was prepared from methyl 1-methyl-3-[(3S)-morpholin-3-ylmethyl]-1H-indole-5-carboxylate (WO 2008/001076, *Intermediate 77*) and 3-fluoro-5-hydroxybenzoic acid at r.t. according to *Method F* and was isolated as a yellow solid. LCMS (ES⁺) 427 (M+H)⁺.

INTERMEDIATE 66

3-[(S)-4-(3-Fluoro-5-hydroxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid

To a stirred solution of *Intermediate 65* (0.9 g, 2.11 mmol) in THF (5 mL) and water (5 mL) was added lithium hydroxide monohydrate (0.25 g, 5.95 mmol). The reaction mixture was heated to 75°C for 3 h, then cooled and neutralised with 2M HCl. The precipitate was filtered, washed with water and dried *in vacuo*, yielding the *title compound* (0.84 g, 96%) as a yellow solid. LCMS (ES⁺) 413 (M+H)⁺.

INTERMEDIATE 67

(S)-3-[5-(2-Oxopyrrolidin-1-yl)-2-(trimethylsilanyl)-1H-indol-3-ylmethyl]morpholine-4-carboxylic acid *tert*-butyl ester

5 To a stirred solution of *Intermediate 46* (400 mg, 1.0 mmol) in DCM (5 mL) at 0°C were added triethylamine (276 µL, 2.0 mmol) and 4-chlorobutyl chloride (133 µL, 1.2 mmol). The reaction mixture was stirred at r.t. for 18 h, then quenched with water. The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The resulting material was dissolved in MeCN (5 mL), potassium carbonate (350 mg, 2.5
10 mmol) was added and the reaction heated at 80°C for 1.5 h. The reaction mixture was partitioned between DCM (20 mL) and water (20 mL), dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-1% MeOH/DCM), yielding a colourless oil. LCMS (ES⁺) 472 (M+H)⁺.

15 **INTERMEDIATE 68**

1-{3-[(3*S*)-Morpholin-3-ylmethyl]-1*H*-indol-5-yl}pyrrolidin-2-one

The *title compound* was prepared from *Intermediate 67* according to *Method J* and was isolated as a colourless oil. LCMS (ES⁺) 300 (M+H)⁺.

20

INTERMEDIATE 69

(2-Chloro-5-fluoro-6-methoxypyridin-3-yl)-[(S)-3-(1-methyl-5-nitro-1*H*-indol-3-ylmethyl)morpholin-4-yl]-methanone

25 The *title compound* was prepared from *Intermediate 20* and 2-chloro-5-fluoro-6-methoxynicotinic acid at r.t. according to *Method A* and was isolated as a yellow solid. LCMS (ES⁺) 463 (M+H)⁺.

INTERMEDIATE 70

[(S)-3-(5-Amino-1-methyl-1H-indol-3-ylmethyl)morpholin-4-yl]-(2-chloro-5-fluoro-6-methoxypyridin-3-yl)-methanone

- 5 To a stirred solution of *Intermediate 69* (1.5 g, 3.24 mmol) in AcOH (4 mL) was added zinc powder (1.5 g, 23.0 mmol). The reaction mixture was heated at 80°C for 1 h, then cooled and quenched with water (50 mL) and saturated sodium carbonate solution (100 mL), and partitioned with EtOAc. The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The residue was purified by column
10 chromatography (SiO₂, 1% TEA/EtOAc), yielding a red solid. LCMS (ES⁺) 433 (M+H)⁺.

INTERMEDIATE 71

- 1-(Carboxymethyl)-3-[(S)-4-(5-chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide
- 15

- To a stirred solution of *Example 99* (550 mg, 1.2 mmol) in DMF (10 mL) at 0°C was added sodium hydride (60% dispersion in oil, 58 mg, 1.44 mmol). The reaction mixture was stirred at r.t. for 1 h and then cooled to 0°C prior to the addition of bromoacetic acid methyl ester (138 µL, 1.44 mmol). The reaction mixture was stirred at r.t. for
20 2 h, then partitioned between DCM (20 mL) and water (20 mL). The combined organic layers were dried (sodium sulphate), filtered and concentrated *in vacuo*. The residue was dissolved in THF (5 mL) and water (5 mL), and lithium hydroxide monohydrate (152 mg, 3.6 mmol) was added. The reaction mixture was stirred at r.t for 1.5 h, then neutralised with 2M HCl. The precipitate was filtered, washed with water and dried *in vacuo*,
25 yielding the *title compound* (412 mg, 66%) as a white solid. LCMS (ES⁺) 515 (M+H)⁺.

INTERMEDIATE 72

- 3-[(S)-4-(5-Cyano-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid
- 30

To a stirred solution of methyl 1-methyl-3-[(3S)-morpholin-3-ylmethyl]-1H-indole-5-carboxylate (WO 2008/001076, *Intermediate 77*; 150 mg, 0.52 mmol) in DCM (5 mL) at 0°C were added DIPEA (427 µL, 2.6 mmol) and 5-cyano-6-methoxynicotinoyl

chloride hydrochloride (120 mg, 0.52 mmol). The reaction mixture was stirred at r.t. for 1 h, then quenched with water. The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 75-100% EtOAc/isohexane), yielding a white solid. LCMS (ES⁺) 449 (M+H)⁺. This material was dissolved in THF (5 mL) and water (5 mL), and lithium hydroxide monohydrate (50 mg, 1.2 mmol) was added. The reaction mixture was heated to reflux for 1.5 h, then cooled and neutralised with 2M HCl. The precipitate was filtered, washed with water and dried *in vacuo*, yielding the *title compound* (87 mg, 22%) as a white solid. LCMS (ES⁺) 435 (M+H)⁺.

10

INTERMEDIATE 73

3-[(S)-4-(tert-Butoxycarbonyl)morpholin-3-ylmethyl]-1-methyl-2-(trimethylsilyl)-1H-indole-5-carboxylic acid

15 Methyl 3-{[(3S)-4-(tert-butoxycarbonyl)morpholin-3-yl]methyl}-2-(trimethylsilyl)-1H-indole-5-carboxylate (WO 2008/001076, *Intermediate 77*; 4.7 g, 10.0 mmol) was dissolved in THF (75 mL), cooled to -78°C and treated with methyl iodide (1.6 mL, 25.0 mmol). LiHMDS (1M in THF, 20 mL, 20.0 mmol) was added and the reaction mixture was stirred at -78°C for 30 minutes. After warming to r.t., the mixture was
20 diluted with ethyl acetate (100 mL) and washed with saturated ammonium chloride solution (2 x 100 mL). The organic phase was dried (sodium sulphate) and concentrated *in vacuo*, yielding a colourless oil. The resulting material was dissolved in EtOH (100 mL) and water (50 mL), and sodium hydroxide (1 g, 25.0 mmol) was added. The reaction mixture was heated to reflux for 2.5 h, then cooled and concentrated *in vacuo*. The
25 resulting residue was acidified with citric acid (10% aqueous solution) and extracted with EtOAc. The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*, yielding a white solid. δ_H (CDCl₃) 8.47-8.37 (m, 1H), 7.83 (dd, *J* 8.6, 1.3 Hz, 1H), 7.14 (d, *J* 8.8 Hz, 1H), 7.10 (s, 1H), 4.12-4.05 (m, 1H), 3.79 (dd, *J* 10.9, 2.5 Hz, 1H), 3.70 (s, 4H), 3.45-3.42 (m, 1H), 3.38-3.32 (m, 2H), 3.23-3.14 (m, 2H), 2.91-2.88 (m, 1H),
30 1.31 (s, 9H), 0.36 (s, 9H).

INTERMEDIATE 74

3-[(S)-4-(tert-Butoxycarbonyl)morpholin-3-ylmethyl]-1-methyl-2-(trimethylsilyl)-1H-indole-5-carboxylic acid pentafluorophenyl ester

- 5 To a stirred solution of *Intermediate 73* (4.46 g, 10.0 mmol), EDC (3.0 g, 12.0 mmol) and HOBT (1.35 g, 10.0 mmol) in DCM (50 mL) were added DIPEA (4.2 mL, 30.0 mmol) and pentafluorophenol (2.2 g, 12.0 mmol). The reaction mixture was stirred at r.t. for 5 h, then quenched with water (10 mL). The organic layer was separated, dried (magnesium sulphate), concentrated *in vacuo* and purified by column chromatography
10 (SiO₂, 5-15% EtOAc/isohehexane), yielding the *title compound* (4 g, 65%) as a white solid. δ_{H} (CDCl₃) 8.70 (s, 1H), 8.06 (dd, *J* 8.6, 1.3 Hz, 1H), 7.37 (d, *J* 8.8 Hz, 1H), 4.30-4.22 (m, 1H), 3.93-3.90 (m, 1H), 3.91 (s, 4H), 3.61-3.59 (m, 1H), 3.57-3.45 (m, 2H), 3.35 (dd, *J* 10.9, 3.0 Hz, 2H), 3.08 (dd, *J* 13.9, 5.1 Hz, 1H), 1.43 (s, 9H), 0.55 (s, 9H). LCMS (ES⁺) 613 (M+H)⁺.

15

INTERMEDIATE 75

1-Methyl-3-[(3S)-morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid pentafluorophenyl ester hydrochloride

- 20 The *title compound* was prepared from *Intermediate 74* at r.t. according to *Method J* and the hydrochloride salt was isolated as a yellow solid. δ_{H} (d₆-DMSO) 9.59 (s, 1H), 9.14 (s, 1H), 8.61 (d, *J* 1.3 Hz, 1H), 7.98 (dd, *J* 8.8, 1.5 Hz, 1H), 7.69 (d, *J* 8.6 Hz, 1H), 7.50 (s, 1H), 3.94-3.91 (m, 1H), 3.86 (s, 4H), 3.73-3.70 (m, 1H), 3.68-3.57 (m, 1H), 3.54-3.46 (m, 1H), 3.24-3.21 (m, 1H), 3.17-3.03 (m, 3H). LCMS (ES⁺) 441 (M+H)⁺.

25

INTERMEDIATE 76

3-[(S)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid pentafluorophenyl ester

- 30 To a stirred solution of *Intermediate 61* (2.3 g, 5.0 mmol) in THF (10 mL) and water (10 mL) was added lithium hydroxide monohydrate (0.850 g, 20.0 mmol). The reaction mixture was heated to 75°C for 17 h, then cooled and neutralised with 2M HCl. The precipitate was filtered, washed with water and dried *in vacuo*, yielding a white solid.

The resulting material was dissolved in DCM (50 mL), and EDC (1.5 g, 6.0 mmol), HOBT (0.68 g, 5.0 mmol), DIPEA (2.1 mL, 15.0 mmol) and pentafluorophenol (1.1 g, 6.0 mmol) were added. The reaction mixture was stirred at r.t. for 5 h, then quenched with water (10 mL). The organic layer was separated, dried (magnesium sulphate), concentrated *in vacuo* and purified by column chromatography (SiO₂, 5-15% EtOAc/isohexane), yielding a colourless oil (1.3 g, 43%). LCMS (ES⁺) 610 (M+H)⁺.

INTERMEDIATE 77

10 2-(Methylsulfanyl)ethylamine hydrochloride

To a stirred solution of 2-hydroxyethylcarbamic acid *tert*-butyl ester (5.0 g, 31.0 mmol) in pyridine (10 mL) at 0°C was added methanesulfonyl chloride (3.1 mL, 31.0 mmol). The reaction mixture was stirred at r.t. for 18 h, then concentrated *in vacuo* and the residue partitioned in EtOAc (50 mL) and water (50 mL). The organic layer was separated, dried (magnesium sulphate), concentrated *in vacuo* and purified by column chromatography (SiO₂, 30% EtOAc/isohexane). The resulting material was dissolved in DMF (10 mL) and sodium methanethiolate (345 mg, 5.0 mmol) was added. The reaction mixture was stirred at r.t. for 18 h, then concentrated *in vacuo* and the residue partitioned in EtOAc (50 mL) and water (50 mL). The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The residue was treated with HCl in 1,4-dioxane (5 mL, 4M solution) and stirred at r.t. for 4 h. The reaction mixture was concentrated *in vacuo*, yielding the *title compound* as a yellow solid. δ_{H} (d₆-DMSO) 8.15 (dd, *J* 1.1, 0.8 Hz, 3H), 3.04-2.91 (m, 2H), 2.74-2.69 (m, 2H), 2.10 (s, 3H).

INTERMEDIATE 78

3-[(*S*)-4-(2-Chloro-5-fluoro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carboxylic acid methyl ester

The *title compound* was prepared from methyl 1-methyl-3-[(3*S*)-morpholin-3-ylmethyl]-1*H*-indole-5-carboxylate (WO 2008/001076, *Intermediate 77*) and 2-chloro-5-fluoro-6-methoxynicotinic acid at r.t. according to *Method A* and was isolated as a white solid. LCMS (ES⁺) 476 (M+H)⁺.

INTERMEDIATE 79

3-[(S)-4-(2-Chloro-5-fluoro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid

To a stirred solution of *Intermediate 78* (0.7 g, 1.47 mmol) in THF (15 mL) and water (5 mL) was added lithium hydroxide monohydrate (0.62 g, 14.7 mmol). The reaction mixture was heated to 75°C for 18 h, then cooled and neutralised with 2M HCl. The precipitate was filtered, washed with water and dried *in vacuo*, yielding the *title compound* as a white solid. LCMS (ES⁺) 462 (M+H)⁺.

INTERMEDIATE 80

3-[(S)-4-(5,6-Dichloropyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

The *title compound* was prepared from *Intermediate 3* and 5,6-dichloronicotinic acid according to *Method A* and was isolated as a white solid (224 mg) after purification by preparative HPLC. LCMS (ES⁺) 475 (M+H)⁺.

EXAMPLE 1 (METHOD A)

3-[(S)-4-(4-Aminobenzoyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

To a stirred solution of *Intermediate 3* (150 mg, 0.50 mmol), 4-aminobenzoic acid (68 mg, 0.50 mmol), EDC (144 mg, 0.75 mmol) and HOBt (76 mg, 0.50 mmol) in DMF (10 mL) was added DIPEA (0.11 mL, 0.10 mmol). The reaction mixture was heated at 90°C for 2 h. After cooling, the mixture was partitioned between ethyl acetate (10 mL) and water (10 mL). The organic layer was washed with water (3 x 10 mL), dried (phase separator filters), concentrated *in vacuo* and chromatographed (SiO₂, 20-60% EtOAc/hexanes) to yield an off-white solid which was purified further using preparative HPLC, yielding the *title compound* (22 mg, 100%) as a white solid. δ_{H} (d₆-DMSO) 7.58 (d, *J* 0.8 Hz, 1H), 7.39 (d, *J* 8.6 Hz, 1H), 7.19 (dd, *J* 8.3, 1.5 Hz, 1H), 7.11 (s, 1H), 6.95 (d, *J* 8.6 Hz, 2H), 6.50 (d, *J* 8.3 Hz, 2H), 5.15 (br s, 2H), 4.40-4.30 (m, 1H), 3.92-3.85 (m, 1H),

3.79-3.71 (m, 5H), 3.52-3.39 (m, 3H), 3.25 (dd, J 14.4, 8.8 Hz, 1H), 3.03-3.01 (m, 1H), 2.99 (s, 6H). LCMS (ES+) 421 (M+H)⁺.

EXAMPLE 2

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3-[(S)-4-[6-(Acetylamino)pyridine-3-carbonyl]morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

The *title compound* was prepared from *Intermediate 3* and *Intermediate 4* according to *Method A* and was isolated as a white solid (39 mg) after purification by preparative HPLC. δ_{H} (d₆-DMSO) 10.25 (s, 1H), 8.02 (dd, J 1.8, 0.8 Hz, 1H), 7.91 (d, J 8.3 Hz, 1H), 7.54 (s, 1H), 7.47-7.41 (m, 1H), 7.39 (d, J 8.6 Hz, 1H), 7.19 (dd, J 8.6, 1.5 Hz, 1H), 7.12 (s, 1H), 4.28 (d, J 2.0 Hz, 1H), 3.90-3.96 (m, 1H), 3.82 (d, J 11.6 Hz, 1H), 3.77 (s, 4H), 3.57-3.64 (m, 1H), 3.45-3.56 (m, 2H), 3.12-3.20 (m, 2H), 2.97 (s, 6H), 2.11 (s, 3H). LCMS (ES+) 464 (M+H)⁺.

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EXAMPLE 3

3-[(S)-4-(2-Amino-1,3-thiazole-5-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

The *title compound* was prepared from *Intermediate 3* and 2-amino-1,3-thiazole-5-carboxylic acid according to *Method A* and was isolated as an off-white solid (12 mg) after purification by preparative HPLC. δ_{H} (d₆-DMSO) 7.67 (d, J 1.0 Hz, 1H), 7.39 (d, J 8.3 Hz, 1H), 7.23-7.19 (m, 2H), 7.17 (s, 1H), 7.09 (s, 2H), 4.52-4.46 (m, 1H), 4.02-3.90 (m, 2H), 3.80-3.74 (m, 4H), 3.61-3.42 (m, 3H), 3.28 (dd, J 14.1, 9.1 Hz, 1H), 3.00 (s, 6H), 2.99-2.96 (m, 1H). LCMS (ES+) 428 (M+H)⁺.

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EXAMPLE 4

3-[(S)-4-[2-(Acetylamino)-1,3-thiazole-5-carbonyl]morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

30

The *title compound* was prepared from *Intermediate 3* and *Intermediate 5* according to *Method A* and was isolated as a white solid (98 mg) after purification by preparative HPLC. δ_{H} (d₆-DMSO) 7.65 (s, 1H), 7.56 (s, 1H), 7.41 (d, J 8.4 Hz, 1H), 7.21

(d, *J* 8.4 Hz, 1H), 7.20 (s, 1H), 4.56-4.52 (m, 1H), 4.05-3.99 (m, 2H), 3.88 (d, *J* 11.5 Hz, 1H), 3.80 (s, 3H), 3.68-3.49 (m, 3H), 3.27 (dd, *J* 8.0, 14.3 Hz, 1H), 3.12 (dd, *J* 8.0, 14.2 Hz, 1H), 3.04 (s, 6H), 2.21 (s, 3H). LCMS (ES+) 470 (M+H)⁺.

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EXAMPLE 5**(6-Aminopyridin-3-yl)-[(S)-3-(1*H*-indol-3-ylmethyl)morpholin-4-yl]-methanone**

The *title compound* was prepared from (S)-3-(1*H*-indol-3-ylmethyl)morpholine and 6-aminonicotinic acid according to *Method A* and was isolated as a white solid (205 mg). δ_{H} (d₆-DMSO at 100°C) 10.61 (s, 1H), 7.90 (d, *J* 2.2 Hz, 1H), 7.35-7.31 (m, 2H), 7.22 (dd, *J* 8.5, 2.4 Hz, 1H), 7.07-7.03 (m, 2H), 6.94-6.90 (m, 1H), 6.38 (d, *J* 8.5 Hz, 1H), 6.02 (s, 2H), 4.38-4.30 (m, 1H), 3.90 (d, *J* 7.8 Hz, 1H), 3.80-3.71 (m, 2H), 3.52-3.44 (m, 3H), 3.29-3.20 (m, 1H), 2.98 (dd, *J* 13.1, 7.2 Hz, 1H). LCMS (ES+) 337 (M+H)⁺.

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EXAMPLE 6**3-[(S)-4-(6-Chloropyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carboxylic acid dimethylamide**

The *title compound* was prepared from *Intermediate 3* and 6-chloronicotinic acid according to *Method A* and was isolated as a white solid (100 mg). δ_{H} (d₆-DMSO at 100°C) 8.09 (s, 1H), 7.52-7.33 (m, 4H), 7.20 (d, *J* 8.6 Hz, 1H), 7.12 (s, 1H), 4.25-4.10 (m, 1H), 3.95-3.93 (m, 1H), 3.83 (d, *J* 11.6 Hz, 1H), 3.78 (s, 3H), 3.64-3.62 (m, 1H), 3.52 (d, *J* 9.0 Hz, 2H), 3.16 (d, *J* 7.3 Hz, 2H), 2.99-2.97 (m, 7H). LCMS (ES+) 441 (M+H)⁺.

25

EXAMPLE 7**1-Methyl-3-[(S)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1*H*-indole-5-carboxylic acid dimethylamide**

The *title compound* was prepared from *Intermediate 3* and 6-methylnicotinic acid according to *Method A* and was isolated as a white solid (164 mg). δ_{H} (d₆-DMSO at 100°C) 8.19 (s, 1H), 7.48 (s, 1H), 7.39 (d, *J* 8.3 Hz, 1H), 7.30 (s, 1H), 7.19 (d, *J* 8.2 Hz, 1H), 7.11 (s, 2H), 4.28-4.15 (m, 1H), 3.93 (d, *J* 6.8 Hz, 1H), 3.82-3.76 (m, 5H), 3.69 (d, *J*

11.4 Hz, 1H), 3.49 (d, *J* 8.3 Hz, 2H), 3.18-3.13 (m, 2H), 2.99 (s, 6H), 2.45 (s, 3H).
LCMS (ES+) 421 (M+H)⁺.

EXAMPLE 8

5

3-[(S)-4-(2-Amino-4-methyl-1,3-thiazole-5-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carboxylic acid dimethylamide

The *title compound* was prepared from *Intermediate 3* and 2-amino-4-methyl-1,3-thiazole-5-carboxylic acid according to *Method A* and was isolated as a white solid (20
10 mg). δ_{H} (d₆-DMSO at 90°C) 7.62 (s, 1H), 7.39 (d, *J* 8.4 Hz, 1H), 7.19 (dd, *J* 8.4, 1.5 Hz, 1H), 7.16 (s, 1H), 6.92 (s, 2H), 4.50-4.35 (m, 1H), 3.93-3.85 (m, 1H), 3.79-3.72 (m, 4H), 3.49-3.37 (m, 4H), 3.23 (dd, *J* 8.5, 8.2 Hz, 1H), 3.04-2.98 (m, 7H), 1.93 (s, 3H). LCMS (ES+) 442 (M+H)⁺.

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EXAMPLE 9

3-[(S)-4-Acetylmorpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carboxylic acid dimethylamide

The *title compound* was prepared from *Intermediate 3* and 2-amino-4-methyl-1,3-thiazole-5-carboxylic acid sodium acetate salt according to *Method A* and was isolated as
20 a white solid (53 mg). δ_{H} (d₆-DMSO) 7.82 (s, 0.5H), 7.70 (s, 0.5H), 7.43 (t, *J* 8.1 Hz, 1H), 7.26-7.18 (m, 2H), 4.47-4.41 (m, 0.5H), 4.18-4.10 (m, 0.5H), 3.97-3.85 (m, 2H), 3.76 (s, 3H), 3.62 (m, 1H), 3.54-3.04 (m, 4H), 3.01 (s, 3H), 2.98 (s, 3H), 2.72-2.64 (m, 1H), 2.03 (s, 1.5H), 1.62 (s, 1.5H). LCMS (ES+) 344 (M+H)⁺.

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EXAMPLE 10

3-{(S)-4-[2-(6-Aminopyridin-2-yl)acetyl]morpholin-3-ylmethyl}-1-methyl-1*H*-indole-5-carboxylic acid dimethylamide

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The *title compound* was prepared from *Intermediate 3* and [6-(*tert*-butoxy-carbonylamino)pyridin-2-yl]acetic acid according to *Method A* and was isolated as a white solid (17 mg). δ_{H} (d₆-DMSO) 7.81 (s, 0.5H), 7.70 (s, 0.5H), 7.43 (t, *J* 8.6 Hz, 1H), 7.27 (m, 1H), 7.21 (d, *J* 10.6 Hz, 2H), 6.30 (m, 1H), 6.21 (m, 1H), 5.80 (dd, *J* 2.5, 1.5 Hz,

2H), 4.53-4.47 (m, 1H), 4.21-4.10 (m, 1H), 3.95-3.82 (m, 1H), 3.77 (d, *J* 6.6 Hz, 3H), 3.60-3.70 (m, 2H), 3.50-3.09 (m, 5H), 2.99 (s, 3H), 2.95 (s, 3H), 2.75 (dd, *J* 13.6, 4.3 Hz, 1H). LCMS (ES+) 436 (M+H)⁺.

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EXAMPLE 11

3-[(S)-4-[2-(3-Ethylureido)-1,3-thiazole-5-carbonyl]morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

Example 3 (150 mg, 0.35 mmol) was dissolved in ethyl isocyanate (2 mL). The reaction mixture was heated at 60°C for 1 h. After cooling, the solution was concentrated *in vacuo* and purified using preparative HPLC to yield the *title compound* (111 mg, 64%) as a white solid. δ_{H} (d₆-DMSO) 7.66 (s, 1H), 7.47 (s, 1H), 7.42 (d, *J* 8.3 Hz, 1H), 7.23 (d, *J* 8.3 Hz, 1H), 7.22 (s, 1H), 6.66 (t, *J* 5.5 Hz, 1H), 4.58-4.52 (m, 1H), 4.06-3.99 (m, 2H), 3.86 (d, *J* 11.5 Hz, 1H), 3.80 (s, 3H), 3.67-3.48 (m, 4H), 3.35-3.22 (m, 3H), 3.19-3.06 (m, 1H), 3.04 (s, 6H), 1.16 (t, *J* 7.2 Hz, 3H). LCMS (ES+) 499 (M+H)⁺.

EXAMPLE 12

3-[(S)-4-(6-Aminopyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

To a stirred solution of *Intermediate 3* (200 mg, 0.66 mmol) in DCM (5 mL) were added 6-aminonicotinic acid (101 mg, 0.73 mmol), HOBT (100 mg, 0.66 mmol), DIPEA (233 μ L, 1.32 mmol) and EDC (192 mg, 0.99 mmol). The mixture was stirred overnight, diluted with DCM (10 mL) and shaken with water (15 mL). The organic layer was separated and concentrated *in vacuo* to afford a white gum which was purified by preparative HPLC to afford the *title compound* (36 mg, 13%) as a white solid. δ_{H} (d₆-DMSO at 110°C) 7.84 (d, *J* 1.8 Hz, 1H), 7.59 (s, 1H), 7.38 (d, *J* 8.6 Hz, 1H), 7.25-7.14 (m, 2H), 7.09 (s, 1H), 6.38 (d, *J* 8.6 Hz, 1H), 5.81 (s, 2H), 4.41-4.30 (m, 1H), 3.96-3.87 (m, 1H), 3.83-3.69 (m, 5H), 3.59-3.43 (m, 3H), 3.30-3.18 (m, 1H), 3.13-3.03 (m, 1H), 3.00 (s, 6H). LCMS (ES+) 422 (M+H)⁺.

EXAMPLE 13**1-Methyl-3-[(S)-4-(pyridine-3-carbonyl)morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide**

5 To a stirred solution of *Intermediate 3* (210 mg, 700 μ mol) in DCM (5 mL) were added nicotinic acid (94 mg, 0.77 mmol), HOBT (107 mg, 700 μ mol), DIPEA (250 μ L, 1.40 mmol) and EDC (202 mg, 1.05 mmol). The reaction mixture was stirred overnight, diluted with DCM (10 mL) and shaken with water (15 mL). The organic layer was separated and concentrated *in vacuo* to afford a white gum which was purified by
10 preparative HPLC to afford the *title compound* (160 mg, 56%) as a white solid. δ_{H} (d_6 -DMSO at 120°C) 8.50-8.52 (m, 1H), 8.33 (s, 1H), 8.21 (br s, 1H), 7.44 (br s, 1H), 7.39 (d, *J* 8.5 Hz, 1H), 7.28-7.24 (m, 1H), 7.20-7.17 (m, 1H), 7.09 (m, 1H), 4.22 (br s, 1H), 3.97-3.88 (m, 1H), 3.82-3.71 (m, 5H), 3.60 (dd, *J* 11.6, 3.1 Hz, 1H), 3.58-3.40 (m, 2H), 3.27-3.10 (m, 2H), 2.99 (s, 6H). LCMS (ES+) 407 (M+H)⁺.

EXAMPLE 14**3-[(S)-4-(6-Aminopyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid methyl ester**

20 To a stirred solution of 1-methyl-3-[(S)-morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid methyl ester (500 mg, 1.74 mmol) and 6-aminonicotinic acid (263 mg, 1.91 mmol) in DMF (10 mL) were added EDC (501 mg, 2.61 mmol), HOBT (266 mg, 1.74 mmol) and DIPEA (576 μ L, 3.5 mmol). The reaction mixture was stirred at 60°C for 2 h, cooled and partitioned between EtOAc (50 mL) and water (50 mL). The organic
25 layer was washed with brine (50 mL), dried (magnesium sulfate) and concentrated *in vacuo* to afford the *title compound* (465 mg, 56%) as a white solid. δ_{H} (d_6 -DMSO at 80°C) 8.20 (s, 1H), 7.79-7.75 (m, 2H), 7.44 (d, *J* 8.7 Hz, 1H), 7.19 (s, 1H), 7.12 (d, *J* 7.1 Hz, 1H), 6.30 (d, *J* 8.5 Hz, 1H), 5.99 (br s, 2H), 4.43-4.35 (m, 1H), 3.93-3.70 (m, 9H), 3.61-3.40 (m, 3H), 3.26-3.05 (m, 2H). LCMS (ES+) 409 (M+H)⁺.

EXAMPLE 15

(6-Aminopyridin-3-yl)-[(S)-3-(1-methyl-1H-indol-3-ylmethyl)morpholin-4-yl]-methanone

- 5 To a stirred solution of *Example 5* (157 mg, 0.45 mmol) in DMF (3 mL) in a sealed tube were added methyl carbonate (60 μ L, 0.67 mmol) and DABCO (5 mg, 45 μ mol). The reaction mixture was heated in a microwave at 160°C for 20 minutes. Additional methyl carbonate (40 μ L) was added, and the mixture was heated for a further 20 minutes. The cooled solution containing the crude product was purified by preparative
- 10 HPLC to afford the *title compound* (28 mg, 18%) as a white solid. δ_{H} (d_6 -DMSO) 8.37 (br s, 1H), 7.89 (s, 1H), 7.35 (d, J 8.3 Hz, 1H), 7.30-7.17 (m, 1H), 7.16-7.07 (m, 2H), 7.00-6.87 (m, 1H), 6.35 (s, 3H), 3.90 (m, 1H), 3.72 (s, 3H), 3.68 (s, 1H), 3.53-3.10 (m, 6H), 2.89 (dd, J 13.9, 5.6 Hz, 1H). LCMS (ES+) 409 (M+H)⁺.

15

EXAMPLE 16

3-[(S)-4-[6-(3-Ethylureido)pyridine-3-carbonyl]morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

- To a stirred solution of *Example 12* (200 mg, 475 μ mol) in ethyl isocyanate (3
- 20 mL) was added DMAP (3 mg). The reaction mixture was heated at reflux for 30 minutes and concentrated *in vacuo* to give an oil, which was purified by preparative HPLC to afford the *title compound* (28 mg, 12%) as a yellow solid. δ_{H} (d_6 -DMSO) 9.01 (s, 1H), 7.90 (s, 1H), 7.70 (s, 1H), 7.52 (s, 1H), 7.39 (d, J 8.7 Hz, 1H), 7.35-7.30 (m, 2H), 7.18 (d, J 8.7 Hz, 1H), 7.12 (s, 1H), 4.30-4.20 (m, 1H), 3.93-3.87 (m, 1H), 3.83-3.72 (m, 5H),
- 25 3.63-3.42 (m, 3H), 3.25-3.02 (m, 4H), 2.96 (s, 6H), 1.12 (t, J 6.5 Hz, 3H). LCMS (ES+) 493 (M+H)⁺.

EXAMPLE 17

- 30 3-[(S)-4-[6-(3-Butylureido)pyridine-3-carbonyl]morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

To a stirred solution of *Example 12* (93 mg, 221 μ mol) in *n*-butyl isocyanate (2 mL) was added DMAP (2 mg). The mixture was heated at 80°C for 1 h and concentrated

in vacuo to give an oil, which was purified by preparative HPLC to afford the *title compound* (28 mg, 24%) as a white solid. δ_{H} (d_6 -DMSO) 9.33-9.11 (m, 1H), 7.96-7.02 (m, 8H), 4.07-3.84 (m, 1H), 3.79 (m, 4H), 3.69-3.40 (m, 2H), 3.30 (s, 6H), 3.20-2.80 (m, 7H), 1.62-1.17 (m, 4H), 1.03-0.82 (t, J 7.2 Hz, 3H). LCMS (ES+) 521 (M+H)⁺.

5

EXAMPLE 18

1-Methyl-3-[(S)-4-[6-(3-phenylureido)pyridine-3-carbonyl]morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide

10 To a stirred solution of *Example 12* (105 mg, 250 μmol) in pyridine (1 mL) was added phenyl isocyanate (500 μL). The mixture was heated at 60°C for 30 minutes, cooled and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the *title compound* (50 mg, 37%) as a white solid. δ_{H} (d_6 -DMSO at 80°C) 10.07 (s, 1H), 9.30 (s, 1H), 7.98 (s, 1H), 7.52-7.50 (m, 3H), 7.42-7.30 (m, 5H), 7.18-7.13 (m, 2H),
15 7.07-7.02 (m, 1H), 4.33-4.20 (m, 1H), 3.95-3.91 (m, 1H), 3.95-3.81 (m, 2H), 3.77 (s, 3H), 3.63-3.61 (m, 1H), 3.54-3.47 (m, 2H), 3.18-3.16 (m, 2H), 2.95 (s, 6H). LCMS (ES+) 556 (M+H)⁺.

EXAMPLE 19

20

[(S)-3-(5-Benzyloxy-1-methyl-1H-indol-3-ylmethyl)morpholin-4-yl]-(6-chloropyridin-3-yl)-methanone

Intermediate 13 (194 mg, 445 μmol) was dissolved in HCl (4M solution in 1,4-dioxane, 5 mL). After 1 h the solution was concentrated *in vacuo* and the residue
25 dissolved in DCM (5 mL). The stirred solution was cooled to 0°C and TEA (285 μL , 2 mmol) and 6-chloronicotinoyl chloride (78 mg, 445 μmol) were added. The reaction mixture was stirred at r.t. for 1 h, shaken with water (10 mL) and the organic layer separated, dried (magnesium sulphate) and chromatographed on silica gel to afford the *title compound* (170 mg, 80%) as a white solid. δ_{H} (d_6 -DMSO at 80°C) 8.06 (m, 1H),
30 7.51-7.44 (m, 2H), 7.43-7.35 (m, 2H), 7.26 (m, 4H), 7.05-6.96 (m, 1H), 6.90-6.83 (m, 2H), 5.09-4.96 (m, 2H), 3.99-3.90 (m, 1H), 3.82 (m, 2H), 3.75-3.61 (m, 5H), 3.49 (m, 2H), 3.19-3.07 (m, 2H). LCMS (ES+) 476 (M+H)⁺.

EXAMPLE 20

(5-{{(S)-3-[5-(Dimethylcarbamoyl)-1-methyl-1*H*-indol-3-ylmethyl]morpholine-4-carbonyl}pyridin-2-yl)carbamic acid benzyl ester

- 5 To a stirred solution of *Example 12* (102 mg, 242 μ mol) in DCM at 0°C was added TEA (70 μ L, 484 μ mol) and benzyl chloroformate (51 μ L, 363 μ mol). The reaction mixture was stirred at r.t. for 30 minutes, and shaken with water (10 mL). The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo* to afford a yellow oil which was purified by preparative HPLC to afford the *title compound*
- 10 (48 mg, 36%) as a white solid. δ_{H} (d_6 -DMSO at 80°C) 8.01 (d, *J* 1.1 Hz, 1H), 7.67 (d, *J* 8.9 Hz, 1H), 7.52 (m, 1H), 7.47-7.30 (m, 8H), 7.21-7.14 (m, 1H), 7.11 (s, 1H), 5.21 (s, 2H), 4.34-4.17 (m, 1H), 3.97-3.88 (m, 1H), 3.85-3.70 (m, 6H), 3.64-3.55 (m, 1H), 3.55-3.45 (m, 2H), 3.19-3.01 (m, 7H). LCMS (ES+) 556 (M+H)⁺.

15

EXAMPLE 21

(5-{{(S)-3-[5-(Dimethylcarbamoyl)-1-methyl-1*H*-indol-3-ylmethyl]morpholine-4-carbonyl}pyridin-2-yl)carbamic acid ethyl ester

- 20 To a stirred solution of *Example 12* (170 mg, 403 μ mol) in DCM at 0°C was added TEA (115 μ L, 810 μ mol) and ethyl chloroformate (42 μ L, 440 μ mol). The reaction mixture was stirred at r.t. for 30 minutes, and shaken with water (10 mL). The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo* to afford a yellow oil which was purified by preparative HPLC to afford the *title compound* (49 mg, 25%) as a white solid. δ_{H} (d_6 -DMSO at 80°C) 9.78 (br s, 1H), 8.01 (s, 1H), 7.72-7.64 (m, 1H), 7.53 (s, 1H), 7.47-7.35 (m, 2H), 7.22-7.14 (m, 1H), 7.11 (s, 1H), 4.27 (m, 1H), 4.18 (q, *J* 7.2 Hz, 2H), 3.97-3.88 (m, 1H), 3.83 (s, 1H), 3.80-3.77 (m, 1H), 3.65-3.55 (m, 1H), 3.46-3.44 (m, 2H), 3.24-3.05 (m, 11H), 1.27 (t, *J* 7.2 Hz, 3H). LCMS (ES+) 494 (M+H)⁺.
- 25

EXAMPLE 22

(6-Chloropyridin-3-yl)-{(S)-3-[1-methyl-5-(o-tolyl)-1H-indol-3-ylmethyl]morpholin-4-yl}-methanone

- 5 *Intermediate 8* (265 mg, 460 μ mol) was dissolved in HCl (4M solution in 1,4-dioxane, 5 mL). After 1 h the solution was concentrated *in vacuo*, and the residue was dissolved in DCM (5 mL) and shaken with aqueous sodium carbonate. The organic layer was separated, dried (magnesium sulphate) and cooled at 0°C. TEA (285 μ L, 2 mmol) and 6-chloronicotinoyl chloride (78 mg, 445 μ mol) were added to the stirred solution.
- 10 The reaction mixture was stirred at r.t. for 1 h, shaken with water (10 mL) and the organic layer separated, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the *title compound* (16 mg, 8%) as a white solid. δ_{H} (d_6 -DMSO at 90°C) 8.05 (m, 1H), 7.44-7.38 (m, 1H), 7.37-7.15 (m, 7H), 7.12-7.05 (m, 2H), 3.96-3.90 (m, 1H), 3.83 (m, 5H), 3.69-3.60 (m, 1H), 3.57-3.46 (m, 2H),
- 15 3.23-3.09 (m, 3H), 2.22 (s, 3H). LCMS (ES+) 460 (M+H)⁺.

EXAMPLE 23

(6-Chloropyridin-3-yl)-{(S)-3-[5-(4-fluorophenyl)-1H-indol-3-ylmethyl]morpholin-4-yl}-methanone

- 20 To a stirred solution of *Intermediate 10* (236 mg, 760 μ mol) in DCM (5 mL) at 0°C was added TEA (164 μ L, 1.14 mmol) and 6-chloronicotinoyl chloride (78 mg, 445 μ mol). The reaction mixture was stirred at r.t. for 1 h, shaken with water (10 mL) and the organic layer separated, dried (magnesium sulphate) and concentrated *in vacuo*. The
- 25 residue was purified by chromatography on silica gel to afford a yellow oil, which was purified further by preparative HPLC to afford the *title compound* (50 mg, 38%) as a white solid. δ_{H} (d_6 -DMSO at 90°C) 10.71 (br s, 1H), 8.04 (br s, 1H), 7.64-7.49 (m, 3H), 7.45-7.38 (m, 1H), 7.35-7.28 (m, 1H), 7.26-7.16 (m, 3H), 7.15-7.08 (m, 2H), 4.23 (br s, 1H), 4.00-3.91 (m, 1H), 3.91-3.78 (m, 2H), 3.75-3.68 (m, 1H), 3.56-3.46 (m, 2H), 3.33-
- 30 3.05 (m, 2H). LCMS (ES+) 450 (M+H)⁺.

EXAMPLE 24

(6-Chloropyridin-3-yl)-{(S)-3-[5-(4-fluorophenyl)-1-methyl-1H-indol-3-ylmethyl]-morpholin-4-yl}-methanone

- 5 To a stirred solution of *Example 23* (200 mg 445 μmol) in DMF (4 mL) at 0°C were added iodomethane (81 μL , 1.3 mmol) and sodium hydride (27 mg, 668 μmol). The reaction mixture was stirred at r.t. for 10 minutes, quenched by the addition of water (20 mL) and extracted with EtOAc (20 mL). The organic extract was washed with brine (20 mL), dried (magnesium sulphate) and concentrated *in vacuo*. The residue was purified by
10 preparative HPLC to afford the *title compound* (55 mg, 27%) as a white solid. δ_{H} (d_6 -DMSO at 90°C) 8.04 (br s, 1H), 7.66-7.49 (m, 3H), 7.48-7.34 (m, 2H), 7.30-7.13 (m, 4H), 7.09 (s, 1H), 4.24 (br s, 1H), 4.01-3.92 (m, 1H), 3.90-3.81 (m, 3H), 3.78 (s, 3H), 3.73-3.64 (m, 1H), 3.60-3.44 (m, 3H). LCMS (ES+) 450 (M+H)⁺.

15

EXAMPLE 25

3-[(S)-4-Benzoylmorpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

- To a stirred solution of *Intermediate 3* (200 mg, 0.7 mmol) and DIPEA (141 μL ,
20 0.84 mmol) in DCM (5 mL) was added a solution of benzoyl chloride (85 μL , 0.77 mmol) in DCM (2 mL) dropwise. The reaction mixture was stirred overnight at room temperature. After quenching with water (10 mL), the organic solution was dried (phase separator filters) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 100% EtOAc) yielded the *title compound* (123 mg, 43%) as a white solid. δ_{H} (d_6 -DMSO at 120°C) 7.43 (s, 1H), 7.39-7.29 (m, 4H), 7.19-7.15 (m, 3H), 7.08 (s, 1H), 4.30-4.23 (m, 1H), 3.91 (d, *J* 7.7 Hz, 1H), 3.78-3.75 (m, 5H), 3.54 (dd, *J* 11.7, 3.1 Hz, 1H), 3.49-3.46 (m, 2H), 3.25 (dd, *J* 14.3, 8.5 Hz, 1H), 3.06 (dd, *J* 14.3, 6.5 Hz, 1H), 2.98 (s, 6H). LCMS (ES+) 406 (M+H)⁺.

EXAMPLE 26**1-Methyl-3-[(S)-4-(pyridine-4-carbonyl)morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide**

- 5 To a stirred solution of *Intermediate 3* (200 mg, 0.7 mmol) and DIPEA (420 μ L, 2.45 mmol) in DCM (10 mL) was added a solution of isonicotinoyl chloride mono-hydrochloride (130 μ L, 0.77 mmol) in DCM (2 mL) dropwise. The reaction mixture was stirred overnight at room temperature. After quenching with water (10 mL), the organic solution was dried (phase separator) and concentrated *in vacuo*. Purification by column
- 10 chromatography (SiO₂, 5-10% MeOH/EtOAc) yielded the *title compound* (110 mg, 39%) as a white solid. δ_{H} (d₆-DMSO at 120°C) 8.49 (d, *J* 5.1 Hz, 2H), 7.48 (s, 1H), 7.40 (d, *J* 8.4 Hz, 1H), 7.20 (dd, *J* 8.4, 1.5 Hz, 1H), 7.11 (s, 1H), 7.03 (d, *J* 3.7 Hz, 2H), 4.20-4.10 (m, 1H), 3.93 (d, *J* 7.0 Hz, 1H), 3.82-3.77 (m, 5H), 3.59 (dd, *J* 11.6, 3.1 Hz, 1H), 3.50 (d, *J* 8.9 Hz, 2H), 3.22 (dd, *J* 14.3, 7.8 Hz, 1H), 3.13 (dd, *J* 14.3, 7.2 Hz, 1H), 2.98 (s, 6H).
- 15 LCMS (ES+) 407 (M+H)⁺.

EXAMPLE 27 (METHOD B)

20 **3-{(S)-4-[6-(Dimethylamino)pyridine-3-carbonyl]morpholin-3-ylmethyl}-1-methyl-1H-indole-5-carboxylic acid dimethylamide**

- Dimethylamine (3 mL) at 0°C was added to *Example 6* (20 mg, 0.045 mmol) in a microwave vial. The reaction mixture was then heated to 100°C for 3 h. The experiment was repeated four more times. The products were combined, dissolved in EtOAc, concentrated *in vacuo* and the residue was purified by preparative HPLC to yield the *title*
- 25 *compound* (75 mg, 93%) as a white solid. δ_{H} (d₆-DMSO at 80°C) 7.96 (s, 1H), 7.56 (s, 1H), 7.39 (d, *J* 8.5 Hz, 1H), 7.21-7.17 (m, 2H), 7.12 (s, 1H), 6.45 (d, *J* 8.8 Hz, 1H), 4.35-4.27 (m, 1H), 3.91 (d, *J* 7.5 Hz, 1H), 3.80-3.75 (m, 5H), 3.58-3.47 (m, 3H), 3.22-3.08 (m, 2H), 3.03 (s, 6H), 2.97 (s, 6H). LCMS (ES+) 450 (M+H)⁺.

EXAMPLE 28**1-Methyl-3-[(S)-4-[6-(methylamino)pyridine-3-carbonyl]morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide**

5 The *title compound* was prepared from *Example 6* and methylamine (2N in THF, 2 mL) according to *Method B* and was isolated as a white solid (75 mg). δ_{H} (d_6 -DMSO at 80°C) 7.91 (s, 1H), 7.57 (s, 1H), 7.39 (d, *J* 8.4 Hz, 1H), 7.20-7.12 (m, 3H), 6.53 (s, 1H), 6.31 (d, *J* 8.6 Hz, 1H), 4.35-4.30 (m, 1H), 3.91 (d, *J* 8.4 Hz, 1H), 3.79-3.76 (m, 5H), 3.55-3.42 (m, 3H), 3.21 (dd, *J* 14.2, 8.3 Hz, 1H), 3.06 (dd, *J* 14.2, 6.8 Hz, 1H), 2.98 (s, 6H),
10 2.79 (d, *J* 3.2 Hz, 3H). LCMS (ES+) 436 (M+H)⁺.

EXAMPLE 29**3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide**

15 To a stirred solution of *Example 6* (100 mg, 0.227 mmol) in MeOH (2 mL) was added sodium methoxide (120 mg, 2.27 mmol). The resulting solution was heated in a microwave at 100°C for 1 h. The reaction mixture was quenched with water (0.5 mL) and concentrated *in vacuo* after stirring for 2 minutes. The residue was dissolved in DCM (5
20 mL), washed with water (5 mL), dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by preparative HPLC to yield the *title compound* (43 mg, 43%) as a white solid. δ_{H} (d_6 -DMSO at 80°C) 7.95 (s, 1H), 7.48 (s, 1H), 7.40-7.32 (m, 2H), 7.18 (dd, *J* 8.4, 1.2 Hz, 1H), 7.12 (s, 1H), 6.64 (d, *J* 8.4 Hz, 1H), 4.32-4.24 (m, 1H), 3.93 (d, *J* 7.6 Hz, 1H), 3.86 (s, 3H), 3.81 (d, *J* 11.5 Hz, 2H), 3.77 (s, 3H), 3.59 (dd, *J* 11.5, 2.9 Hz,
25 1H), 3.51-3.48 (m, 2H), 3.16-3.08 (m, 2H), 2.97 (s, 6H). LCMS (ES+) 437 (M+H)⁺.

EXAMPLE 30**1-Methyl-3-[(S)-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide**

30 *Example 29* (200 mg, 0.475 mmol) was dissolved in a solution of H₂SO₄ (1 mL; 600 μ L conc. H₂SO₄ and 400 μ L water) and stirred at r.t. for 5 minutes. A solution of sodium nitrite (36 mg, 0.523 mmol) in water (0.5 mL) was added dropwise to the reaction

mixture whilst the temperature was maintained between 0 and 5°C. On complete addition, the reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was neutralized with conc. sodium hydroxide solution and extracted with DCM (3 x 10 mL). The combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by preparative HPLC to yield the *title compound* (10 mg, 5%) as a white solid. δ_{H} (d₆-DMSO at 80°C) 11.40 (s, 1H), 7.58 (s, 1H), 7.38 (d, *J* 8.4 Hz, 1H), 7.25 (s, 1H), 7.19-7.13 (m, 3H), 6.16 (d, *J* 9.4 Hz, 1H), 4.32-4.22 (m, 1H), 3.91 (d, *J* 7.7 Hz, 1H), 3.80-3.73 (m, 5H), 3.55 (dd, *J* 11.6, 2.7 Hz, 1H), 3.50-3.42 (m, 2H), 3.18 (dd, *J* 14.3, 7.8 Hz, 1H), 3.10-3.05 (m, 1H), 2.98 (s, 6H). LCMS (ES+) 423 (M+H)⁺.

EXAMPLE 31 (METHOD C)

1-Methyl-3-[(S)-4-propionylmorpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide

To a stirred solution of *Intermediate 3* (200 mg, 0.67 mmol) in DCM (5 mL) at 0-5°C were added triethylamine (143 μ L, 1.0 mmol) and propionyl chloride (69 μ L, 0.80 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 30 minutes. The mixture was quenched with water (5 mL), then the organic layer was separated, dried (MgSO₄) and concentrated *in vacuo*. The residue was chromatographed (SiO₂, 50% EtOAc/hexanes), yielding the *title compound* (120 mg, 50%) as a white solid. δ_{H} (d₆-DMSO) 7.81 (s, 0.5H), 7.70 (s, 0.5H), 7.42 (d, *J* 8.3 Hz, 1H), 7.21 (m, 2H), 4.51-4.40 (m, 1H), 4.16-3.84 (m, 2H), 3.76 (s, 3H), 3.63 (d, *J* 11.7 Hz, 1H), 3.51-3.05 (m, 4H), 3.00 (s, 6H), 2.81-2.60 (m, 1H), 2.46-2.06 (m, 2H), 1.85-1.66 (m, 1H), 1.00 (t, *J* 7.3 Hz, 1H), 0.70 (t, *J* 7.2 Hz, 1H). LCMS (ES+) 358 (M+H)⁺.

EXAMPLE 32

3-[(S)-4-(2,2-Dimethylpropionyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

The *title compound* was prepared from *Intermediate 3* and pivaloyl chloride according to *Method C* and was isolated as a white solid (140 mg, 54%). δ_{H} (d₆-DMSO) 7.79 (s, 1H), 7.42 (d, *J* 8.3 Hz, 1H), 7.23 (s, 1H), 7.21 (dd, *J* 8.3, 1.3 Hz, 1H), 4.49-4.40

(m, 1H), 3.97 (d, *J* 13.1 Hz, 1H), 3.87 (d, *J* 9.6 Hz, 1H), 3.76 (s, 3H), 3.65 (d, *J* 11.4 Hz, 1H), 3.51-3.31 (m, 4H), 3.00 (s, 6H), 2.73 (dd, *J* 14.1, 4.8 Hz, 1H), 1.18 (s, 9H). LCMS (ES+) 386 (M+H)⁺.

5

EXAMPLE 33**3-[(S)-4-(Cyclopropanecarbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carboxylic acid dimethylamide**

The *title compound* was prepared from *Intermediate 3* and cyclopropanecarbonyl chloride according to *Method C* and was isolated as a white solid (140 mg, 57%). δ_H (d₆-DMSO) 7.73 (m, 1H), 7.41 (d, *J* 8.3 Hz, 1H), 7.23-7.17 (m, 2H), 4.49-4.29 (m, 1H), 4.12-4.00 (m, 1H), 3.95-3.89 (m, 1H), 3.87-3.80 (m, 1H), 3.75 (s, 3H), 3.63-3.32 (m, 2H), 3.22-3.06 (m, 2H), 2.97 (d, *J* 5.6 Hz, 6H), 1.46 (m, 1H), 0.83-0.57 (m, 2H), 0.44 (ddd, *J* 4.3, 1.5, 0.8 Hz, 1H), 0.17-0.10 (m, 1H), -0.15 to -0.06 (m, 1H). LCMS (ES+) 370 (M+H)⁺.

15

EXAMPLE 34 (METHOD D)**(6-Chloropyridin-3-yl)-[(S)-3-(1-methyl-5-phenyl-1*H*-indol-3-ylmethyl)morpholin-4-yl]-methanone**

20

To a stirred solution of *Intermediate 11* (70 mg, 0.23 mmol) in DCM (5 mL) at 0°C were added triethylamine (72 μL, 0.46 mmol) and 6-chloronicotinoyl chloride (230 μL, 0.23 mmol). The reaction mixture was stirred at room temperature for 1 h, then quenched with water. The organic layer was separated, dried (MgSO₄) and concentrated *in vacuo* to yield an oil which was purified by preparative HPLC to give *title compound* (22 mg, 21%) as a yellow solid. δ_H (d₆-DMSO at 90°C) 8.06 (s, 1H), 7.60 (d, *J* 7.3 Hz, 3H), 7.43 (dd, *J* 7.6, 7.6 Hz, 4H), 7.31-7.26 (m, 2H), 7.25-7.10 (m, 1H), 7.09 (s, 1H), 4.30-4.12 (m, 1H), 3.95 (d, *J* 6.7 Hz, 1H), 3.86 (d, *J* 11.5 Hz, 2H), 3.78 (s, 3H), 3.69-3.67 (m, 1H), 3.52 (d, *J* 9.0 Hz, 2H), 3.22-3.15 (m, 2H). LCMS (ES+) 446 (M+H)⁺.

30

EXAMPLE 35**1-Methyl-3-[(S)-4-(3-methylbenzoyl)morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide**

5 The *title compound* was prepared from *Intermediate 3* and *m*-toluoyl chloride according to *Method D* and was isolated as a white solid (70 mg) after purification by preparative HPLC. δ_{H} (d_6 -DMSO at 110°C) 7.42 (s, 1H), 7.38 (d, *J* 8.5 Hz, 1H), 7.22-7.14 (m, 3H), 7.09 (s, 1H), 6.96 (d, *J* 7.1 Hz, 1H), 6.91 (s, 1H), 4.26-4.24 (m, 1H), 3.91 (d, *J* 7.7 Hz, 1H), 3.79-3.75 (m, 5H), 3.53 (dd, *J* 11.4, 3.1 Hz, 1H), 3.48-3.45 (m, 2H),
10 3.23 (dd, *J* 14.2, 8.3 Hz, 1H), 3.06 (dd, *J* 14.2, 6.7 Hz, 1H), 2.97 (s, 6H), 2.25 (s, 3H). LCMS (ES+) 420 (M+H)⁺.

EXAMPLE 36**1-Methyl-3-[(S)-4-(4-methylbenzoyl)morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide**

 The *title compound* was prepared from *Intermediate 3* and *p*-toluoyl chloride according to *Method D* and was isolated as a white solid (70 mg) after purification by preparative HPLC. δ_{H} (d_6 -DMSO at 110°C) 7.49 (s, 1H), 7.38 (d, *J* 8.4 Hz, 1H), 7.19 (dd, *J* 8.4, 1.2 Hz, 1H), 7.13-7.04 (m, 5H), 4.28-4.19 (m, 1H), 3.90 (d, *J* 7.5 Hz, 1H), 3.79-3.60 (m, 5H), 3.52 (dd, *J* 11.5, 3.2 Hz, 1H), 3.46 (d, *J* 8.9 Hz, 2H), 3.24 (dd, *J* 14.3, 8.4 Hz, 1H), 3.06 (dd, *J* 14.3, 6.7 Hz, 1H), 2.98 (s, 6H), 2.31 (s, 3H). LCMS (ES+) 420 (M+H)⁺.

25

EXAMPLE 37**3-[(S)-4-(3-Chlorobenzoyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide**

 The *title compound* was prepared from *Intermediate 3* and *m*-chlorobenzoyl chloride according to *Method D* and was isolated as a white solid (70 mg) after purification by preparative HPLC. δ_{H} (d_6 -DMSO at 110°C) 7.45-7.26 (m, 4H), 7.18 (d, *J* 8.4 Hz, 1H), 7.10-7.05 (m, 3H), 4.25-4.19 (m, 1H), 3.92 (d, *J* 7.5 Hz, 1H), 3.82-3.76 (m,

5H), 3.58 (dd, J 11.6, 3.1 Hz, 1H), 3.49 (d, J 8.9 Hz, 2H), 3.21 (dd, J 14.4, 7.7 Hz, 1H), 3.12 (dd, J 14.4, 7.3 Hz, 1H), 2.98 (s, 6H). LCMS (ES+) 440 (M+H)⁺.

EXAMPLE 38

5

3-[(S)-4-(4-Chlorobenzoyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

The *title compound* was prepared from *Intermediate 3* and *p*-chlorobenzoyl chloride according to *Method D* and was isolated as a white solid (70 mg) after purification by preparative HPLC. δ_{H} (d₆-DMSO at 110°C) 7.52 (s, 1H), 7.39 (d, J 8.4 Hz, 1H), 7.31 (d, J 8.3 Hz, 2H), 7.20 (dd, J 8.4, 1.3 Hz, 1H), 7.13-7.10 (m, 3H), 4.23-4.19 (m, 1H), 3.92 (d, J 7.6 Hz, 1H), 3.82-3.75 (m, 5H), 3.56 (dd, J 11.6, 3.1 Hz, 1H), 3.48 (d, J 8.9 Hz, 2H), 3.22 (dd, J 14.3, 7.9 Hz, 1H), 3.11 (d, J 14.3, 7.1 Hz, 1H), 2.99 (s, 6H). LCMS (ES+) 440 (M+H)⁺.

15

EXAMPLE 39

1-Methyl-3-[(S)-4-(naphthalene-1-carbonyl)morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide

The *title compound* was prepared from *Intermediate 3* and 1-naphthoyl chloride according to *Method D* and was isolated as a white solid (70 mg) after purification by preparative HPLC. δ_{H} (d₆-DMSO at 130°C) 7.92-7.87 (m, 2H), 7.70-7.60 (m, 1H), 7.53-7.37 (m, 5H), 7.19-7.16 (m, 2H), 7.15-7.01 (m, 1H), 3.90-3.85 (m, 1H), 3.77-3.72 (m, 4H), 3.60-3.42 (m, 4H), 3.30 (dd, J 14.4, 8.4 Hz, 1H), 3.20-3.02 (m, 1H), 2.96 (s, 6H), 2.86-2.70 (m, 1H). LCMS (ES+) 456 (M+H)⁺.

25

EXAMPLE 40

1-Methyl-3-[(S)-4-(naphthalene-2-carbonyl)morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide

30

The *title compound* was prepared from *Intermediate 3* and 2-naphthoyl chloride according to *Method D* and was isolated as a white solid (70 mg) after purification by preparative HPLC. δ_{H} (d₆-DMSO at 110°C) 7.89-7.80 (m, 3H), 7.61 (s, 1H), 7.56-7.49

(m, 3H), 7.38 (d, *J* 8.4 Hz, 1H), 7.23 (dd, *J* 8.4, 1.5 Hz, 1H), 7.16 (dd, *J* 8.4, 1.5 Hz, 1H), 7.10 (s, 1H), 4.36-4.30 (m, 1H), 3.94-3.79 (m, 3H), 3.76 (s, 3H), 3.61 (dd, *J* 11.6, 3.2 Hz, 1H), 3.56-3.52 (m, 2H), 3.29-3.13 (m, 2H), 2.88 (s, 6H). LCMS (ES+) 456 (M+H)⁺.

5

EXAMPLE 41**3-[(S)-4-(3-Methoxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carboxylic acid dimethylamide**

The *title compound* was prepared from *Intermediate 3* and 3-methoxybenzoyl chloride according to *Method D* and was isolated as a white solid (70 mg) after purification by preparative HPLC. δ_{H} (d₆-DMSO at 90°C) 7.44 (br s, 1H), 7.39 (d, *J* 8.4 Hz, 1H), 7.25-7.17 (m, 2H), 7.11 (s, 1H), 6.91 (dd, *J* 8.2, 2.1 Hz, 1H), 6.72 (d, *J* 7.4 Hz, 1H), 6.68 (s, 1H), 4.30-4.15 (m, 1H), 3.92-3.90 (m, 1H), 3.76 (s, 4H), 3.74, (s, 3H), 3.53 (dd, *J* 15.3, 3.0 Hz, 1H), 3.47-3.45 (m, 2H), 3.24 (dd, *J* 14.2, 8.5 Hz, 2H), 3.05 (dd, *J* 14.2, 6.7 Hz, 1H), 2.98 (s, 6H). LCMS (ES+) 436 (M+H)⁺.

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EXAMPLE 42**1-Methyl-3-{(S)-4-[4-methyl-3-(trifluoromethyl)benzoyl]morpholin-3-ylmethyl}-1*H*-indole-5-carboxylic acid dimethylamide**

20

The *title compound* was prepared from *Intermediate 3* and 4-methyl-3-(trifluoromethyl)benzoyl chloride according to *Method D* and was isolated as a white solid (80 mg). δ_{H} (d₆-DMSO at 110°C) 7.49 (s, 1H), 7.37 (d, *J* 8.4 Hz, 1H), 7.30 (s, 2H), 7.25 (d, *J* 7.7 Hz, 1H), 7.18 (d, *J* 8.4 Hz, 1H), 7.10 (s, 1H), 4.26-4.20 (m, 1H), 3.92 (d, *J* 7.4 Hz, 1H), 3.82 (d, *J* 11.6 Hz, 1H), 3.75-3.70 (m, 4H), 3.60 (dd, *J* 11.6, 3.1 Hz, 1H), 3.55-3.46 (m, 2H), 3.17 (dd, *J* 7.5, 2.7 Hz, 2H), 2.91 (s, 6H), 2.43 (s, 3H). LCMS (ES+) 488 (M+H)⁺.

25

EXAMPLE 43

3-((S)-4-[4-Fluoro-3-(trifluoromethyl)benzoyl]morpholin-3-ylmethyl)-1-methyl-1H-indole-5-carboxylic acid dimethylamide

- 5 The *title compound* was prepared from *Intermediate 3* and 4-fluoro-3-(trifluoromethyl)benzoyl chloride according to *Method D* and was isolated as a white solid (75 mg). δ_{H} (d_6 -DMSO at 110°C) 7.48-7.29 (m, 5H), 7.18 (dd, J 7.4, 1.5 Hz, 1H), 7.11 (s, 1H), 4.25-4.20 (m, 1H), 3.93 (d, J 7.2 Hz, 1H), 3.83 (d, J 11.5 Hz, 1H), 3.77 (s, 4H), 3.64 (dd, J 11.5, 3.1 Hz, 1H), 3.52 (d, J 8.8 Hz, 2H), 3.17 (d, J 7.5 Hz, 2H), 2.91 (s, 6H).
- 10 LCMS (ES+) 492 (M+H)⁺. The *title compound* was also prepared by *Method F*.

EXAMPLE 44

1-Methyl-3-((S)-4-{2-[3-(trifluoromethyl)phenyl]acetyl}morpholin-3-ylmethyl)-1H-indole-5-carboxylic acid dimethylamide

- 15 The *title compound* was prepared from *Intermediate 3* and 3-(trifluoromethyl)-phenylacetyl chloride according to *Method D* and was isolated as a white solid (47 mg). δ_{H} (d_6 -DMSO at 110°C) 7.78 (d, J 0.8 Hz, 1H), 7.62-7.36 (m, 4H), 7.29-7.18 (m, 2H), 7.00-6.92 (m, 1H), 4.53-4.46 (m, 1H), 4.15 (d, J 11.4 Hz, 1H), 3.97-3.80 (m, 3H), 3.76 (d, J 7.3 Hz, 3H), 3.70-3.64 (m, 1H), 3.58-3.33 (m, 3H), 3.25-3.14 (m, 2H), 3.04 (d, J 16.2 Hz, 1H), 2.97 (s, 3H), 2.91 (s, 2H). LCMS (ES+) 488 (M+H)⁺.
- 20

EXAMPLE 45

3-((S)-4-[4-Methoxy-3-(trifluoromethyl)benzoyl]morpholin-3-ylmethyl)-1-methyl-1H-indole-5-carboxylic acid dimethylamide

- 25 The *title compound* was prepared from *Intermediate 3* and 4-methoxy-3-(trifluoromethyl)benzoyl chloride according to *Method D* and was isolated as a white solid (76 mg). δ_{H} (d_6 -DMSO at 90°C) 7.49 (s, 1H), 7.39-7.33 (m, 2H), 7.25 (s, 1H), 7.17 (d, J 8.4 Hz, 1H), 7.11-7.09 (m, 2H), 4.25-4.20 (m, 1H), 3.92 (d, J 7.7 Hz, 1H), 3.89 (s, 3H), 3.81 (d, J 11.5 Hz, 1H), 3.77 (s, 3H), 3.60 (dd, J 11.6, 3.0 Hz, 1H), 3.50 (d, J 9.0 Hz, 2H), 3.16 (J 7.5 Hz, 2H), 2.99-2.97 (m, 1H), 2.96 (s, 6H). LCMS (ES+) 504 (M+H)⁺.
- 30

EXAMPLE 46 (METHOD E)**3-[(S)-4-[6-(*tert*-Butyl)pyridine-3-carbonyl]morpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carboxylic acid dimethylamide**

5 To a solution of *Intermediate 3* (250 mg, 0.83 mmol), *tert*-butylcarboxylic acid (89 mg, 0.88 mmol), 6-(*tert*-butyl)pyridine-3-carboxylic acid (158 mg, 0.88 mmol), EDC (270 mg, 1.25 mmol) and HOBt (150 mg, 0.83 mmol) in DCM (5 mL) was added DIPEA (250 μ L, 1.66 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with water (10 mL). The organic layer was separated,
10 dried (MgSO₄), concentrated *in vacuo* and chromatographed (SiO₂, 20:1 EtOAc/MeOH), yielding the *title compound* (140 mg, 34%) as a white solid after freeze-drying with 1:1 MeCN-water. δ_{H} (d₆-DMSO) 8.30 (s, 1H), 7.61 (s, 1H), 7.41-7.37 (m, 2H), 7.32 (d, *J* 8.1 Hz, 1H), 7.21 (dd, *J* 8.4, 1.4 Hz, 1H), 7.07 (s, 1H), 4.30-4.18 (m, 1H), 3.93-3.90 (m, 1H), 3.82 (d, *J* 11.6 Hz, 1H), 3.78-3.75 (m, 4H), 3.59 (dd, *J* 11.7, 3.2 Hz, 1H), 3.57-3.50 (m,
15 2H), 3.22-3.14 (m, 2H), 2.99 (s, 6H), 1.33 (s, 9H). LCMS (ES⁺) 463 (M+H)⁺.

EXAMPLE 47**1-Methyl-3-[(S)-4-[5-(trifluoromethyl)pyridine-3-carbonyl]morpholin-3-ylmethyl]-1*H*-indole-5-carboxylic acid dimethylamide**

The *title compound* was prepared from *Intermediate 3* and 5-(trifluoromethyl)-nicotinic acid according to *Method E* and was isolated as a white solid (85 mg). δ_{H} (d₆-DMSO at 110°C) 8.84 (s, 1H), 8.54 (s, 1H), 7.76 (s, 1H), 7.48 (s, 1H), 7.38 (d, *J* 8.4 Hz, 1H), 7.18 (dd, *J* 8.4, 1.4 Hz, 1H), 7.12 (s, 1H), 4.30-4.15 (m, 1H), 3.94 (d, *J* 7.3 Hz, 1H),
25 3.84 (d, *J* 11.6 Hz, 1H), 3.77-3.75 (m, 4H), 3.69 (dd, *J* 11.6, 2.9 Hz, 1H), 3.61-3.52 (m, 2H), 3.21-3.18 (m, 2H), 2.97 (s, 6H). LCMS (ES⁺) 475 (M+H)⁺.

EXAMPLE 48**1-Methyl-3-[(S)-4-(1,3-oxazole-5-carbonyl)morpholin-3-ylmethyl]-1*H*-indole-5-carboxylic acid dimethylamide**

The *title compound* was prepared from *Intermediate 3* and 1,3-oxazole-5-carboxylic acid according to *Method E* and was isolated as an off-white solid (86 mg). δ_{H}

(d₆-DMSO at 80°C) 8.27 (s, 1H), 7.64 (s, 1H), 7.39-7.36 (m, 2H), 7.21-7.15 (m, 2H), 4.50-4.42 (m, 1H), 4.04-3.96 (m, 2H), 3.83 (d, *J* 11.7 Hz, 1H), 3.75 (s, 3H), 3.59-3.46 (m, 3H), 3.27 (dd, *J* 14.2, 8.1 Hz, 1H), 3.08 (dd, *J* 14.2, 6.8 Hz, 1H), 3.01 (s, 6H). LCMS (ES+) 397 (M+H)⁺.

5

EXAMPLE 49

1-Methyl-3-[(S)-4-(1H-pyrazole-3-carbonyl)morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide

10 The *title compound* was prepared from *Intermediate 3* and 1H-pyrazole-3-carboxylic acid according to *Method E* and was isolated as an off-white solid (53 mg). δ_H (d₆-DMSO at 90°C) 7.66 (br s, 2H), 7.38 (d, *J* 8.4 Hz, 1H), 7.20 (dd, *J* 8.4, 1.4 Hz, 1H), 7.14 (s, 1H), 6.45 (s, 1H), 4.75-4.71 (m, 1H), 4.45-4.30 (m, 1H), 3.94 (d, *J* 7.4 Hz, 1H), 3.76-3.73 (m, 4H), 3.48-3.44 (m, 3H), 3.34 (dd, *J* 14.1, 9.6 Hz, 1H), 3.12-3.00 (m, 7H).
15 LCMS (ES+) 396 (M+H)⁺.

EXAMPLE 50

3-[(S)-4-[2-(1H-Indol-3-yl)acetyl]morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

20 The *title compound* was prepared from *Intermediate 3* and indole-3-acetic acid according to *Method E* and was isolated as an off-white solid (78 mg). δ_H (d₆-DMSO) 10.50 (br s, 1H), 7.75 (s, 1H), 7.43 (br s, 1H), 7.39 (d, *J* 8.3 Hz, 1H), 7.34 (d, *J* 8.1 Hz, 1H), 7.22 (dd, *J* 8.3, 1.5 Hz, 1H), 7.10-7.03 (m, 3H), 6.95 (t, *J* 7.3 Hz, 1H), 4.46-4.32 (m, 1H), 4.07-3.94 (m, 1H), 3.86 (d, *J* 7.3 Hz, 1H), 3.77-3.66 (m, 6H), 3.63-3.53 (m, 1H),
25 3.37-3.28 (m, 3H), 3.20 (dd, *J* 14.1, 8.6 Hz, 1H), 2.99 (s, 6H). LCMS (ES+) 459 (M+H)⁺.

EXAMPLE 51

3-[(S)-4-[2-(2-Amino-1,3-thiazol-5-yl)acetyl]morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

30 The *title compound* was prepared from *Intermediate 3* and 2-amino-1,3-thiazole-5-acetic acid according to *Method E* and was isolated as an off-white solid (29 mg). δ_H

(d₆-DMSO at 110°C) 7.75 (s, 1H), 7.40 (d, *J* 8.6 Hz, 1H), 7.22 (dd, *J* 8.3, 1.3 Hz, 1H), 7.17 (s, 1H), 6.43 (br s, 2H), 6.13 (s, 1H), 4.45-4.32 (m, 1H), 4.03-3.85 (m, 2H), 3.77 (s, 3H), 3.72 (d, *J* 11.6 Hz, 1H), 3.52-3.25 (m, 6H), 3.00 (s, 6H), 2.98-2.87 (m, 1H). LCMS (ES+) 442 (M+H)⁺.

5

EXAMPLE 52

1-Methyl-3-[(S)-4-[2-(1H-tetrazol-5-yl)acetyl]morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide

10

The *title compound* was prepared from *Intermediate 3* and 1H-tetrazole-5-acetic acid according to *Method E* and was isolated as a white solid (60 mg). δ_H (d₆-DMSO at 110°C) 7.74 (s, 1H), 7.39 (d, *J* 8.4 Hz, 1H), 7.21 (dd, *J* 8.4, 1.5 Hz, 1H), 7.18 (s, 1H), 4.45-4.40 (m, 1H), 4.10-3.98 (m, 1H), 3.86-3.82 (m, 2H), 3.77 (s, 3H), 3.71 (d, *J* 11.5 Hz, 2H), 3.38-3.27 (m, 3H), 3.24 (dd, *J* 14.1, 9.3 Hz, 1H), 2.99 (s, 6H), 2.98-2.89 (m, 1H).

15 LCMS (ES+) 412 (M+H)⁺.

EXAMPLE 53

1-Methyl-3-[(S)-4-[2-(5-methyl-2H-[1,2,4]triazol-3-yl)acetyl]morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide

20

The *title compound* was prepared from *Intermediate 3* and 2-(3-methyl-1H-[1,2,4]triazol-5-yl)acetic acid according to *Method E* and was isolated as a white solid (47 mg). δ_H (d₆-DMSO at 110°C) 7.74 (s, 1H), 7.40 (d, *J* 8.3 Hz, 1H), 7.21 (dd, *J* 8.3, 1.3 Hz, 1H), 7.18 (s, 1H), 4.44-4.33 (m, 1H), 4.03-3.93 (m, 1H), 3.90 (d, *J* 7.3 Hz, 1H), 3.77 (s, 3H), 3.74 (d, *J* 11.6 Hz, 2H), 3.68-3.50 (m, 2H), 3.44-3.34 (m, 3H), 3.26 (dd, *J* 14.4, 9.3 Hz, 1H), 2.99 (s, 6H), 2.27 (s, 3H). LCMS (ES+) 425 (M+H)⁺.

25

EXAMPLE 54

3-[(S)-4-[2-(3H-Imidazol-4-yl)acetyl]morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

30

The *title compound* was prepared from *Intermediate 3* and imidazole-4-acetic acid hydrochloride salt according to *Method E* and was isolated as a white solid (7 mg). δ_H

(d₆-DMSO at 110°C) 7.74 (s, 1H), 7.46 (s, 1H), 7.40 (d, *J* 8.6 Hz, 1H), 7.22 (dd, *J* 8.3, 1.3 Hz, 1H), 7.16 (s, 1H), 6.75 (s, 1H), 4.46-4.37 (m, 1H), 4.05-3.96 (m, 1H), 3.88 (d, *J* 7.6 Hz, 1H), 3.76 (s, 3H), 3.73 (d, *J* 11.6 Hz, 1H), 3.58-3.50 (m, 1H), 3.48-3.43 (m, 1H), 3.36 (dd, *J* 10.9, 3.0 Hz, 3H), 3.24 (dd, *J* 14.1, 9.1 Hz, 1H), 3.01 (m, 6H), 2.98-2.90 (m, 1H).

5 LCMS (ES+) 410 (M+H)⁺.

EXAMPLE 55

10 3-[(S)-4-[2-(Imidazo[1,2-a]pyridin-2-yl)acetyl]morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

The *title compound* was prepared from *Intermediate 3* and imidazo[1,2-a]-pyridine-2-acetic acid hydrochloride salt according to *Method E* and was isolated as a white solid (60 mg). δ_H (d₆-DMSO at 110°C) 8.40 (d, *J* 6.6 Hz, 1H), 7.76 (s, 1H), 7.64 (s, 1H), 7.42 (d, *J* 9.1 Hz, 1H), 7.39 (d, *J* 8.3 Hz, 1H), 7.21 (dd, *J* 8.3, 1.5 Hz, 1H), 7.16 (m, 2H), 6.80 (t, *J* 6.8 Hz, 1H), 4.49-4.41 (m, 1H), 4.10-4.01 (m, 1H), 3.90 (d, *J* 7.3 Hz, 2H), 3.77-3.71 (m, 5H), 3.45-3.34 (m, 3H), 3.25 (dd, *J* 14.1, 8.8 Hz, 1H), 3.01-2.98 (s, 6H), 2.96-2.92 (m, 1H). LCMS (ES+) 460 (M+H)⁺.

EXAMPLE 56

20 1-Methyl-3-[(S)-4-(1H-pyrrolo[2,3-b]pyridine-5-carbonyl)morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide

The *title compound* was prepared from *Intermediate 3* and 1H-pyrrolo[2,3-b]-pyridine-5-carboxylic acid according to *Method E* and was isolated as a white solid (15 mg). δ_H (d₆-DMSO at 80°C) 11.51 (s, 1H), 8.01 (s, 1H), 7.66 (s, 1H), 7.52 (s, 1H), 7.45 (t, *J* 3.0 Hz, 1H), 7.39 (d, *J* 8.4 Hz, 1H), 7.16 (dd, *J* 1.4, 8.4 Hz, 1H), 7.11 (s, 1H), 6.41 (dd, *J* 1.7, 3.3 Hz, 1H), 4.36 (br s, 1H), 3.92 (d, *J* 8.2 Hz, 1H), 3.82-3.76 (m, 4H), 3.60 (dd, *J* 3.0, 11.4 Hz, 1H), 3.56-3.47 (m, 2H), 3.25-2.95 (m, 3H), 2.91 (s, 6H). LCMS (ES+) 446 (M+H)⁺.

30

EXAMPLE 57**1-Methyl-3-[(S)-4-[2-(pyridin-2-yl)acetyl]morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide**

- 5 To a solution of *Intermediate 3* (150 mg, 0.50 mmol), 2-pyridylacetic acid (86 mg, 0.50 mmol), EDC (142 mg, 0.75 mmol) and HOBT (75 mg, 0.50 mmol) in DCM (5 mL) was added DIPEA (177 μ L, 1.00 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with water (5 mL) and stirred for a further 30 minutes. The organic layer was separated, dried (phase separator),
- 10 concentrated *in vacuo* and purified by preparative HPLC, yielding the *title compound* (42 mg, 20%) as a white solid. δ_{H} (d_6 -DMSO at 100°C) 8.45-8.43 (m, 1H), 7.74 (s, 1H), 7.67 (t, *J* 7.6 Hz, 1H), 7.40 (d, *J* 8.4 Hz, 1H), 7.22-7.13 (m, 4H), 4.50-4.35 (m, 1H), 4.10-3.92 (m, 1H), 3.89 (d, *J* 7.2 Hz, 1H), 3.77-3.70 (m, 6H), 3.39-3.34 (m, 4H), 3.24 (dd, *J* 14.2, 8.9 Hz, 1H), 2.98 (s, 6H). LCMS (ES+) 421(M+H)⁺.

15

EXAMPLE 58**3-[(S)-4-[2-(2-Amino-1,3-thiazol-4-yl)acetyl]morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide**

- 20 To a stirred solution of (2-amino-1,3-thiazol-4-yl)acetic acid ethyl ester (500 mg, 2.70 mmol) in THF (3 mL) was added a solution of LiOH (130 mg, 3.10 mmol) in water (1 mL). The mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* and treated with DMF (10 mL), followed by EDC (1 g, 6.44 mmol), HOBT (500 mg, 3.70 mmol) and DIPEA (1 mL, 5.74 mmol). After stirring for 30
- 25 minutes at r.t. the reaction mixture was treated with a solution of *Intermediate 3* (200 mg, 0.66 mmol) in DMF (1 mL) and heated to 70°C for 2 h. The reaction mixture was partitioned between water (30 mL) and DCM (30 mL). The aqueous was washed with DCM (2 x 20mL) and the combined organics were dried (Na₂SO₄ and phase separator), filtered and concentrated *in vacuo*. The residue was chromatographed (SiO₂, 0-20%
- 30 MeOH/EtOAc) yielding an off-white solid, which was further purified by preparative HPLC to yield the *title compound* (70 mg, 6%) as a white solid. δ_{H} (d_6 -DMSO) 7.81 (s, 0.5H), 7.70 (s, 0.5H), 7.43 (t, *J* 8.3 Hz, 1H), 7.21 (s, 2H), 6.82 (d, *J* 13.6 Hz, 2H), 6.12 (d, *J* 13.1 Hz, 1H), 4.52-4.45 (m, 1H), 4.20-4.11 (m, 1H), 3.95-3.82 (m, 1H), 3.79-3.74 (m,

4H), 3.67 (dd, J 24.0, 11.1 Hz, 1H), 3.53 (s, 1H), 3.29-3.12 (m, 3H), 3.02-2.94 (m, 7H), 2.78-2.70 (m, 1H). LCMS (ES+) 442 (M+H)⁺.

EXAMPLE 59

5

3-[(S)-4-(2-Aminopyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

To a stirred solution of 2-aminonicotinic acid (45 mg, 0.33 mmol) in DMF (3 mL) was added EDC (150 mg, 0.96 mmol), HOBT (80 mg, 0.59 mmol) and DIPEA (180 μ L, 1.03 mmol). The reaction mixture was stirred at 50°C for 2 h. To the resulting pale yellow solution was added *Intermediate 3* (100 mg, 0.33 mmol) in DMF (3 mL) and the mixture was heated to 80°C for 2 h. The reaction mixture was partitioned between water (10 mL) and EtOAc (10 mL). The aqueous was washed with DCM (2 x 15 mL) and the combined organics were dried (Na₂SO₄ and phase separator), filtered, concentrated *in vacuo* and azeotroped with heptane (3 x 15 mL). The residue was purified by preparative HPLC, yielding the *title compound* (65 mg, 47%) as an off-white solid. δ_{H} (d₆-DMSO at 90°C) 7.94 (d, J 4.8 Hz, 1H), 7.44 (s, 1H), 7.39 (d, J 8.5 Hz, 1H), 7.18 (d, J 8.4 Hz, 1H), 7.12 (s, 1H), 7.08 (d, J 7.3 Hz, 1H), 6.46 (dd, J 7.1, 5.1 Hz, 1H), 5.56 (br s, 2H), 4.25-4.18 (m, 1H), 3.90 (d, J 10.8 Hz, 1H), 3.76-3.70 (m, 4H), 3.59-3.42 (m, 4H), 3.24 (dd, J 14.2, 8.8 Hz, 1H), 3.04 (dd, J 14.2, 6.5 Hz, 1H), 2.99 (s, 6H). LCMS (ES+) 422 (M+H)⁺.

EXAMPLE 60

(6-Chloropyridin-3-yl)-{(S)-3-[1-methyl-5-(2-methylimidazol-1-yl)-1H-indol-3-ylmethyl]morpholin-4-yl}-methanone

To a stirred solution of *Intermediate 12* (155 mg, 0.50 mmol) in DCM (5 mL) at 0°C was added triethylamine (144 μ L, 0.10 mmol) and 6-chloronicotinoyl chloride (97 mg, 0.55 mmol). The reaction mixture was stirred at room temperature for 1 h. The mixture was quenched with water. The organic layer was separated, dried (MgSO₄) and concentrated *in vacuo* to yield an oil which was purified by preparative HPLC to give the *title compound* (32 mg, 14%) as an off-white solid. δ_{H} (d₆-DMSO at 90°C) 7.98 (br s, 1H), 7.49 (d, J 8.6 Hz, 1H), 7.43-7.18 (m, 4H), 7.12-7.09 (m, 2H), 6.88 (d, J 1.2 Hz, 1H), 4.20-4.13 (m, 1H), 3.94-3.92 (m, 1H), 3.86-3.81 (m, 5H), 3.67 (d, J 10.8 Hz, 1H), 3.51 (d,

J 9.0 Hz, 2H), 3.21 (dd, *J* 14.1, 8.2 Hz, 1H), 3.12-3.06 (m, 1H), 2.22 (s, 3H). LCMS (ES⁺) 450 (M+H)⁺.

EXAMPLES 61 TO 75

5

General Procedure

To a stirred solution of the relevant carboxylic acid (0.036 mmol), Mukaiyama resin supported reagent from Polymer Labs (44 mg, 0.046 mmol, CPT004, 1.04 mmol/g) and *Intermediate 3* (9.3 mg, 0.03 mmol) in DMF (1 mL) was added DIPEA (26.8 μ L, 0.153 mmol). The reaction mixture was shaken for 16 h. The mixture was filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC (*Method 4*), yielding the *title compound*.

Example No.	Compound Name	Accurate Mass
61	3-[(<i>S</i>)-4-(1,5-Dimethyl-1 <i>H</i> -[1,2,3]triazole-4-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	424.2223
62	1-Methyl-3-[(<i>S</i>)-4-(4-methyl-1,3-thiazole-5-carbonyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	426.1726
63	3-{(<i>S</i>)-4-[5-(Methoxymethyl)thiophene-2-carbonyl]-morpholin-3-ylmethyl}-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	455.1879
64	3-[(<i>S</i>)-4-(1,2-Dimethyl-1 <i>H</i> -benzimidazole-5-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	473.2427
65	1-Methyl-3-[(<i>S</i>)-4-(1-methyl-1 <i>H</i> -imidazole-2-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	409.2114
66	3-[(<i>S</i>)-4-(2,3-Dihydrobenzo[1,4]dioxine-6-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	463.5256
67	3-[(<i>S</i>)-4-(5-Ethyl-2-methyl-2 <i>H</i> -pyrazole-3-carbonyl)-	437.2427

	morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	
68	3-[(<i>S</i>)-4-(3,5-Dimethylisoxazole-4-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	424.2111
69	3-[(<i>S</i>)-4-(Furan-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	395.1845
70	1-Methyl-3-[(<i>S</i>)-4-(5-nitrofuran-2-carbonyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	440.1696
71	3-[(<i>S</i>)-4-(Imidazo[1,2- <i>a</i>]pyridine-3-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	445.2114
72	3-[(<i>S</i>)-4-(Furazan-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	397.1750
73	3-[(<i>S</i>)-4-(4-Methoxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	435.2158
74	1-Methyl-3-[(<i>S</i>)-4-(quinoline-5-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	456.2161
75	3-[(<i>S</i>)-4-(1-Benzyl-1 <i>H</i> -imidazole-4-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	485.2427

EXAMPLES 76 TO 90

General Procedure

- 5 To a stirred solution of the relevant alcohol (0.05 mmol) in DCM (300 μ L) at 0°C were successively added a solution of 4-nitrophenyl chloroformate (12 mg, 0.06 mmol) in DCM (200 μ L) and a solution of DIPEA (9.5 mg, 0.07 mmol) in DCM (100 μ L). The mixture was stirred for 1 h at 0°C and 4 h at r.t. The reaction mixture was cooled to 0°C prior to the successive addition of a solution of *Intermediate 3* (30 mg, 0.1 mmol) in
- 10 DCM (200 μ L) and a solution of DIPEA (19 mg, 0.14 mmol) in DCM (100 μ L). The reaction mixture was stirred at r.t. overnight. The reaction was then concentrated *in*

vacuo (Genevac, EZ2) and the residue was purified by preparative HPLC (*Method 4*), yielding the *title compound*.

Example No.	Compound Name	Accurate Mass
76	(S)-3-[5-(Dimethylcarbamoyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholine-4-carboxylic acid 2-(2,5-dioxo-pyrrolidin-1-yl)ethyl ester	470.2165
77	(S)-3-[5-(Dimethylcarbamoyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholine-4-carboxylic acid 2-oxopropyl ester	401.4562
78	(S)-3-[5-(Dimethylcarbamoyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholine-4-carboxylic acid 1-hydroxy-pyridin-3-yl ester	438.1903
79	(S)-3-[5-(Dimethylcarbamoyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholine-4-carboxylic acid 2-(2-oxo-pyrrolidin-1-yl)ethyl ester	456.2373
80	(S)-3-[5-(Dimethylcarbamoyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholine-4-carboxylic acid 2-oxo-1 <i>H</i> -pyridin-1-ylmethyl ester	452.2060
81	(S)-3-[5-(Dimethylcarbamoyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholine-4-carboxylic acid 2-cyanoethyl ester	398.1954
82	(S)-3-[5-(Dimethylcarbamoyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholine-4-carboxylic acid 3-methyl-oxetan-3-ylmethyl ester	429.2264
83	(S)-3-[5-(Dimethylcarbamoyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholine-4-carboxylic acid pyridin-3-yl ester	422.1954
84	(S)-3-[5-(Dimethylcarbamoyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholine-4-carboxylic acid 4,4-dimethyl-2-oxotetrahydrofuran-3-yl ester	457.2213
85	(S)-3-[5-(Dimethylcarbamoyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholine-4-carboxylic acid furan-3-yl-	425.1951

	methyl ester	
86	(<i>S</i>)-3-[5-(Dimethylcarbamoyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholine-4-carboxylic acid 5-(methoxycarbonyl)isoxazol-3-yl ester	470.1801
87	(<i>S</i>)-3-[5-(Dimethylcarbamoyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholine-4-carboxylic acid 2-cyanopyridin-3-yl ester	447.1907
88	(<i>S</i>)-3-[5-(Dimethylcarbamoyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholine-4-carboxylic acid furan-2-ylmethyl ester	425.1951
89	(<i>S</i>)-3-[5-(Dimethylcarbamoyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholine-4-carboxylic acid 4-oxocyclohexylmethyl ester	455.2420
90	(<i>S</i>)-3-[5-(Dimethylcarbamoyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholine-4-carboxylic acid benzotriazol-1-ylmethyl ester	476.2172

EXAMPLES 91 TO 97

The following compounds were prepared from the relevant carboxylic acid and the appropriate amine according to *Method A*, with heating to 45°C.

Example No.	Compound Name	¹ H NMR/LCMS
91	{3-[(<i>S</i>)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}-(pyrrolidin-1-yl)-methanone	δ _H (d ₆ -DMSO at 110°C) 7.95 (s, 1H), 7.63 (s, 1H), 7.41-7.27 (m, 3H), 7.10 (s, 1H), 6.64 (d, <i>J</i> 8.6 Hz, 1H), 4.31-4.23 (m, 1H), 3.93 (d, <i>J</i> 7.3 Hz, 1H), 3.87 (s, 3H), 3.84-3.75 (m, 5H), 3.60 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.54-3.44 (m, 6H), 3.24-3.09 (m, 2H), 1.87 (t, <i>J</i> 6.6 Hz, 4H). LCMS (ES ⁺) 463 (M+H) ⁺ .
92	(Azetidin-1-yl)-{3-[(<i>S</i>)-4-(6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}-methanone	δ _H (d ₆ -DMSO at 110°C) 7.97 (d, <i>J</i> 2.0 Hz, 1H), 7.75 (s, 1H), 7.45 (m, 1H), 7.41-7.31 (m, 2H), 7.12 (s, 1H), 6.64 (d, <i>J</i> 8.3 Hz, 1H), 4.36-4.26 (m, 1H), 4.23-4.15 (m, 4H), 3.94 (d, <i>J</i> 7.8 Hz, 1H), 3.90-3.68 (m, 7H), 3.61 (dd, <i>J</i> 11.6, 3.0 Hz, 2H), 3.55-3.47 (m, 2H),

		3.26-3.10 (m, 2H), 2.35-2.23 (m, 2H). LCMS (ES ⁺) 449 (M+H) ⁺ .
93	3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid <i>N</i> -(2-hydroxyethyl)- <i>N</i> -methanamide	δ_{H} (d ₆ -DMSO at 110°C) 7.97 (d, <i>J</i> 2.2 Hz, 1H), 7.52 (s, 1H), 7.38 (d, <i>J</i> 8.5 Hz, 2H), 7.19 (dd, <i>J</i> 8.4, 1.5 Hz, 1H), 7.09 (s, 1H), 6.66 (d, <i>J</i> 8.5 Hz, 1H), 4.32-4.26 (m, 1H), 3.94-3.92 (m, 1H), 3.88 (s, 3H), 3.82 (d, <i>J</i> 11.5 Hz, 1H), 3.76 (s, 3H), 3.64-3.58 (m, 3H), 3.52-3.44 (m, 5H), 3.23-3.10 (m, 2H), 3.02 (m, 3H). LCMS (ES ⁺) 467 (M+H) ⁺ .
94	3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid <i>N</i> -benzyl- <i>N</i> -methanamide	δ_{H} (d ₆ -DMSO at 110°C) 7.94 (s, 1H), 7.57 (s, 1H), 7.42-7.21 (m, 8H), 7.10 (s, 1H), 6.63 (d, <i>J</i> 8.6 Hz, 1H), 4.63 (s, 2H), 4.27-4.19 (m, 1H), 3.92 (d, <i>J</i> 7.6 Hz, 1H), 3.86 (s, 3H), 3.81-3.74 (m, 5H), 3.58 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.52-3.45 (m, 2H), 3.13 (d, <i>J</i> 7.6 Hz, 2H) 3.02 (s, 3H). LCMS (ES ⁺) 513 (M+H) ⁺ .
95	3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid <i>N</i> -(2-methoxyethyl)- <i>N</i> -methanamide	δ_{H} (d ₆ -DMSO at 110°C) 7.97 (s, 1H), 7.52 (s, 1H), 7.39 (d, <i>J</i> 8.3 Hz, 2H), 7.17 (d, <i>J</i> 8.3 Hz, 1H), 7.10 (s, 1H), 6.66 (d, <i>J</i> 8.3 Hz, 1H), 4.32-4.24 (m, 1H), 3.95-3.90 (m, 1H), 3.88 (s, 3H), 3.82 (m, 1H), 3.77 (s, 3H), 3.60 (dd, <i>J</i> 11.4, 2.8 Hz, 1H), 3.56-3.48 (m, 6H), 3.28 (s, 3H), 3.25-3.08 (m, 3H), 2.99 (s, 3H). LCMS (ES ⁺) 481 (M+H) ⁺ .
96	3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid 3-(morpholin-4-yl)propylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.98 (s, 1H), 7.90 (s, 1H), 7.81-7.76 (m, 1H), 7.65 (d, <i>J</i> 8.6 Hz, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.29 (d, <i>J</i> 8.6 Hz, 1H), 7.09 (s, 1H), 6.60 (d, <i>J</i> 8.3 Hz, 1H), 4.39-4.32 (m, 1H), 3.96-3.92 (m, 1H), 3.89-3.74 (m, 8H), 3.66 (dd, <i>J</i> 11.4, 2.8 Hz, 1H), 3.62-3.57 (m, 4H), 3.54-3.48 (m, 2H), 3.42-3.33 (m, 2H), 3.27-3.11 (m, 2H), 2.46-2.37 (m, 6H), 1.81-1.71 (m, 2H). LCMS (ES ⁺) 536 (M+H) ⁺ .
97	{3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}-(4-methyl-piperazin-1-yl)-methanone	δ_{H} (d ₆ -DMSO at 110°C) 7.95 (d, <i>J</i> 0.5 Hz, 1H), 7.51 (s, 1H), 7.43-7.33 (m, 2H), 7.17 (d, <i>J</i> 8.3 Hz, 1H), 7.11 (s, 1H), 6.65 (d, <i>J</i> 8.8 Hz, 1H), 4.32-4.22 (m, 1H), 3.95-3.90 (m, 1H), 3.88 (s, 3H), 3.85-3.74 (m, 5H), 3.64-3.58 (m, 1H), 3.54-3.47 (m, 6H), 3.25-3.08 (m, 2H), 2.38-2.30 (m, 4H), 2.24 (s, 3H). LCMS (ES ⁺) 492 (M+H) ⁺ .

EXAMPLES 98 TO 132

The following compounds were prepared from the relevant amine and the appropriate carboxylic acid according to *Method A*.

5

Example No.	Compound Name	¹ H NMR/LCMS
98	[(<i>S</i>)-3-(1-Methyl-5-nitro-1 <i>H</i> -indol-3-ylmethyl)morpholin-4-yl]-(6-methylpyridin-3-yl)-methanone	δ_{H} (d ₆ -DMSO at 110°C) 8.31 (s, 1H), 8.08 (s, 1H), 8.00 (dd, <i>J</i> 9.1, 2.3 Hz, 1H), 7.55 (d, <i>J</i> 8.8 Hz, 1H), 7.32 (s, 1H), 7.26-7.20 (m, 1H), 7.03 (d, <i>J</i> 7.6 Hz, 1H), 4.37-4.29 (m, 1H), 3.98-3.91 (m, 1H), 3.88-3.78 (m, 5H), 3.68 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.57-3.46 (m, 2H), 3.26 (dd, <i>J</i> 14.7, 8.3 Hz, 1H), 3.18 (dd, <i>J</i> 14.4, 6.8 Hz, 1H), 2.40 (s, 3H). LCMS (ES ⁺) 395 (M+H) ⁺ .
99	3-[(<i>S</i>)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 10.74 (s, 1H), 7.87 (d, <i>J</i> 2.0 Hz, 1H), 7.48 (s, 1H), 7.37 (dd, <i>J</i> 8.3, 0.5 Hz, 2H), 7.13-7.11 (m, 2H), 4.30-4.24 (m, 1H), 3.97-3.92 (m, 4H), 3.86-3.77 (m, 2H), 3.65 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.55-3.51 (m, 2H), 3.21-3.16 (m, 2H), 2.97 (s, 6H). LCMS (ES ⁺) 457 (M+H) ⁺ .
100	3-[(<i>S</i>)-4-(2-Chloro-5-fluoro-6-methoxypyridine-3-carbonyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 10.78 (s, 1H), 7.70-7.32 (m, 3H), 7.22-7.08 (m, 2H), 3.97 (s, 5H), 3.84 (d, <i>J</i> 11.6 Hz, 1H), 3.67-3.59 (m, 1H), 3.52-3.48 (m, 3H), 3.28-3.12 (m, 2H), 2.99 (s, 6H). LCMS (ES ⁺) 475 (M+H) ⁺ .
101	3-[(<i>S</i>)-4-(6-Chloro-5-cyano-2-methylpyridine-3-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.62-7.49 (m, 1H), 7.41 (d, <i>J</i> 8.4 Hz, 1H), 7.22 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.21-7.19 (m, 1H), 3.91-3.88 (m, 1H), 3.84 (d, <i>J</i> 11.6 Hz, 1H), 3.80-3.77 (m, 1H), 3.79 (s, 3H), 3.72-3.61 (m, 1H), 3.52-3.50 (m, 1H), 3.20-3.17 (m, 2H), 2.99 (s, 6H), 2.98 (s, 3H), 2.27 (s, 3H). LCMS (ES ⁺) 480 (M+H) ⁺ .
102	3-[(<i>S</i>)-4-(5-Cyano-6-methoxy-2-methylpyridine-3-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.53 (br s, 1H), 7.40 (d, <i>J</i> 8.6 Hz, 1H), 7.20 (dd, <i>J</i> 8.4, 1.3 Hz, 1H), 7.16 (s, 1H), 4.00 (s, 3H), 3.91-3.90 (m, 1H), 3.82 (d, <i>J</i> 11.6 Hz, 1H), 3.78 (s, 3H), 3.56 (d, <i>J</i> 11.6 Hz, 2H), 3.49 (d, <i>J</i> 8.7 Hz, 4H), 3.18 (d, <i>J</i> 7.4 Hz, 2H), 2.98 (s, 6H), 2.23 (s, 3H). LCMS (ES ⁺) 476

		(M+H) ⁺ .
103	1-Carbamoylmethyl-3-[(S)-4-(5-chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 7.94 (d, <i>J</i> 2.0 Hz, 1H), 7.50 (d, <i>J</i> 2.0 Hz, 2H), 7.36 (d, <i>J</i> 8.3 Hz, 1H), 7.19 (d, <i>J</i> 1.5 Hz, 1H), 7.16 (s, 2H), 6.91 (s, 2H), 4.75 (s, 2H), 4.33-4.27 (m, 1H), 3.97 (s, 3H), 3.94 (d, <i>J</i> 7.3 Hz, 1H), 3.86-3.84 (m, 1H), 3.84-3.80 (m, 1H), 3.64 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.53-3.51 (m, 1H), 3.18 (d, <i>J</i> 7.6 Hz, 2H), 2.98 (s, 6H). LCMS (ES ⁺) 514 (M+H) ⁺ .
104	3-[(S)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-(methylcarbamoylmethyl)-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 7.92 (d, <i>J</i> 2.0 Hz, 1H), 7.50-7.48 (m, 3H), 7.36 (d, <i>J</i> 8.6 Hz, 1H), 7.18 (d, <i>J</i> 1.5 Hz, 1H), 7.16 (s, 2H), 4.75 (s, 1H), 4.34-4.28 (m, 1H), 3.97 (s, 3H), 3.93 (d, <i>J</i> 7.6 Hz, 1H), 3.87-3.84 (m, 1H), 3.79-3.77 (m, 1H), 3.65 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.56-3.51 (m, 2H), 3.18 (d, <i>J</i> 7.3 Hz, 2H), 2.98 (s, 6H), 2.66 (d, <i>J</i> 4.8 Hz, 3H). LCMS (ES ⁺) 528 (M+H) ⁺ .
105	3-[(S)-4-(4-Chloro-3-hydroxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 7.55 (s, 1H), 7.38 (d, <i>J</i> 8.3 Hz, 1H), 7.24-7.18 (m, 2H), 7.09 (s, 1H), 6.81 (d, <i>J</i> 1.8 Hz, 1H), 6.57 (dd, <i>J</i> 7.8, 1.8 Hz, 1H), 4.33-4.25 (m, 1H), 3.91-3.89 (m, 1H), 3.81-3.69 (m, 5H), 3.52 (dd, <i>J</i> 11.6, 3.0 Hz, 2H), 3.48-3.43 (m, 1H), 3.25 (dd, <i>J</i> 14.4, 8.3 Hz, 1H), 3.12-2.97 (m, 2H), 2.99 (s, 6H). LCMS (ES ⁺) 456 (M+H) ⁺ .
106	3-[(S)-4-(3-Hydroxy-4-methoxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 7.54 (s, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.08 (s, 1H), 6.83 (d, <i>J</i> 8.1 Hz, 1H), 6.70 (d, <i>J</i> 2.3 Hz, 1H), 6.61 (dd, <i>J</i> 8.1, 2.0 Hz, 1H), 4.34-4.31 (m, 1H), 3.93-3.85 (m, 1H), 3.80 (s, 3H), 3.78-3.74 (m, 2H), 3.75 (s, 3H), 3.50 (dd, <i>J</i> 11.4, 3.3 Hz, 1H), 3.45-3.40 (m, 2H), 3.25 (dd, <i>J</i> 14.1, 8.6 Hz, 1H), 3.04 (dd, <i>J</i> 14.4, 6.6 Hz, 1H), 2.98 (s, 6H). LCMS (ES ⁺) 452 (M+H) ⁺ .
107	3-[(S)-4-(2,6-Dimethoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 7.49 (br s, 1H), 7.38 (d, <i>J</i> 8.3 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.08 (s, 1H), 7.14 (br s, 1H), 6.21 (br s, 1H), 4.06 (br s, 1H), 3.93-3.88 (m, 2H), 3.88 (s, 6H), 3.79-3.76 (m, 1H), 3.76 (s, 3H), 3.50 (dd, <i>J</i> 11.4, 2.5 Hz, 1H), 3.46-3.37 (m, 2H), 3.21 (dd, <i>J</i> 14.1, 9.1 Hz, 1H), 3.02 (dd, <i>J</i> 14.4, 6.6 Hz, 1H),

		2.97 (s, 6H). LCMS (ES ⁺) 467 (M+H) ⁺ .
108	3-[(<i>S</i>)-4-(2-Chloro-6-methoxy-pyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.54 (s, 1H), 7.40 (d, <i>J</i> 8.6 Hz, 1H), 7.20 (d, <i>J</i> 8.3 Hz, 1H), 7.14 (br s, 2H), 6.68 (br s, 1H), 4.59 (br s, 1H), 3.94-3.87 (m, 1H), 3.87 (s, 3H), 3.81 (d, <i>J</i> 11.6 Hz, 1H), 3.79-3.77 (m, 1H), 3.77 (s, 3H), 3.64-3.43 (m, 3H), 3.23-3.08 (m, 2H), 2.98 (s, 6H). LCMS (ES ⁺) 473 (M+H) ⁺ .
109	3-[(<i>S</i>)-4-(2-Chloro-5-fluoro-6-methoxypyridine-3-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.60 (br s, 1H), 7.40 (d, <i>J</i> 8.3 Hz, 1H), 7.20 (d, <i>J</i> 8.1 Hz, 1H), 7.20-7.15 (br s, 2H), 4.69 (br s, 1H), 3.96-3.94 (m, 1H), 3.96 (s, 3H), 3.83 (d, <i>J</i> 11.4 Hz, 1H), 3.77-3.75 (m, 1H), 3.77 (s, 3H), 3.64-3.45 (m, 3H), 3.22-3.14 (m, 2H), 2.97 (s, 6H). LCMS (ES ⁺) 489 (M+H) ⁺ .
110	3-[(<i>S</i>)-4-(5-Fluoro-6-methoxy-pyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.74 (br s, 1H), 7.40 (d, <i>J</i> 8.3 Hz, 1H), 7.21-7.10 (m, 2H), 6.80 (br s, 1H), 6.25 (br s, 1H), 4.70 (br s, 1H), 4.26 (br s, 1H), 3.96 (s, 3H), 3.96-3.94 (m, 1H), 3.84 (d, <i>J</i> 11.6 Hz, 1H), 3.77 (s, 3H), 3.63-3.47 (m, 3H), 3.23-3.08 (m, 2H), 2.98 (s, 6H). LCMS (ES ⁺) 455 (M+H) ⁺ .
111	3-[(<i>S</i>)-4-(5-Chloro-6-methoxy-pyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.87 (d, <i>J</i> 1.8 Hz, 1H), 7.49 (s, 1H), 7.39 (dd, <i>J</i> 8.3, 0.5 Hz, 1H), 7.36 (s, 1H), 7.18 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.09 (s, 1H), 4.25-4.23 (m, 1H), 3.95 (s, 3H), 3.95-3.93 (m, 1H), 3.84 (d, <i>J</i> 11.6 Hz, 1H), 3.80-3.77 (m, 1H), 3.77 (s, 3H), 3.66 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.55-3.47 (m, 2H), 3.19 (dd, <i>J</i> 14.7, 7.8 Hz, 1H), 3.14 (dd, <i>J</i> 14.1, 6.8 Hz, 1H), 2.97 (s, 6H). LCMS (ES ⁺) 471 (M+H) ⁺ .
112	3-[(<i>S</i>)-4-(5-Chloro-6-ethoxy-pyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.85 (d, <i>J</i> 2.0 Hz, 1H), 7.52 (s, 1H), 7.39-7.37 (m, 2H), 7.19 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.09 (s, 1H), 4.42 (q, <i>J</i> 6.8 Hz, 2H), 4.28-4.24 (m, 1H), 3.97-3.89 (m, 1H), 3.84 (d, <i>J</i> 11.6 Hz, 1H), 3.81-3.79 (m, 1H), 3.77 (s, 3H), 3.65 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.56-3.48 (m, 2H), 3.19 (dd, <i>J</i> 14.4, 7.6 Hz, 1H), 3.15 (dd, <i>J</i> 14.4, 7.3 Hz, 1H), 2.97 (s, 6H), 1.36 (t, <i>J</i> 7.1 Hz, 3H). LCMS (ES ⁺) 485 (M+H) ⁺ .

113	3-[(<i>S</i>)-4-(2-Hydroxypyrimidine-5-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d_6 -DMSO at 110°C) 8.00 (s, 2H), 7.62-7.61 (m, 1H), 7.38 (d, <i>J</i> 8.3 Hz, 1H), 7.20 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.12 (s, 1H), 4.31-4.27 (m, 1H), 3.97-3.89 (m, 1H), 3.83 (d, <i>J</i> 11.6 Hz, 1H), 3.79-3.76 (m, 1H), 3.76 (s, 3H), 3.61 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.58-3.46 (m, 2H), 3.20 (dd, <i>J</i> 14.4, 7.3 Hz, 1H), 3.14 (dd, <i>J</i> 14.4, 7.3 Hz, 1H), 3.00 (s, 6H). LCMS (ES^+) 423 ($\text{M}+\text{H}$) ⁺ .
114	3-[(<i>S</i>)-4-(2-Methoxy-6-methylpyrimidine-4-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d_6 -DMSO at 110°C) 8.51 (br s, 1H), 7.38 (d, <i>J</i> 8.3 Hz, 1H), 7.19 (d, <i>J</i> 8.3 Hz, 1H), 7.09 (br s, 1H), 6.45 (br s, 1H), 4.26 (br s, 1H), 3.96 (br s, 1H), 3.89 (s, 3H), 3.96-3.85 (m, 1H), 3.84 (d, <i>J</i> 11.6 Hz, 1H), 3.77 (s, 3H), 3.60-3.47 (m, 3H), 3.25-3.15 (m, 2H), 2.98 (s, 6H), 2.30 (s, 3H). LCMS (ES^+) 452 ($\text{M}+\text{H}$) ⁺ .
115	3-[(<i>S</i>)-4-(2-Bromo-1-methyl-1 <i>H</i> -imidazole-4-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d_6 -DMSO at 110°C) 8.00 (s, 1H), 7.38 (d, <i>J</i> 8.3 Hz, 1H), 7.21 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.14 (s, 1H), 7.01 (s, 1H), 4.56-4.51 (m, 1H), 3.96-3.93 (m, 2H), 3.86 (d, <i>J</i> 11.6 Hz, 1H), 3.75 (s, 3H), 3.62 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.58-3.45 (m, 2H), 3.30 (s, 3H), 3.18-3.16 (m, 2H), 3.00 (s, 6H). LCMS (ES^+) 488 ($\text{M}+\text{H}$) ⁺ .
116	{3-[(<i>S</i>)-4-(2-Chloro-5-fluoro-6-methoxypyridine-3-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}-(3-hydroxyazetidin-1-yl)-methanone	δ_{H} (d_6 -DMSO at 110°C) 7.86 (br s, 2H), 7.47-7.45 (m, 1H), 7.41-7.39 (m, 1H), 7.17 (dd, <i>J</i> 2.0, 1.3 Hz, 1H), 5.27 (d, <i>J</i> 5.6 Hz, 1H), 4.53-4.52 (m, 1H), 4.40-4.31 (m, 2H), 3.99-3.91 (m, 6H), 3.86 (d, <i>J</i> 11.4 Hz, 2H), 3.78 (s, 3H), 3.69-3.59 (m, 2H), 3.51 (d, <i>J</i> 7.3 Hz, 2H), 3.25-3.14 (m, 2H). LCMS (ES^+) 517 ($\text{M}+\text{H}$) ⁺ .
117	3-[(<i>S</i>)-4-(2-Chloro-5-fluoro-6-methoxypyridine-3-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid <i>N</i> -(2-methoxyethyl)- <i>N</i> -methylamide	δ_{H} (d_6 -DMSO at 110°C) 7.54 (br s, 2H), 7.41 (d, <i>J</i> 8.3 Hz, 1H), 7.19 (d, <i>J</i> 8.3 Hz, 1H), 7.16 (s, 1H), 4.00-3.89 (m, 4H), 3.84 (d, <i>J</i> 11.6 Hz, 2H), 3.78 (s, 3H), 3.66-3.60 (m, 2H), 3.55 (s, 4H), 3.51 (d, <i>J</i> 7.8 Hz, 2H), 3.29 (s, 3H), 3.25-3.13 (m, 2H), 3.00 (s, 3H). LCMS (ES^+) 533 ($\text{M}+\text{H}$) ⁺ .
118	(2-Chloro-5-fluoro-6-methoxypyridin-3-yl)-[(<i>S</i>)-3-{5-[3-(hydroxymethyl)azetidine-1-carbonyl]-1-methyl-1 <i>H</i> -indol-3-ylmethyl}-morpholin-4-yl]-methanone	δ_{H} (d_6 -DMSO at 110°C) 7.88-7.75 (m, 2H), 7.47-7.45 (m, 1H), 7.41-7.39 (m, 1H), 7.16 (br s, 1H), 4.33 (t, <i>J</i> 4.5 Hz, 1H), 4.21-4.18 (m, 2H), 4.00-3.89 (m, 6H), 3.86 (d, <i>J</i> 11.9 Hz, 2H), 3.78 (s, 3H), 3.60 (t, <i>J</i> 5.3 Hz, 3H), 3.52-3.50 (m, 2H), 3.30-3.11 (m, 3H), 2.78-2.67 (m, 1H).

		LCMS (ES ⁺) 531 (M+H) ⁺ .
119	3-[(<i>S</i>)-4-(2-Chloro-5-fluoro-6-methoxypyridine-3-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid amide	δ_{H} (d ₆ -DMSO at 110°C) 8.04 (br s, 2H), 7.71 (d, <i>J</i> 8.6 Hz, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.15 (br s, 1H), 6.93 (br s, 2H), 3.95 (s, 3H), 3.88 (d, <i>J</i> 11.4 Hz, 2H), 3.78 (s, 3H), 3.74-3.67 (m, 2H), 3.52 (d, <i>J</i> 7.6 Hz, 2H), 3.31-3.08 (m, 3H). LCMS (ES ⁺) 461 (M+H) ⁺ .
120	{(<i>S</i>)-3-[5-(Azetidine-1-carbonyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]-morpholin-4-yl}-(2-chloro-5-fluoro-6-methoxypyridin-3-yl)-methanone	δ_{H} (d ₆ -DMSO at 110°C) 7.96-7.67 (m, 2H), 7.47-7.45 (m, 1H), 7.41-7.39 (m, 1H), 7.17 (br s, 1H), 4.20 (s, 5H), 3.97-3.95 (m, 4H), 3.86-3.84 (m, 1H), 3.78 (s, 3H), 3.69-3.58 (m, 1H), 3.52-3.50 (m, 3H), 3.32-3.12 (m, 2H), 2.33-2.25 (m, 2H). LCMS (ES ⁺) 501 (M+H) ⁺ .
121	3-[(<i>S</i>)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid <i>N</i> -(2-methoxyethyl)- <i>N</i> -methanamide	δ_{H} (d ₆ -DMSO at 110°C) 7.87 (d, <i>J</i> 2.0 Hz, 1H), 7.51 (s, 1H), 7.40 (s, 1H), 7.38 (s, 2H), 7.17 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.10 (s, 1H), 4.30-4.24 (m, 1H), 3.97 (s, 3H), 3.94 (d, <i>J</i> 7.3 Hz, 1H), 3.85-3.82 (m, 1H), 3.82-3.79 (m, 1H), 3.78 (s, 3H), 3.65 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.55-3.48 (m, 5H), 3.29 (s, 3H), 3.17 (dd, <i>J</i> 7.6, 4.8 Hz, 2H), 2.99 (s, 3H). LCMS (ES ⁺) 515.
122	3-[(<i>S</i>)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid amide	δ_{H} (d ₆ -DMSO at 110°C) 8.00 (s, 1H), 7.77 (d, <i>J</i> 1.5 Hz, 1H), 7.69 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.36 (d, <i>J</i> 8.6 Hz, 1H), 7.22 (s, 1H), 7.09 (s, 1H), 6.89 (d, <i>J</i> 1.3 Hz, 2H), 4.40-4.32 (m, 1H), 3.97-3.91 (m, 3H), 3.88-3.87 (m, 1H), 3.85-3.82 (m, 1H), 3.77 (s, 3H), 3.73 (dd, <i>J</i> 11.6, 3.3 Hz, 2H), 3.54-3.49 (m, 2H), 3.29 (dd, <i>J</i> 14.7, 8.8 Hz, 1H), 3.08 (dd, <i>J</i> 14.7, 6.1 Hz, 1H). LCMS (ES ⁺) 443.
123	{(<i>S</i>)-3-[5-(Azetidine-1-carbonyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]-morpholin-4-yl}-(5-chloro-6-methoxypyridin-3-yl)-methanone	δ_{H} (d ₆ -DMSO at 110°C) 7.86 (d, <i>J</i> 1.8 Hz, 1H), 7.73 (s, 1H), 7.45-4.43 (m, 1H), 7.39-7.37 (m, 1H), 7.34 (s, 1H), 7.11 (s, 1H), 4.34-4.20 (m, 1H), 4.20-4.48 (m, 4H), 3.96 (s, 3H), 3.94 (s, 1H), 3.87-3.84 (m, 1H), 3.81 (d, <i>J</i> 10.1 Hz, 1H), 3.78 (s, 3H), 3.68 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.53-3.51 (m, 2H), 3.22-3.15 (m, 2H), 2.29-2.24 (m, 2H). LCMS (ES ⁺) 483.
124	(5-Chloro-6-methoxypyridin-3-yl)-{(<i>S</i>)-3-[5-(3-hydroxyazetidine-1-carbonyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholin-4-yl}-methanone	δ_{H} (d ₆ -DMSO at 110°C) 7.87 (d, <i>J</i> 1.8 Hz, 1H), 7.75 (s, 1H), 7.45-7.43 (m, 1H), 7.39-7.37 (m, 1H), 7.33 (s, 1H), 7.11 (s, 1H), 5.28 (d, <i>J</i> 5.1 Hz, 1H), 4.56-4.48 (m, 1H), 4.38-4.26 (m, 4H), 3.97-3.90 (m, 6H), 3.88-

		3.85 (m, 1H), 3.83-3.76 (m, 3H), 3.68 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.53 (d, <i>J</i> 9.1 Hz, 2H), 3.18-3.12 (m, 2H). LCMS (ES ⁺) 499.
125	1-Methyl-3-[(<i>S</i>)-4-(1-oxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 8.06 (d, <i>J</i> 6.3 Hz, 1H), 7.83 (s, 1H), 7.52-7.50 (m, 1H), 7.42-7.38 (m, 1H), 7.25-7.18 (m, 2H), 7.12 (s, 1H), 6.89 (d, <i>J</i> 7.3 Hz, 1H), 4.28-4.17 (m, 1H), 3.94-3.92 (m, 1H), 3.85-3.74 (m, 4H), 3.63 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.60-3.49 (m, 2H), 3.23-3.13 (m, 2H), 3.10-2.96 (m, 7H). LCMS (ES ⁺) 423 (M+H) ⁺ .
126	1-Methyl-3-[(<i>S</i>)-4-(6-methyl-1-oxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 8.24 (s, 1H), 7.88 (s, 1H), 7.53 (s, 1H), 7.39 (d, <i>J</i> 8.3 Hz, 1H), 7.26-7.18 (m, 2H), 7.11 (s, 1H), 6.80 (d, <i>J</i> 7.8 Hz, 1H), 4.27-4.20 (m, 1H), 3.98-3.89 (m, 1H), 3.86-3.74 (m, 4H), 3.63 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.53 (m, 1H), 3.17 (d, <i>J</i> 7.6 Hz, 3H), 2.99 (s, 6H), 2.33 (s, 3H). LCMS (ES ⁺) 437 (M+H) ⁺ .
127	3-[(<i>S</i>)-4-(6-Chloro-1-oxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 8.01 (s, 1H), 7.56 (s, 1H), 7.52 (d, <i>J</i> 8.1 Hz, 1H), 7.39 (d, <i>J</i> 8.3 Hz, 1H), 7.20 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.13 (s, 1H), 6.88-6.86 (m, 1H), 4.27-4.17 (m, 1H), 3.97-3.93 (m, 1H), 3.85-3.82 (m, 1H), 3.79 (s, 3H), 3.66 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.55-3.49 (m, 2H), 3.18 (dd, <i>J</i> 7.3, 4.3 Hz, 3H), 2.99 (s, 6H). LCMS (ES ⁺) 457 (M+H) ⁺ .
128	1-{3-[(<i>S</i>)-4-(3-Fluoro-5-hydroxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carbonyl}-azetidine-3-carbonitrile	δ_{H} (d ₆ -DMSO at 110°C) 9.61 (d, <i>J</i> 0.8 Hz, 1H), 7.83 (s, 1H), 7.49-7.38 (m, 2H), 7.14 (s, 1H), 6.54 (dt, <i>J</i> 10.9, 2.3 Hz, 1H), 6.44 (d, <i>J</i> 1.5 Hz, 1H), 6.29-6.27 (m, 1H), 4.54-4.45 (m, 3H), 4.41-4.29 (m, 4H), 3.92 (d, <i>J</i> 7.8 Hz, 1H), 3.86-3.61 (m, 6H), 3.56 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.51-3.43 (m, 2H). LCMS (ES ⁺) 477 (M+H) ⁺ .
129	3-[(<i>S</i>)-4-(6-Methoxy-1-oxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.87 (d, <i>J</i> 1.5 Hz, 1H), 7.53 (s, 1H), 7.39 (d, <i>J</i> 8.6 Hz, 1H), 7.19 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.11 (s, 1H), 6.95-6.86 (m, 2H), 4.28-4.21 (m, 1H), 3.99 (s, 3H), 3.96-3.90 (m, 1H), 3.84-3.75 (m, 4H), 3.63 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.53-3.47 (m, 2H), 3.17 (d, <i>J</i> 7.6 Hz, 3H), 2.99 (s, 6H). LCMS (ES ⁺) 453 (M+H) ⁺ .

130	(5-Chloro-6-methoxypyridin-3-yl)-[(S)-3-{5-[3-hydroxy-3-(hydroxymethyl)azetidine-1-carbonyl]-1-methyl-1 <i>H</i> -indol-3-ylmethyl}-morpholin-4-yl]-methanone	δ_H (d_6 -DMSO at 110°C) 7.88 (d, <i>J</i> 2.0 Hz, 1H), 7.79 (s, 1H), 7.45-7.43 (m, 1H), 7.39 (dd, <i>J</i> 8.6, 0.5 Hz, 1H), 7.35 (s, 1H), 7.11 (s, 1H), 4.36-4.27 (m, 1H), 4.18 (d, <i>J</i> 9.3 Hz, 2H), 3.97 (s, 4H), 3.94 (m, 4H), 3.86 (d, <i>J</i> 11.6 Hz, 1H), 3.78 (s, 3H), 3.67 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.53-3.50 (m, 2H), 3.49 (s, 3H), 3.20-3.14 (m, 2H). LCMS (ES ⁺) 529 (M+H) ⁺ .
131	3-[(S)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid <i>N</i> -(2-hydroxyethyl)- <i>N</i> -methanamide	δ_H (d_6 -DMSO at 110°C) 7.87 (d, <i>J</i> 2.0 Hz, 1H), 7.53 (s, 1H), 7.38-7.35 (m, 2H), 7.19 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.09 (s, 1H), 4.33-4.21 (m, 1H), 3.97 (s, 3H), 3.94 (d, <i>J</i> 7.6 Hz, 1H), 3.85-3.83 (m, 1H), 3.77 (s, 3H), 3.67 (d, <i>J</i> 3.3 Hz, 1H), 3.65-3.60 (m, 3H), 3.52-3.50 (m, 3H), 3.45 (t, <i>J</i> 6.1 Hz, 2H), 3.17 (t, <i>J</i> 7.3 Hz, 2H), 3.00 (s, 3H). LCMS (ES ⁺) 501 (M+H) ⁺ .
132	3-[(S)-4-(6-Amino-5-chloropyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethanamide	δ_H (d_6 -DMSO at 110°C) 7.77 (d, <i>J</i> 2.0 Hz, 1H), 7.57 (d, <i>J</i> 0.8 Hz, 1H), 7.38 (dd, <i>J</i> 8.6, 0.8 Hz, 1H), 7.19-7.17 (m, 2H), 7.09 (s, 1H), 6.10 (s, 2H), 4.34-4.29 (m, 1H), 3.92 (d, <i>J</i> 7.1 Hz, 1H), 3.85-3.83 (m, 1H), 3.77 (s, 4H), 3.60 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.53-3.48 (m, 2H), 3.16 (t, <i>J</i> 7.6 Hz, 2H), 2.99 (s, 6H). LCMS (ES ⁺) 456 (M+H) ⁺ .

EXAMPLES 133 TO 250 (METHOD F)

To a stirred solution of the appropriate amine (0.72 mmol), EDC (1.14 mmol) and HOBT (0.76 mmol) in DCM (5 mL) were added DIPEA (1.52 mmol) and the relevant carboxylic acid (0.76 mmol). The reaction mixture was stirred at r.t. for 18 h, then quenched with water (10 mL). The organic layer was separated, dried (magnesium sulphate), concentrated *in vacuo* and purified using preparative HPLC, to yield the *title compound*.

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Example No.	Compound Name	¹ H NMR/LCMS
133	3-[(S)-4-(6-Chloro-5-trifluoromethylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid	δ_H (d_6 -DMSO at 110°C) 8.34 (s, 1H), 7.76 (br s, 1H), 7.55 (s, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.13 (s, 1H), 4.29-4.17 (m, 1H), 3.95 (d, <i>J</i> 6.8 Hz, 1H), 3.89-3.83 (m, 1H), 3.77 (s, 3H), 3.74-3.68

	dimethylamide	(m, 1H), 3.62-3.51 (m, 2H), 3.25 (m, 1H), 3.18-2.94 (m, 8H). LCMS (ES ⁺) 509 (M+H) ⁺ .
134	3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid amide	δ_H (d ₆ -DMSO at 110°C) 8.02 (s, 1H), 7.88 (d, <i>J</i> 1.5 Hz, 1H), 7.69 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.36 (d, <i>J</i> 8.6 Hz, 1H), 7.26 (d, <i>J</i> 8.6 Hz, 1H), 7.09 (s, 1H), 7.00-6.90 (m, 2H), 6.57 (d, <i>J</i> 8.3 Hz, 1H), 4.39-4.32 (m, 1H), 3.94 (d, <i>J</i> 7.3 Hz, 1H), 3.89-3.79 (m, 4H), 3.76 (s, 3H), 3.66 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.51 (m, 2H), 3.30-3.08 (m, 3H). LCMS (ES ⁺) 409 (M+H) ⁺ .
135	3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid methylamide	δ_H (d ₆ -DMSO at 110°C) 7.99-7.86 (m, 2H), 7.76-7.68 (m, 1H), 7.65 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.36 (d, <i>J</i> 8.6 Hz, 1H), 7.30-7.23 (m, 1H), 7.09 (s, 1H), 6.58 (d, <i>J</i> 8.6 Hz, 1H), 4.40-4.30 (m, 1H), 3.97-3.92 (m, 1H), 3.88-3.80 (m, 5H), 3.76 (s, 3H), 3.67 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.53-3.48 (m, 2H), 3.29-3.20 (m, 1H), 3.17-3.10 (m, 1H), 2.85 (d, <i>J</i> 4.8 Hz, 3H). LCMS (ES ⁺) 423 (M+H) ⁺ .
136	3-[(S)-4-(6-Methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 10.82-10.70 (m, 1H), 8.22 (d, <i>J</i> 1.8 Hz, 1H), 7.47 (s, 1H), 7.37 (dd, <i>J</i> 8.3, 0.5 Hz, 1H), 7.33-7.27 (m, 1H), 7.15-7.11 (m, 2H), 7.09 (d, <i>J</i> 7.8 Hz, 1H), 4.29-4.22 (m, 1H), 3.95-3.91 (m, 1H), 3.82-3.75 (m, 2H), 3.59 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.52-3.48 (m, 2H), 3.22 (m, 1H), 3.14 (m, 1H), 2.98 (s, 6H), 2.45 (s, 3H). LCMS (ES ⁺) 407 (M+H) ⁺ .
137	3-[(S)-4-(6-Methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid d ₆ -dimethylamide	δ_H (d ₆ -DMSO at 110°C) 10.79-10.71 (m, 1H), 8.22 (m, 1H), 7.47 (s, 1H), 7.37 (d, <i>J</i> 8.3 Hz, 1H), 7.33-7.27 (m, 1H), 7.16-7.11 (m, 2H), 7.09 (d, <i>J</i> 7.6 Hz, 1H), 4.30-4.20 (m, 1H), 3.93 (d, <i>J</i> 7.6 Hz, 1H), 3.84-3.74 (m, 2H), 3.59 (dd, <i>J</i> 11.4, 3.3 Hz, 1H), 3.54-3.46 (m, 2H), 3.22 (dd, <i>J</i> 14.7, 7.8 Hz, 1H), 3.14 (dd, <i>J</i> 14.4, 7.3 Hz, 1H), 2.45 (s, 3H). LCMS (ES ⁺) 413 (M+H) ⁺ .
138	3-[(S)-4-(6-Methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid <i>N</i> -(2-methoxy-ethyl)- <i>N</i> -methylamide	δ_H (d ₆ -DMSO at 110°C) 10.79-10.70 (m, 1H), 8.21 (m, 1H), 7.48 (s, 1H), 7.37 (dd, <i>J</i> 8.3, 0.8 Hz, 1H), 7.30 (ddd, <i>J</i> 8.1, 1.5, 0.5 Hz, 1H), 7.15-7.07 (m, 3H), 4.31-4.22 (m, 1H), 3.95-3.89 (m, 1H), 3.82-3.73 (m, 2H), 3.59 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.54 (s, 4H), 3.51 (m, 2H), 3.28 (s,

		3H), 3.22 (m, 1H), 3.15 (m, 1H), 3.00 (s, 3H), 2.45 (s, 3H). LCMS (ES ⁺) 451 (M+H) ⁺ .
139	1-Methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid d ₆ -dimethylamide	δ_H (d ₆ -DMSO at 110°C) 8.21 (d, <i>J</i> 1.8 Hz, 1H), 7.49 (s, 1H), 7.39 (d, <i>J</i> 8.6 Hz, 1H), 7.34-7.29 (m, 1H), 7.20 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.14-7.06 (m, 2H), 4.29-4.21 (m, 1H), 3.93 (d, <i>J</i> 7.3 Hz, 1H), 3.84-3.80 (m, 1H), 3.77 (s, 4H), 3.59 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.54-3.46 (m, 2H), 3.20 (m, 1H), 3.12 (m, 1H), 2.45 (s, 3H). LCMS (ES ⁺) 427 (M+H) ⁺ .
140	1-Methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid <i>N</i> -(2-methoxyethyl)- <i>N</i> -methylamide	δ_H (d ₆ -DMSO at 110°C) 8.20 (s, 1H), 7.50 (s, 1H), 7.39 (d, <i>J</i> 8.3 Hz, 1H), 7.34-7.29 (m, 1H), 7.18 (d, <i>J</i> 8.3 Hz, 1H), 7.13-7.08 (m, 2H), 4.30-4.21 (m, 1H), 3.92 (d, <i>J</i> 7.6 Hz, 1H), 3.81 (m, 1H), 3.77 (d, <i>J</i> 0.8 Hz, 4H), 3.60 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.54 (s, 3H), 3.50 (m, 2H), 3.28 (d, <i>J</i> 0.8 Hz, 3H), 3.20 (m, 1H), 3.13 (dd, <i>J</i> 14.7, 7.6 Hz, 1H), 3.05-2.89 (m, 4H), 2.46 (s, 3H). LCMS (ES ⁺) 465 (M+H) ⁺ .
141	1-Methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid <i>N</i> -(2-hydroxyethyl)- <i>N</i> -methylamide	δ_H (d ₆ -DMSO at 110°C) 8.21 (m, 1H), 7.51 (d, <i>J</i> 0.5 Hz, 1H), 7.38 (d, <i>J</i> 8.3 Hz, 1H), 7.34-7.29 (m, 1H), 7.20 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.13-7.07 (m, 2H), 4.30-4.22 (m, 1H), 3.92 (m, 1H), 3.81 (m, 1H), 3.77 (s, 4H), 3.65-3.57 (m, 3H), 3.53-3.41 (m, 4H), 3.23-3.10 (m, 2H), 3.05-2.94 (m, 4H), 2.46 (s, 3H). LCMS (ES ⁺) 451 (M+H) ⁺ .
142	[(<i>S</i>)-3-{5-[(<i>R</i>)-3-Hydroxypiperidine-1-carbonyl]-1-methyl-1 <i>H</i> -indol-3-ylmethyl}morpholin-4-yl]-(6-methylpyridin-3-yl)-methanone	δ_H (d ₆ -DMSO at 110°C) 8.21 (s, 1H), 7.61 (s, 1H), 7.39 (m, 1H), 7.34-7.27 (m, 2H), 7.14-7.06 (m, 2H), 4.60-4.55 (m, 1H), 4.35-4.22 (m, 2H), 3.95-3.89 (m, 1H), 3.82 (m, 1H), 3.77 (s, 4H), 3.67-3.57 (m, 3H), 3.55-3.45 (m, 3H), 3.39-3.32 (m, 1H), 3.21 (dd, <i>J</i> 14.4, 7.6 Hz, 1H), 3.14 (dd, <i>J</i> 14.4, 7.3 Hz, 1H), 3.05-2.94 (m, 2H), 2.46 (s, 3H), 2.02-1.91 (m, 1H), 1.88-1.76 (m, 1H). LCMS (ES ⁺) 477 (M+H) ⁺ .
143	[(<i>S</i>)-3-{5-[(<i>S</i>)-3-Hydroxypiperidine-1-carbonyl]-1-methyl-1 <i>H</i> -indol-3-ylmethyl}morpholin-4-yl]-(6-methylpyridin-3-yl)-methanone	δ_H (d ₆ -DMSO at 110°C) 8.21 (s, 1H), 7.61 (s, 1H), 7.38 (m, 1H), 7.34-7.28 (m, 2H), 7.13-7.06 (m, 2H), 4.59 (s, 1H), 4.35-4.21 (m, 2H), 3.93 (d, <i>J</i> 7.6 Hz, 1H), 3.85-3.73 (m, 5H), 3.66-3.56 (m, 3H), 3.55-3.45 (m, 3H), 3.36 (d, <i>J</i> 11.4 Hz, 1H), 3.22 (dd, <i>J</i> 14.4, 7.8 Hz, 1H), 3.13 (dd, <i>J</i> 14.4,

		7.3 Hz, 1H), 2.93-2.88 (m, 2H), 2.45 (s, 3H), 2.02-1.92 (m, 1H), 1.88-1.78 (m, 1H). LCMS (ES ⁺) 477 (M+H) ⁺ .
144	1-{1-Methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carbonyl}-[1,4]diazepan-5-one	δ_H (d ₆ -DMSO at 110°C) 8.17 (s, 1H), 7.51 (s, 1H), 7.41 (d, <i>J</i> 8.3 Hz, 1H), 7.32-7.18 (m, 3H), 7.12-7.08 (m, 2H), 4.31-4.23 (m, 1H), 3.93 (d, <i>J</i> 7.6 Hz, 1H), 3.83 (m, 1H), 3.77 (s, 4H), 3.67-3.57 (m, 5H), 3.53-3.48 (m, 2H), 3.30-3.24 (m, 2H), 3.20-3.13 (m, 2H), 2.55 (m, 2H), 2.45 (s, 3H). LCMS (ES ⁺) 490 (M+H) ⁺ .
145	[(<i>S</i>)-3-{5-[(<i>R</i>)-3-(Hydroxymethyl)piperidine-1-carbonyl]-1-methyl-1 <i>H</i> -indol-3-ylmethyl}morpholin-4-yl]-(6-methylpyridin-3-yl)-methanone	δ_H (d ₆ -DMSO at 110°C) 8.19 (s, 1H), 7.61 (s, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.29 (d, <i>J</i> 8.3 Hz, 2H), 7.12-7.06 (m, 2H), 4.44-4.37 (m, 1H), 4.31-4.24 (m, 1H), 4.22-4.16 (m, 1H), 3.95-3.88 (m, 1H), 3.82 (m, 1H), 3.77 (s, 4H), 3.63-3.55 (m, 3H), 3.54-3.41 (m, 5H), 3.20-3.13 (m, 2H), 2.46 (s, 3H), 2.07-1.95 (m, 1H), 1.94-1.83 (m, 2H), 1.80-1.69 (m, 1H). LCMS (ES ⁺) 491 (M+H) ⁺ .
146	[(<i>S</i>)-3-{5-[(<i>S</i>)-3-(Hydroxymethyl)piperidine-1-carbonyl]-1-methyl-1 <i>H</i> -indol-3-ylmethyl}morpholin-4-yl]-(6-methylpyridin-3-yl)-methanone	δ_H (d ₆ -DMSO at 110°C) 8.20 (s, 1H), 7.61 (s, 1H), 7.38 (m, 1H), 7.35-7.26 (m, 2H), 7.14-7.07 (m, 2H), 4.44-4.38 (m, 1H), 4.30-4.15 (m, 2H), 3.95-3.89 (m, 1H), 3.82 (m, 1H), 3.77 (s, 4H), 3.64-3.54 (m, 2H), 3.52-3.40 (m, 5H), 3.21 (dd, <i>J</i> 14.4, 7.6 Hz, 1H), 3.14 (dd, <i>J</i> 14.7, 7.3 Hz, 1H), 2.93-2.88 (m, 2H), 2.45 (s, 3H), 2.05-1.96 (m, 1H), 1.95-1.84 (m, 2H), 1.80-1.68 (m, 1H). LCMS (ES ⁺) 491 (M+H) ⁺ .
147	{(<i>S</i>)-3-[5-(3-Hydroxyazetidine-1-carbonyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholin-4-yl}-(6-methylpyridin-3-yl)-methanone	δ_H (d ₆ -DMSO at 110°C) 8.20 (s, 1H), 7.73 (s, 1H), 7.46 (m, 1H), 7.39 (m, 1H), 7.33-7.26 (m, 1H), 7.13-7.06 (m, 2H), 5.35-5.28 (m, 1H), 4.56-4.47 (m, 1H), 4.39-4.25 (m, 3H), 3.98-3.88 (m, 3H), 3.82 (m, 1H), 3.77 (s, 4H), 3.61 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.51 (d, <i>J</i> 9.1 Hz, 2H), 3.21 (dd, <i>J</i> 14.7, 7.8 Hz, 1H), 3.15 (dd, <i>J</i> 14.7, 7.3 Hz, 1H), 2.45 (s, 3H). LCMS (ES ⁺) 449 (M+H) ⁺ .
148	[(<i>S</i>)-3-{5-[4-(Methanesulfonyl)piperazine-1-carbonyl]-1-methyl-1 <i>H</i> -indol-3-ylmethyl}morpholin-4-yl]-(6-methylpyridin-3-yl)-methanone	δ_H (d ₆ -DMSO at 110°C) 8.19 (s, 1H), 7.57 (s, 1H), 7.42 (d, <i>J</i> 8.6 Hz, 1H), 7.33 (d, <i>J</i> 7.6 Hz, 1H), 7.23 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.15-7.09 (m, 2H), 4.34-4.24 (m, 1H), 3.94-3.89 (m, 1H), 3.82 (m, 1H), 3.79-3.71 (m, 4H), 3.68-3.57 (m, 5H), 3.56-3.46 (m, 2H), 3.26-3.18 (m, 5H), 3.14 (dd,

		J 14.4, 7.3 Hz, 1H), 2.88 (s, 3H), 2.46 (s, 3H). LCMS (ES ⁺) 540 (M+H) ⁺ .
149	1-Methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid <i>N</i> -(2,3-dihydroxypropyl)- <i>N</i> -methanone	δ_H (d ₆ -DMSO at 110°C) 8.21 (s, 1H), 7.53 (d, J 1.3 Hz, 1H), 7.38 (m, 1H), 7.34-7.28 (m, 1H), 7.21 (d, J 8.6 Hz, 1H), 7.14-7.07 (m, 2H), 4.40-4.35 (m, 1H), 4.31-4.22 (m, 1H), 4.10 (s, 1H), 3.96-3.89 (m, 1H), 3.85-3.78 (m, 2H), 3.77 (s, 4H), 3.60 (dd, J 11.6, 3.0 Hz, 1H), 3.55-3.47 (m, 3H), 3.46-3.39 (m, 1H), 3.40-3.33 (m, 2H), 3.24-3.08 (m, 2H), 3.03 (s, 3H), 2.46 (s, 3H). LCMS (ES ⁺) 481 (M+H) ⁺ .
150	{(<i>S</i>)-3-[5-(4-Hydroxyisoxazolidine-2-carbonyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholin-4-yl}-(6-methylpyridin-3-yl)-methanone	δ_H (d ₆ -DMSO at 110°C) 8.20 (s, 1H), 7.88 (d, J 0.5 Hz, 1H), 7.55 (d, J 8.6 Hz, 1H), 7.39 (d, J 8.6 Hz, 1H), 7.33-7.26 (m, 1H), 7.14-7.04 (m, 2H), 5.08 (s, 1H), 4.72-4.65 (m, 1H), 4.33-4.24 (m, 1H), 4.00-3.88 (m, 3H), 3.86-3.70 (m, 6H), 3.66-3.56 (m, 2H), 3.54-3.45 (m, 2H), 3.21-3.11 (m, 2H), 2.45 (s, 3H). LCMS (ES ⁺) 465 (M+H) ⁺ .
151	{(<i>S</i>)-3-[1-Methyl-5-(piperazine-1-carbonyl)-1 <i>H</i> -indol-3-ylmethyl]-morpholin-4-yl}-(6-methylpyridin-3-yl)-methanone	δ_H (d ₆ -DMSO at 110°C) 8.19 (s, 1H), 7.47 (s, 1H), 7.39 (d, J 8.3 Hz, 1H), 7.31 (d, J 7.8 Hz, 1H), 7.17 (d, J 8.6 Hz, 1H), 7.11-7.09 (m, 2H), 4.30-4.20 (m, 1H), 3.96-3.89 (m, 1H), 3.82-3.77 (m, 2H), 3.76 (s, 3H), 3.60 (dd, J 11.4, 3.0 Hz, 1H), 3.51-3.43 (m, 6H), 3.20 (dd, J 14.4, 7.8 Hz, 1H), 3.13 (dd, J 14.4, 7.6 Hz, 1H), 2.75-2.72 (m, 4H), 2.45 (s, 3H). LCMS (ES ⁺) 462 (M+H) ⁺ .
152	[(<i>S</i>)-1-{1-Methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carbonyl}pyrrolidin-3-ylmethyl]-carbamic acid <i>tert</i> -butyl ester	δ_H (d ₆ -DMSO at 110°C) 8.22 (s, 1H), 7.60 (s, 1H), 7.37 (d, J 8.6 Hz, 1H), 7.38-7.29 (m, 2H), 7.11-7.09 (m, 2H), 6.43 (s, 1H), 4.30-4.20 (m, 1H), 3.96-3.89 (m, 1H), 3.83-3.72 (m, 2H), 3.76 (s, 3H), 3.60-3.44 (m, 6H), 3.25-3.18 (m, 2H), 3.12 (dd, J 14.1, 7.1 Hz, 1H), 3.08-2.99 (m, 2H), 2.45 (s, 3H), 2.39-2.30 (m, 1H), 1.99-1.92 (m, 1H), 1.68-1.59 (m, 1H), 1.39 (s, 9H). LCMS (ES ⁺) 576 (M+H) ⁺ .
153	[(<i>R</i>)-1-{1-Methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carbonyl}pyrrolidin-3-ylmethyl]-	δ_H (d ₆ -DMSO at 110°C) 8.21 (s, 1H), 7.61 (s, 1H), 7.38 (d, J 8.6 Hz, 1H), 7.32-7.29 (m, 2H), 7.11-7.09 (m, 2H), 6.44 (s, 1H), 4.30-4.20 (m, 1H), 3.96-3.89 (m, 1H), 3.82 (d, J 11.6 Hz, 1H), 3.80-3.75 (m, 1H), 3.76 (s, 3H), 3.62-3.45 (m, 6H), 3.26-3.17

	carbamic acid <i>tert</i> -butyl ester	(m, 2H), 3.16 (dd, <i>J</i> 14.1, 7.1 Hz, 1H), 3.07-2.99 (m, 2H), 2.45 (s, 3H), 2.39-2.30 (m, 1H), 1.99-1.92 (m, 1H), 1.67-1.58 (m, 1H), 1.38 (s, 9H). LCMS (ES ⁺) 576 (M+H) ⁺ .
154	(1-{1-Methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carbonyl}-piperidin-4-yl)carbamic acid <i>tert</i> -butyl ester	δ_H (d ₆ -DMSO at 110°C) 8.18 (s, 1H), 7.46 (s, 1H), 7.40 (d, <i>J</i> 8.3 Hz, 1H), 7.30 (d, <i>J</i> 7.3 Hz, 1H), 7.16 (d, <i>J</i> 8.6 Hz, 1H), 7.10-7.09 (m, 2H), 6.33 (d, <i>J</i> 6.1 Hz, 1H), 4.25 (m, 1H), 4.09-3.96 (m, 2H), 3.93 (d, <i>J</i> 7.6 Hz, 1H), 3.82 (d, <i>J</i> 11.6 Hz, 1H), 3.80-3.75 (m, 1H), 3.76 (s, 3H), 3.60 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.57-3.53 (m, 1H), 3.51-3.46 (m, 2H), 3.19 (dd, <i>J</i> 14.4, 7.6 Hz, 1H), 3.13 (dd, <i>J</i> 14.4, 7.6 Hz, 1H), 3.08-3.01 (m, 2H), 2.45 (s, 3H), 1.82-1.78 (m, 2H), 1.47-1.41 (m, 2H), 1.41 (s, 9H). LCMS (ES ⁺) 576 (M+H) ⁺ .
155	{(<i>S</i>)-3-[5-(Azetidine-1-carbonyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]-morpholin-4-yl}-(6-methylpyridin-3-yl)-methanone	δ_H (d ₆ -DMSO at 110°C) 8.20 (s, 1H), 7.72 (s, 1H), 7.45 (dd, <i>J</i> 8.6, 1.3 Hz, 1H), 7.39 (d, <i>J</i> 8.6 Hz, 1H), 7.30 (d, <i>J</i> 7.3 Hz, 1H), 7.11-7.08 (m, 2H), 4.29-4.23 (m, 1H), 4.21-4.17 (m, 4H), 3.97-3.89 (m, 1H), 3.82 (d, <i>J</i> 11.6 Hz, 1H), 3.78-3.73 (m, 1H), 3.76 (s, 3H), 3.61 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.55-3.46 (m, 2H), 3.21 (dd, <i>J</i> 14.4, 7.8 Hz, 1H), 3.14 (dd, <i>J</i> 14.4, 7.6 Hz, 1H), 2.45 (s, 3H), 2.32-2.24 (m, 2H). LCMS (ES ⁺) 433 (M+H) ⁺ .
156	[(<i>S</i>)-3-{5-[3-Hydroxy-3-(hydroxymethyl)azetidine-1-carbonyl]-1-methyl-1 <i>H</i> -indol-3-ylmethyl}-morpholin-4-yl]-(6-methylpyridin-3-yl)-methanone	δ_H (d ₆ -DMSO at 110°C) 8.21 (s, 1H), 7.75 (s, 1H), 7.46 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.39 (d, <i>J</i> 8.6 Hz, 1H), 7.32-7.30 (m, 1H), 7.11-7.09 (m, 2H), 4.30-4.26 (m, 1H), 4.19-4.17 (m, 2H), 3.97-3.89 (m, 3H), 3.82 (d, <i>J</i> 11.6 Hz, 1H), 3.78-3.76 (m, 1H), 3.76 (s, 3H), 3.61 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.55-3.47 (m, 4H), 3.22 (dd, <i>J</i> 14.7, 8.1 Hz, 1H), 3.14 (dd, <i>J</i> 14.4, 7.3 Hz, 1H), 2.45 (s, 3H). LCMS (ES ⁺) 479 (M+H) ⁺ .
157	3-[(<i>S</i>)-4-(2-Chlorothiazole-5-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 7.66 (s, 1H), 7.58 (s, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.20 (d, <i>J</i> 8.6 Hz, 1H), 7.13 (s, 1H), 4.45-4.39 (m, 1H), 4.00-3.93 (m, 2H), 3.87 (d, <i>J</i> 11.6 Hz, 1H), 3.76 (s, 3H), 3.65 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.60-3.47 (m, 2H), 3.18 (d, <i>J</i> 7.3 Hz, 2H), 3.04 (s, 6H). LCMS (ES ⁺) 447 (M+H) ⁺ .

158	3-[(S)-4-(5-Chloro-6-methoxy-pyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid <i>N</i> -(2-methoxyethyl)- <i>N</i> -methylamide	δ_{H} (d_6 -DMSO at 110°C) 10.74 (dd, <i>J</i> 1.0, 0.5 Hz, 1H), 7.87 (d, <i>J</i> 1.8 Hz, 1H), 7.50 (s, 1H), 7.38 (d, <i>J</i> 8.3 Hz, 2H), 7.13-7.09 (m, 2H), 4.31-4.26 (m, 1H), 3.98-3.91 (m, 4H), 3.85-3.82 (m, 2H), 3.65 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.57-3.48 (m, 6H), 3.29 (s, 3H), 3.20-3.17 (m, 2H), 2.99 (s, 3H). LCMS (ES^+) 501 ($\text{M}+\text{H}$) ⁺ .
159	3-[(S)-4-(2-Chloro-5-fluoro-6-methoxypyridine-3-carbonyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid <i>N</i> -(2-methoxyethyl)- <i>N</i> -methylamide	δ_{H} (d_6 -DMSO at 110°C) 10.77 (s, 1H), 7.67-7.36 (m, 2H), 7.22-7.08 (m, 2H), 4.02-3.90 (m, 4H), 3.84 (d, <i>J</i> 11.1 Hz, 2H), 3.68-3.46 (m, 8H), 3.31-3.13 (m, 6H), 3.00 (s, 3H). LCMS (ES^+) 519 ($\text{M}+\text{H}$) ⁺ .
160	3-[(S)-4-(6-Methoxy-5-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d_6 -DMSO at 110°C) 10.73 (s, 1H), 7.82 (d, <i>J</i> 2.0 Hz, 1H), 7.48 (s, 1H), 7.37 (dd, <i>J</i> 8.3, 0.5 Hz, 1H), 7.12-7.08 (m, 3H), 4.33-4.25 (m, 1H), 3.96-3.88 (m, 4H), 3.82-3.80 (m, 2H), 3.60 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.53-3.47 (m, 2H), 3.18-3.16 (m, 2H), 2.97 (s, 6H), 2.04 (s, 3H). LCMS (ES^+) 437 ($\text{M}+\text{H}$) ⁺ .
161	<i>N</i> -{3-[(S)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}-acetamide	δ_{H} (d_6 -DMSO at 110°C) 10.43 (s, 1H), 9.13 (s, 1H), 7.85 (d, <i>J</i> 2.0 Hz, 1H), 7.57 (s, 1H), 7.33 (d, <i>J</i> 1.5 Hz, 1H), 7.28-7.18 (m, 2H), 7.02 (d, <i>J</i> 2.3 Hz, 1H), 4.35-4.29 (m, 1H), 3.99-3.90 (m, 4H), 3.86-3.75 (m, 2H), 3.67 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.55-3.45 (m, 2H), 3.19 (dd, <i>J</i> 14.7, 8.1 Hz, 1H), 3.07 (dd, <i>J</i> 14.7, 7.1 Hz, 1H), 2.02 (s, 3H). LCMS (ES^+) 443 ($\text{M}+\text{H}$) ⁺ .
162	{3-[(S)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indol-5-yl}carbamic acid methyl ester	δ_{H} (d_6 -DMSO at 110°C) 10.41 (d, <i>J</i> 0.8 Hz, 1H), 8.63 (s, 1H), 7.84 (d, <i>J</i> 2.0 Hz, 1H), 7.46 (s, 1H), 7.33 (d, <i>J</i> 1.5 Hz, 1H), 7.24 (d, <i>J</i> 8.7 Hz, 1H), 7.10 (dd, <i>J</i> 8.8, 2.0 Hz, 1H), 7.02 (d, <i>J</i> 2.0 Hz, 1H), 4.35-4.26 (m, 1H), 3.99-3.89 (m, 4H), 3.86-3.73 (m, 2H), 3.70-3.62 (m, 4H), 3.54-3.46 (m, 2H), 3.19 (dd, <i>J</i> 14.7, 8.3 Hz, 1H), 3.06 (dd, <i>J</i> 14.4, 6.8 Hz, 1H). LCMS (ES^+) 459 ($\text{M}+\text{H}$) ⁺ .
163	Cyclopropanecarboxylic acid {3-[(S)-4-(5-chloro-6-methoxypyridine-3-carbonyl)morpholin-3-	δ_{H} (d_6 -DMSO at 110°C) 10.43 (s, 1H), 9.36 (s, 1H), 7.84 (d, <i>J</i> 2.0 Hz, 1H), 7.61 (s, 1H), 7.32 (d, <i>J</i> 1.5 Hz, 1H), 7.25-7.19 (m, 2H), 7.02 (d, <i>J</i> 2.3 Hz, 1H), 4.34-4.28 (m, 1H), 3.99-3.91 (m, 4H), 3.86-3.76 (m, 2H),

	ylmethyl]-1 <i>H</i> -indol-5-yl}amide	3.68 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.51-3.49 (m, 2H), 3.20 (dd, <i>J</i> 14.4, 8.1 Hz, 1H), 3.05 (dd, <i>J</i> 14.4, 6.8 Hz, 1H), 1.83-1.74 (m, 1H), 0.85-0.82 (m, 2H), 0.75-0.72 (m, 2H). LCMS (ES ⁺) 469 (M+H) ⁺ .
164	(5-Chloro-6-methoxypyridin-3-yl)-{(S)-3-[5-(1,1-dioxo-1 <i>Λ</i> 6-isothiazolidin-2-yl)-1 <i>H</i> -indol-3-ylmethyl]morpholin-4-yl}-methanone	δ_{H} (d ₆ -DMSO at 110°C) 10.63 (s, 1H), 7.86 (d, <i>J</i> 2.0 Hz, 1H), 7.39-7.32 (m, 2H), 7.16-7.05 (m, 2H), 4.35-4.27 (m, 1H), 3.99-3.92 (m, 4H), 3.86-3.75 (m, 2H), 3.71-3.63 (m, 3H), 3.52-3.50 (m, 1H), 3.38-3.34 (m, 2H), 3.18-3.12 (m, 3H), 2.47-2.40 (m, 3H). LCMS (ES ⁺) 505 (M+H) ⁺ .
165	<i>N</i> -{3-[(S)-4-(2-Chloro-5-fluoro-6-methoxypyridine-3-carbonyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indol-5-yl}acetamide	δ_{H} (d ₆ -DMSO at 110°C) 10.47 (s, 1H), 9.19 (s, 1H), 7.67-7.49 (m, 1H), 7.30-7.19 (m, 2H), 7.13-7.02 (m, 1H), 4.02-3.89 (m, 5H), 3.84-3.82 (m, 2H), 3.74-3.61 (m, 1H), 3.55-3.45 (m, 2H), 3.21-3.09 (m, 2H), 2.02 (s, 4H). LCMS (ES ⁺) 461 (M+H) ⁺ .
166	Cyclopropanecarboxylic acid {3-[(S)-4-(2-chloro-5-fluoro-6-methoxypyridine-3-carbonyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indol-5-yl}amide	δ_{H} (d ₆ -DMSO at 110°C) 10.46 (s, 1H), 9.40 (s, 1H), 7.76-7.55 (m, 1H), 7.31-7.19 (m, 2H), 7.09-6.99 (m, 1H), 4.01-3.90 (m, 5H), 3.85-3.82 (m, 2H), 3.75-3.59 (m, 1H), 3.57-3.39 (m, 3H), 3.24-3.03 (m, 2H), 1.85-1.70 (m, 1H), 0.89-0.79 (m, 2H), 0.77-0.69 (m, 2H). LCMS (ES ⁺) 487 (M+H) ⁺ .
167	{3-[(S)-4-(2-Chloro-5-fluoro-6-methoxypyridine-3-carbonyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indol-5-yl}carbamic acid methyl ester	δ_{H} (d ₆ -DMSO at 110°C) 10.46 (s, 1H), 8.68 (s, 1H), 7.63-7.37 (m, 1H), 7.26 (d, <i>J</i> 8.6 Hz, 1H), 7.15-7.00 (m, 2H), 4.00-3.90 (m, 4H), 3.85-3.82 (m, 1H), 3.75-3.61 (m, 5H), 3.56-3.43 (m, 3H), 3.25-3.04 (m, 3H). LCMS (ES ⁺) 477 (M+H) ⁺ .
168	(2-Chloro-5-fluoro-6-methoxypyridin-3-yl)-{(S)-3-[5-(1,1-dioxo-1 <i>Λ</i> 6-isothiazolidin-2-yl)-1 <i>H</i> -indol-3-ylmethyl]morpholin-4-yl}-methanone	δ_{H} (d ₆ -DMSO at 110°C) 10.66 (s, 1H), 7.37 (d, <i>J</i> 8.6 Hz, 2H), 7.20-7.07 (m, 2H), 4.00-3.90 (m, 4H), 3.87-3.79 (m, 2H), 3.75-3.61 (m, 4H), 3.56-3.46 (m, 2H), 3.38-3.35 (m, 2H), 3.25-3.07 (m, 2H), 2.48-2.41 (m, 4H). LCMS (ES ⁺) 523 (M+H) ⁺ .
169	1-{3-[(S)-4-(2-Chloro-5-fluoro-6-methoxypyridine-3-carbonyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indol-5-yl}pyrrolidin-2-one	δ_{H} (d ₆ -DMSO at 110°C) 10.56 (s, 1H), 7.60-7.59 (br s, 1H), 7.41-7.39 (m, 2H), 7.34-7.32 (m, 1H), 7.11 (s, 1H), 3.97 (s, 4H), 3.87-3.77 (m, 4H), 3.72-3.60 (m, 1H), 3.50-3.48 (m, 2H), 3.27-3.11 (m, 2H), 2.46-2.44 (m, 3H), 2.15-2.07 (m, 2H). LCMS

		(ES ⁺) 487 (M+H) ⁺ .
170	<i>N</i> -{3-[(<i>S</i>)-4-(3-Chloro-4-methoxybenzoyl)morpholin-3-ylmethyl]-1 <i>H</i> -indol-5-yl}acetamide	δ_{H} (d ₆ -DMSO at 110°C) 10.43 (d, <i>J</i> 0.5 Hz, 1H), 9.15 (d, <i>J</i> 1.0 Hz, 1H), 7.57 (s, 1H), 7.27-7.21 (m, 2H), 7.13 (d, <i>J</i> 1.8 Hz, 1H), 7.04-6.97 (m, 3H), 4.29-4.25 (m, 1H), 3.87 (s, 4H), 3.78-3.75 (m, 2H), 3.58 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.50-3.46 (m, 2H), 3.13 (d, <i>J</i> 7.6 Hz, 2H), 2.03 (s, 3H). LCMS (ES ⁺) 442 (M+H) ⁺ .
171	3-[(<i>S</i>)-4-(3,4-Dichlorobenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.51 (s, 1H), 7.45 (d, <i>J</i> 8.3 Hz, 1H), 7.40 (d, <i>J</i> 8.3 Hz, 1H), 7.22-7.15 (m, 2H), 7.10 (s, 1H), 7.04 (d, <i>J</i> 7.3 Hz, 1H), 4.24-4.15 (m, 1H), 3.95-3.90 (m, 1H), 3.85-3.71 (m, 5H), 3.62 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.53-3.47 (m, 2H), 3.17 (d, <i>J</i> 7.6 Hz, 2H), 2.98 (s, 6H). LCMS (ES ⁺) 474 (M+H) ⁺ .
172	3-[(<i>S</i>)-4-(3,4-Dimethoxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.53 (s, 1H), 7.38 (d, <i>J</i> 8.3 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.10 (s, 1H), 6.90-6.85 (m, 1H), 6.79-6.71 (m, 2H), 4.38-4.30 (m, 1H), 3.91 (d, <i>J</i> 7.6 Hz, 1H), 3.82-3.70 (m, 11H), 3.58-3.52 (m, 1H), 3.48 (d, <i>J</i> 9.1 Hz, 2H), 3.25 (dd, <i>J</i> 14.4, 8.6 Hz, 1H), 3.09 (dd, <i>J</i> 14.4, 6.8 Hz, 1H), 2.98 (s, 6H). LCMS (ES ⁺) 466 (M+H) ⁺ .
173	1-Methyl-3-{(<i>S</i>)-4-[3-(trifluoromethyl)benzoyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.69-7.63 (m, 1H), 7.55-7.44 (m, 2H), 7.43-7.34 (m, 3H), 7.18 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.10 (s, 1H), 4.29-4.19 (m, 1H), 3.93 (d, <i>J</i> 7.1 Hz, 1H), 3.84-3.70 (m, 5H), 3.62 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.52 (d, <i>J</i> 8.8 Hz, 2H), 3.26-3.12 (m, 2H), 2.97 (s, 6H). LCMS (ES ⁺) 474 (M+H) ⁺ .
174	3-[(<i>S</i>)-4-(3-Chloro-5-fluoro-4-methoxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.53 (s, 1H), 7.40 (d, <i>J</i> 8.3 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.10 (s, 1H), 6.91-6.83 (m, 2H), 4.26-4.16 (m, 1H), 3.95-3.88 (m, 4H), 3.86-3.81 (m, 1H), 3.80-3.73 (m, 4H), 3.64 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.53-3.47 (m, 2H), 3.16 (dd, <i>J</i> 7.6, 4.5 Hz, 2H), 2.98 (s, 6H). LCMS (ES ⁺) 488 (M+H) ⁺ .
175	3-[(<i>S</i>)-4-(3,5-Dichloro-4-methoxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.54 (s, 1H), 7.40 (d, <i>J</i> 8.3 Hz, 1H), 7.19 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.10 (s, 1H), 7.04 (s, 2H), 4.26-4.16 (m, 1H), 3.96-3.89 (m, 1H), 3.87-3.73 (m, 8H), 3.65 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.54-3.48 (m, 2H), 3.25-3.09 (m, 2H), 2.98 (s, 6H).

		LCMS (ES ⁺) 504 (M+H) ⁺ .
176	3-[(S)-4-(4-Methoxy-2-methylbenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.58-7.48 (m, 1H), 7.39 (d, <i>J</i> 8.3 Hz, 1H), 7.20 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.12 (s, 1H), 6.86 (d, <i>J</i> 8.1 Hz, 1H), 6.76 (d, <i>J</i> 2.3 Hz, 1H), 6.68 (dd, <i>J</i> 8.3, 1.8 Hz, 1H), 4.36-4.22 (m, 1H), 3.91-3.85 (m, 1H), 3.80-3.71 (m, 7H), 3.48 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.44-3.39 (m, 2H), 3.28 (dd, <i>J</i> 14.4, 9.1 Hz, 1H), 3.04 (dd, <i>J</i> 14.1, 6.3 Hz, 1H), 2.99 (s, 6H), 2.95-2.81 (m, 1H), 2.11 (s, 3H). LCMS (ES ⁺) 450 (M+H) ⁺ .
177	3-[(S)-4-(3-Fluoro-5-hydroxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.51 (s, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.10 (s, 1H), 6.53 (dt, <i>J</i> 10.9, 2.0 Hz, 1H), 6.45 (s, 1H), 6.31 (d, <i>J</i> 8.6 Hz, 1H), 4.34-4.23 (m, 1H), 3.91 (d, <i>J</i> 7.6 Hz, 1H), 3.81-3.66 (m, 5H), 3.53 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.46 (d, <i>J</i> 9.1 Hz, 2H), 3.25 (dd, <i>J</i> 14.1, 8.3 Hz, 1H), 3.07 (dd, <i>J</i> 14.4, 6.8 Hz, 1H), 2.99 (s, 6H), 2.04 (s, 1H). LCMS (ES ⁺) 440 (M+H) ⁺ .
178	3-[(S)-4-(3-Hydroxy-4-methylbenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.54 (s, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.09 (s, 1H), 7.01 (d, <i>J</i> 7.6 Hz, 1H), 6.70 (s, 1H), 6.54 (dd, <i>J</i> 7.6, 1.0 Hz, 1H), 4.38-4.27 (m, 1H), 3.90 (d, <i>J</i> 7.8 Hz, 1H), 3.82-3.68 (m, 5H), 3.49 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.46-3.42 (m, 2H), 3.28 (dd, <i>J</i> 14.1, 8.8 Hz, 1H), 3.07-3.01 (m, 1H), 3.01-2.96 (m, 7H), 2.15 (s, 3H). LCMS (ES ⁺) 436 (M+H) ⁺ .
179	3-Hydroxy-4-methylbenzoic acid 5-[(S)-3-(5-dimethylcarbamoyl-1-methyl-1 <i>H</i> -indol-3-ylmethyl)-morpholine-4-carbonyl]-2-methylphenyl ester	δ_{H} (d ₆ -DMSO at 110°C) 7.58 (d, <i>J</i> 1.8 Hz, 1H), 7.56-7.51 (m, 2H), 7.35 (d, <i>J</i> 8.6 Hz, 1H), 7.29 (d, <i>J</i> 7.8 Hz, 1H), 7.25 (d, <i>J</i> 7.6 Hz, 1H), 7.18 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.10 (s, 1H), 6.99-6.92 (m, 2H), 4.35-4.27 (m, 1H), 3.92 (d, <i>J</i> 7.6 Hz, 1H), 3.81-3.71 (m, 5H), 3.60-3.52 (m, 1H), 3.52-3.44 (m, 2H), 3.24 (dd, <i>J</i> 14.4, 8.1 Hz, 1H), 3.10 (dd, <i>J</i> 14.4, 7.1 Hz, 2H), 2.98 (s, 6H), 2.27 (s, 3H), 2.18 (s, 3H). LCMS (ES ⁺) 570 (M+H) ⁺ .
180	3-[(S)-4-(2-Chloro-6-methylpyridine-4-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.49 (br s, 1H), 7.42 (d, <i>J</i> 8.6 Hz, 1H), 7.20 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.12 (s, 1H), 6.72-6.89 (m, 2H), 4.27-4.01 (m, 1H), 3.97-3.91 (m, 1H), 3.87-3.73 (m, 5H), 3.63 (dd, <i>J</i> 11.6, 2.8 Hz, 1H), 3.56-3.47 (m, 2H), 3.23-3.11 (m,

		2H), 2.95 (s, 6H), 2.35 (s, 3H). LCMS (ES ⁺) 455 (M+H) ⁺ .
181	3-[(S)-4-(2-Hydroxybenzoyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 9.35-9.20 (m, 1H), 7.42 (s, 1H), 7.37 (d, <i>J</i> 8.3 Hz, 1H), 7.20-7.12 (m, 2H), 7.07 (s, 1H), 6.91 (dd, <i>J</i> 7.3, 1.5 Hz, 1H), 6.86 (d, <i>J</i> 8.1 Hz, 1H), 6.75 (t, <i>J</i> 7.3 Hz, 1H), 4.26-4.15 (m, 1H), 3.93-3.87 (m, 1H), 3.81-3.70 (m, 5H), 3.54-3.39 (m, 4H), 3.29 (dd, <i>J</i> 14.1, 9.6 Hz, 1H), 2.99 (s, 6H). LCMS (ES ⁺) 422 (M+H) ⁺ .
182	3-[(S)-4-(4-Chloro-3-methylbenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 7.51 (s, 1H), 7.40 (d, <i>J</i> 8.3 Hz, 1H), 7.28 (d, <i>J</i> 8.1 Hz, 1H), 7.20 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.10 (s, 1H), 6.99-6.91 (m, 2H), 4.27-4.19 (m, 1H), 3.95-3.90 (m, 1H), 3.83-3.75 (m, 5H), 3.57 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.50-3.46 (m, 2H), 3.24-3.10 (m, 2H), 2.98 (s, 6H), 2.26 (s, 3H). LCMS (ES ⁺) 454 (M+H) ⁺ .
183	3-[(S)-4-(2,6-Dichloropyridine-4-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 7.56-7.50 (m, 1H), 7.42 (d, <i>J</i> 8.3 Hz, 1H), 7.21 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.13 (s, 1H), 7.07-6.98 (m, 2H), 4.26-3.99 (m, 1H), 3.98-3.88 (m, 1H), 3.88-3.73 (m, 5H), 3.72-3.64 (m, 1H), 3.46-3.60 (m, 2H), 3.28-3.07 (m, 2H), 2.99 (s, 6 H). LCMS (ES ⁺) 475 (M+H) ⁺ .
184	3-{(S)-4-[3-Hydroxy-5-(trifluoromethyl)benzoyl]morpholin-3-ylmethyl}-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 7.53 (s, 1H), 7.38 (dd, <i>J</i> 8.3, 0.5 Hz, 1H), 7.18 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.10 (s, 1H), 7.03 (s, 1H), 6.83 (d, <i>J</i> 11.6 Hz, 2H), 4.37-4.25 (m, 1H), 3.92 (d, <i>J</i> 7.8 Hz, 1H), 3.83-3.66 (m, 5H), 3.57 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.52-3.44 (m, 2H), 3.26-3.21 (m, 1H), 3.11 (dd, <i>J</i> 14.4, 7.1 Hz, 1H), 2.98 (s, 6H). LCMS (ES ⁺) 490 (M+H) ⁺ .
185	3-[(S)-4-(2,6-Dimethylpyrimidine-4-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 7.38 (d, <i>J</i> 8.6 Hz, 2H), 7.18 (d, <i>J</i> 8.3 Hz, 2H), 7.12-7.03 (m, 1H), 4.43-4.20 (m, 1H), 4.00-3.89 (m, 1H), 3.83 (d, <i>J</i> 11.6 Hz, 1H), 3.77 (s, 3H), 3.67-3.45 (m, 3H), 3.25-3.09 (m, 3H), 2.98 (s, 9H), 2.32-2.19 (m, 3H). LCMS (ES ⁺) 436 (M+H) ⁺ .
186	3-[(S)-4-(2-Chloro-3-fluoropyridine-4-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 8.00-7.80 (m, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 2H), 7.18-7.16 (m, 2H), 7.15-7.05 (m, 1H), 4.03-3.91 (m, 2H), 3.84 (d, <i>J</i> 11.6 Hz, 1H), 3.76 (s, 3H), 3.61-3.41 (m, 4H), 3.25-3.06 (m, 2H), 2.97 (s, 6H).

		LCMS (ES ⁺) 459 (M+H) ⁺ .
187	1-Methyl-3-[(<i>S</i>)-4-(6-methyl-2-oxo-1,2-dihydropyridine-4-carbonyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 11.14-10.99 (m, 1H), 7.59-7.52 (m, 1H), 7.39-7.66 (m, 1H), 7.18 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.10 (s, 1H), 5.82 (s, 1H), 5.52-5.42 (m, 1H), 4.30-4.16 (m, 1H), 3.89 (d, <i>J</i> 7.3 Hz, 1H), 3.82-3.69 (m, 5H), 3.52 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.46-3.41 (m, 2H), 3.23-3.14 (m, 1H), 3.12-3.04 (m, 1H), 2.98 (s, 6H), 2.06 (s, 3H). LCMS (ES ⁺) 437 (M+H) ⁺ .
188	3-[(<i>S</i>)-4-(2,3-Dichloropyridine-4-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 8.43-8.35 (m, 1H), 7.83-7.73 (m, 1H), 7.39 (d, <i>J</i> 8.3 Hz, 1H), 7.29-7.14 (m, 2H), 7.04-6.98 (m, 1H), 4.09-3.95 (m, 1H), 3.88-3.72 (m, 5H), 3.67-3.38 (m, 3H), 3.36-3.23 (m, 1H), 3.19-3.08 (m, 2H), 3.06-2.83 (m, 6H). LCMS (ES ⁺) 475 (M+H) ⁺ .
189	3-[(<i>S</i>)-4-(4-Fluoro-3-hydroxy-benzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 7.51 (s, 1H), 7.38 (dd, <i>J</i> 8.3, 0.5 Hz, 1H), 7.19 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.09 (s, 1H), 7.00 (dd, <i>J</i> 11.4, 8.3 Hz, 1H), 6.82 (dd, <i>J</i> 8.6, 2.0 Hz, 1H), 6.63-6.55 (m, 1H), 4.34-4.24 (m, 1H), 3.91 (d, <i>J</i> 7.6 Hz, 1H), 3.81-3.72 (m, 5H), 3.52 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.46 (d, <i>J</i> 9.1 Hz, 2H), 3.25 (dd, <i>J</i> 14.4, 8.6 Hz, 1H), 3.06 (dd, <i>J</i> 14.1, 8.6 Hz, 2H), 2.99 (s, 6H). LCMS (ES ⁺) 440 (M+H) ⁺ .
190	3-{(<i>S</i>)-4-[5-(Acetylamino)pyridine-3-carbonyl]morpholin-3-ylmethyl}-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 9.76 (s, 1H), 8.63 (d, <i>J</i> 2.3 Hz, 1H), 8.00 (d, <i>J</i> 1.5 Hz, 1H), 7.77 (t, <i>J</i> 1.8 Hz, 1H), 7.48 (s, 1H), 7.36 (d, <i>J</i> 8.6 Hz, 1H), 7.18 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.09 (s, 1H), 4.34-4.23 (m, 1H), 3.94-3.88 (m, 1H), 3.83-3.74 (m, 5H), 3.60 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.54-3.46 (m, 2H), 3.24-3.20 (m, 1H), 3.13 (dd, <i>J</i> 14.4, 7.3 Hz, 1H), 3.07-2.89 (m, 6H), 2.10 (s, 3H). LCMS (ES ⁺) 464 (M+H) ⁺ .
191	3-[(<i>S</i>)-4-(3-Hydroxy-4-nitro-benzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 7.77 (d, <i>J</i> 8.3 Hz, 1H), 7.51 (s, 1H), 7.41-7.39 (m, 1H), 7.19 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.11 (s, 1H), 6.87 (d, <i>J</i> 1.0 Hz, 1H), 6.65 (d, <i>J</i> 8.1 Hz, 1H), 4.29-4.19 (m, 1H), 3.93 (d, <i>J</i> 7.3 Hz, 1H), 3.84-3.73 (m, 5H), 3.58 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.51-3.46 (m, 2H), 3.22 (dd, <i>J</i> 14.1, 7.6 Hz, 1H), 3.16-3.09 (m, 1H), 2.97 (s, 7H). LCMS (ES ⁺) 467 (M+H) ⁺ .

192	3-[(S)-4-(3-Bromo-5-hydroxy-benzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d_6 -DMSO at 110°C) 7.52 (s, 1H), 7.39 (d, <i>J</i> 8.6 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.10 (s, 1H), 6.94 (t, <i>J</i> 2.0 Hz, 1H), 6.64 (s, 1H), 6.59 (dd, <i>J</i> 2.0, 1.3 Hz, 1H), 4.33-4.23 (m, 1H), 3.91 (d, <i>J</i> 7.6 Hz, 1H), 3.81-3.67 (m, 5H), 3.54 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.47 (d, <i>J</i> 9.1 Hz, 2H), 3.28-3.18 (m, 1H), 3.13-3.05 (m, 2H), 3.00 (s, 6H). LCMS (ES^+) 502 ($\text{M}+\text{H}$) ⁺ .
193	3-[(S)-4-(5-Aminopyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d_6 -DMSO at 110°C) 7.95 (d, <i>J</i> 2.5 Hz, 1H), 7.58 (d, <i>J</i> 1.8 Hz, 1H), 7.53 (s, 1H), 7.41-7.37 (m, 1H), 7.19 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.10 (s, 1H), 6.71 (t, <i>J</i> 2.3 Hz, 1H), 5.01 (s, 2H), 4.36-4.26 (m, 1H), 3.92 (d, <i>J</i> 7.8 Hz, 1H), 3.82-3.71 (m, 5H), 3.53 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.50-3.44 (m, 2H), 3.26 (dd, <i>J</i> 14.4, 8.6 Hz, 1H), 3.06 (dd, <i>J</i> 14.4, 6.6 Hz, 1H), 3.00 (s, 6H). LCMS (ES^+) 422 ($\text{M}+\text{H}$) ⁺ .
194	1-Methyl-3-[(S)-4-[3-(methyl-sulfamoyl)benzoyl]morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d_6 -DMSO at 110°C) 7.78 (dd, <i>J</i> 7.8, 1.0 Hz, 1H), 7.66-7.62 (m, 1H), 7.54-7.46 (m, 2H), 7.39 (d, <i>J</i> 8.3 Hz, 1H), 7.34 (d, <i>J</i> 7.6 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.13-7.05 (m, 2H), 4.32-4.23 (m, 1H), 3.93 (d, <i>J</i> 7.8 Hz, 1H), 3.83-3.69 (m, 5H), 3.59 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.54-3.49 (m, 2H), 3.27 (dd, <i>J</i> 14.4, 8.3 Hz, 1H), 3.11 (dd, <i>J</i> 14.1, 6.8 Hz, 1H), 2.99 (s, 6H), 2.46 (d, <i>J</i> 5.1 Hz, 3H). LCMS (ES^+) 499 ($\text{M}+\text{H}$) ⁺ .
195	3-[(S)-4-(4-Bromo-3-hydroxy-benzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d_6 -DMSO at 110°C) 7.58 (s, 1H), 7.39 (d, <i>J</i> 8.3 Hz, 2H), 7.20 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.10 (s, 1H), 6.82 (d, <i>J</i> 1.8 Hz, 1H), 6.51 (dd, <i>J</i> 8.1, 2.0 Hz, 1H), 4.34-4.27 (m, 1H), 3.96-3.86 (m, 1H), 3.81-3.70 (m, 5H), 3.52 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.49-3.44 (m, 2H), 3.25 (dd, <i>J</i> 14.4, 8.1 Hz, 1H), 3.08 (dd, <i>J</i> 14.1, 6.6 Hz, 1H), 3.00 (s, 6H). LCMS (ES^+) 502 ($\text{M}+\text{H}$) ⁺ .
196	3-[(S)-4-(3,4-Difluoro-5-hydroxy-benzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d_6 -DMSO at 110°C) 7.51 (s, 1H), 7.39 (d, <i>J</i> 8.6 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.10 (s, 1H), 6.61 (d, <i>J</i> 7.1 Hz, 1H), 6.50-6.43 (m, 1H), 4.31-4.24 (m, 1H), 3.91 (d, <i>J</i> 7.6 Hz, 1H), 3.82-3.72 (m, 5H), 3.56 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.47 (d, <i>J</i> 9.1 Hz, 2H), 3.22 (dd, <i>J</i> 14.4, 7.8 Hz, 1H), 3.09 (dd, <i>J</i> 14.1, 6.8 Hz, 1H), 2.99 (s,

		7H). LCMS (ES ⁺) 458 (M+H) ⁺ .
197	3-[(S)-4-(3-Chloro-5-hydroxy-benzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.51 (s, 1H), 7.39 (d, <i>J</i> 8.3 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.10 (s, 1H), 6.79 (t, <i>J</i> 2.0 Hz, 1H), 6.56-6.54 (m, 2H), 4.32-4.24 (m, 1H), 3.91 (d, <i>J</i> 7.3 Hz, 1H), 3.82-3.69 (m, 5H), 3.54 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.47 (d, <i>J</i> 9.1 Hz, 2H), 3.23 (dd, <i>J</i> 14.4, 8.3 Hz, 1H), 3.09 (dd, <i>J</i> 14.1, 6.8 Hz, 2H), 2.99 (s, 6H). LCMS (ES ⁺) 456 (M+H) ⁺ .
198	3-[(S)-4-(2-Fluoro-3-hydroxy-benzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.65-7.55 (m, 1H), 7.39 (d, <i>J</i> 8.3 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 0.8 Hz, 1H), 7.14-7.04 (m, 1H), 6.97-6.85 (m, 2H), 6.52-6.39 (m, 1H), 3.97-3.87 (m, 1H), 3.82-3.69 (m, 5H), 3.40-3.54 (m, 4H), 3.34-3.25 (m, 2H), 2.91-3.07 (m, 2H), 2.99 (s, 6H). LCMS (ES ⁺) 440 (M+H) ⁺ .
199	3-[(S)-4-(2-Fluoro-5-hydroxy-benzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 9.18-8.98 (m, 1H), 7.38 (d, <i>J</i> 8.3 Hz, 2H), 7.23-7.04 (m, 1H), 7.02-6.92 (m, 1H), 6.82-6.73 (m, 1H), 6.55-6.44 (m, 1H), 3.96-3.86 (m, 1H), 3.81-3.70 (m, 5H), 3.51-3.39 (m, 3H), 3.30 (dd, <i>J</i> 14.4, 9.1 Hz, 2H), 3.03-2.95 (m, 2H), 2.87 (s, 6H). LCMS (ES ⁺) 440 (M+H) ⁺ .
200	3-[(S)-4-(6-Cyanopyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 8.34 (s, 1H), 7.77 (d, <i>J</i> 7.8 Hz, 1H), 7.61-7.56 (m, 1H), 7.46 (d, <i>J</i> 0.8 Hz, 1H), 7.39 (d, <i>J</i> 8.3 Hz, 1H), 7.21 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.11 (s, 1H), 4.21-4.09 (m, 1H), 3.98-3.93 (m, 1H), 3.85 (d, <i>J</i> 11.6 Hz, 1H), 3.83-3.78 (m, 1H), 3.78 (s, 3H), 3.68 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.57-3.50 (m, 2H), 3.21-3.15 (m, 2H), 3.00 (s, 6H). LCMS (ES ⁺) 432 (M+H) ⁺ .
201	3-[(S)-4-(3,5-Difluoro-4-methoxy-benzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.52 (s, 1H), 7.39 (d, <i>J</i> 8.3 Hz, 1H), 7.20 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.10 (s, 1H), 6.74-6.72 (m, 2H), 4.21-4.09 (m, 1H), 3.93 (s, 3H), 3.93-3.88 (m, 1H), 3.82 (d, <i>J</i> 11.6 Hz, 1H), 3.77 (s, 3H), 3.77-3.75 (m, 1H), 3.63 (dd, <i>J</i> 11.4, 3.3 Hz, 1H), 3.53-3.44 (m, 2H), 3.16-3.14 (m, 2H), 2.98 (s, 6H). LCMS (ES ⁺) 472 (M+H) ⁺ .
202	3-[(S)-4-(5-Fluoropyridine-3-carbonyl)morpholin-3-ylmethyl]-1-	δ_{H} (d ₆ -DMSO at 110°C) 8.18 (s, 1H), 7.43 (br s, 3H), 7.40 (d, <i>J</i> 8.6 Hz, 1H), 7.20 (dd, <i>J</i> 8.3, 1.0 Hz, 1H), 7.11 (s, 1H), 3.95-3.94 (m, 1H), 3.84

	methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	(d, <i>J</i> 11.6 Hz, 1H), 3.77 (s, 3H), 3.56 (dd, <i>J</i> 11.6, 2.8 Hz, 1H), 3.51-3.44 (m, 2H), 3.22-3.20 (m, 1H), 3.10 (dd, <i>J</i> 14.1, 6.8 Hz, 1H), 2.98 (s, 6H), 2.91-2.90 (m, 2H). LCMS (ES ⁺) 452 (M+H) ⁺ .
203	1-Methyl-3-[(<i>S</i>)-4-(4-methyl-3,4-dihydro-2 <i>H</i> -pyrido[3,2- <i>b</i>][1,4]-oxazine-7-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.56 (d, <i>J</i> 2.0 Hz, 1H), 7.56-7.55 (m, 1H), 7.38 (d, <i>J</i> 8.3 Hz, 1H), 7.19 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.08 (s, 1H), 6.60 (d, <i>J</i> 1.8 Hz, 1H), 4.37-4.33 (m, 1H), 4.18-4.16 (m, 2H), 3.94-3.87 (m, 1H), 3.81-3.78 (m, 2H), 3.76 (s, 3H), 3.57 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.49-3.43 (m, 4H), 3.22-3.20 (dd, <i>J</i> 14.1, 7.8 Hz, 1H), 3.11-3.05 (m, 1H), 3.05 (s, 3H), 2.98 (s, 6H). LCMS (ES ⁺) 478 (M+H) ⁺ .
204	3-[(<i>S</i>)-4-(2-Methoxypyridine-4-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 8.06-8.05 (m, 1H) 7.49 (br s, 1H), 7.39 (dd, <i>J</i> 8.6, 0.5 Hz, 1H), 7.20 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.10 (s, 1H), 6.61 (s, 1H), 6.41 (s, 1H), 4.17 (br s, 1H), 3.94-3.91 (m, 1H), 3.85 (s, 3H), 3.80 (d, <i>J</i> 11.6 Hz, 1H), 3.79-3.77 (m, 1H), 3.77 (s, 3H), 3.58 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.52-3.43 (m, 2H), 3.20 (dd, <i>J</i> 14.1, 7.6 Hz, 1H), 3.12 (dd, <i>J</i> 14.1, 7.3 Hz, 1H), 2.98 (s, 6H). LCMS (ES ⁺) 437 (M+H) ⁺ .
205	3-[(<i>S</i>)-4-(2-Fluoro-4-methoxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.48 (br s, 1H), 7.39 (d, <i>J</i> 8.3 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.09 (s, 1H), 6.92 (s, 1H), 6.72 (dd, <i>J</i> 11.9, 2.0 Hz, 1H), 6.67-6.65 (m, 1H), 4.16 (br s, 1H), 3.96-3.89 (m, 1H), 3.79 (d, <i>J</i> 11.6 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.49 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.42-3.39 (m, 2H), 3.24 (dd, <i>J</i> 14.4, 8.6 Hz, 1H), 3.05-2.98 (m, 2H), 2.98 (s, 6H). LCMS (ES ⁺) 454 (M+H) ⁺ .
206	3-[(<i>S</i>)-4-(3-Hydroxybenzoyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 9.15 (br s, 1H), 7.48 (s, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.18 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.13 (dd, <i>J</i> 7.8, 7.8 Hz, 1H), 7.08 (s, 1H), 6.78 (ddd, <i>J</i> 8.3, 2.5, 1.0 Hz, 1H), 6.63 (dd, <i>J</i> 2.3, 1.5 Hz, 1H), 6.59 (ddd, <i>J</i> 7.6, 1.3, 1.3 Hz, 1H), 4.29-4.27 (m, 1H), 3.93-3.85 (m, 1H), 3.75 (s, 3H), 3.75-3.73 (m, 2H), 3.50-3.47 (m, 1H), 3.44-3.39 (m, 2H), 3.27 (dd, <i>J</i> 14.4, 8.8 Hz, 1H), 3.02 (dd, <i>J</i> 14.1, 6.3 Hz, 1H), 2.98 (s, 6H). LCMS (ES ⁺) 422 (M+H) ⁺ .

207	3-Hydroxybenzoic acid 3- $\{(S)$ -3-[5-(dimethylcarbamoyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholine-4-carbonyl}phenyl ester	δ_H (d_6 -DMSO at 110°C) 9.52 (br s, 1H), 7.57 (ddd, J 7.6, 1.5, 1.0 Hz, 1H) 7.52 (dd, J 2.3, 2.3 Hz, 1H), 7.49 (s, 1H), 7.41-7.36 (m, 2H), 7.34 (dd, J 8.3, 0.5 Hz, 1H), 7.25 (ddd, J 8.1, 2.3, 0.8 Hz, 1H), 7.16 (dd, J 8.6, 1.5 Hz, 1H), 7.14 (ddd, J 8.1, 2.5, 1.0 Hz, 1H), 7.09 (s, 1H), 7.06-7.04 (m, 1H), 7.03-7.02 (m, 1H), 4.28 (s, 1H), 3.96-3.88 (m, 1H), 3.78 (d, J 11.4 Hz, 1H), 3.75-3.74 (m, 1H), 3.74 (s, 3H), 3.57 (dd, J 11.6, 3.0 Hz, 1H), 3.53-3.42 (m, 2H), 3.23 (dd, J 14.1, 8.1 Hz, 1H), 3.10 (dd, J 14.1, 6.8 Hz, 1H), 2.97 (s, 6H). LCMS (ES^+) 542 ($M+H$) $^+$.
208	1-Methyl-3-[(S)-4-(pyrimidine-5-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d_6 -DMSO at 110°C) 9.04 (s, 1H), 8.42 (s, 2H), 7.46 (s, 1H), 7.38 (dd, J 8.6, 0.5 Hz, 1H), 7.19 (dd, J 8.3, 1.5 Hz, 1H), 7.09 (s, 1H), 4.20 (s, 1H), 3.99-3.91 (m, 1H), 3.84 (d, J 11.6 Hz, 1H), 3.80-3.78 (m, 1H), 3.76 (s, 3H), 3.67 (dd, J 11.6, 3.0 Hz, 1H), 3.58-3.49 (m, 2H), 3.22-3.12 (m, 2H), 2.98 (s, 6H). LCMS (ES^+) 408 ($M+H$) $^+$.
209	3-[(S)-4-(2-Aminopyrimidine-5-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d_6 -DMSO at 110°C) 7.60-7.59 (m, 1H), 7.38 (dd, J 8.3, 0.5 Hz, 1H), 7.20 (dd, J 8.6, 1.5 Hz, 1H), 7.10 (s, 1H), 6.51 (s, 2H), 4.34-4.30 (m, 1H), 3.93-3.90 (m, 1H), 3.82 (d, J 11.4 Hz, 1H), 3.78-3.75 (m, 1H), 3.75 (s, 3H), 3.59 (dd, J 11.9, 3.3 Hz, 1H), 3.54-3.49 (m, 2H), 3.20 (dd, J 14.4, 7.8 Hz, 1H), 3.12 (dd, J 14.4, 7.1 Hz, 1H), 2.99 (s, 6H). LCMS (ES^+) 423 ($M+H$) $^+$.
210	-	-
211	3-[(S)-4-(2-Methoxypyrimidine-5-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d_6 -DMSO at 110°C) 8.25 (s, 1H), 7.52 (s, 1H), 7.39 (d, J 8.6 Hz, 1H), 7.19 (dd, J 8.3, 1.3 Hz, 1H), 7.10 (s, 1H), 4.25-4.22 (m, 1H), 3.98-3.91 (m, 1H), 3.94 (s, 3H), 3.85 (d, J 11.6 Hz, 1H), 3.83-3.80 (m, 1H), 3.76 (s, 3H), 3.66 (dd, J 11.6, 3.3 Hz, 1H), 3.59-3.48 (m, 2H), 3.19 (dd, J 14.4, 7.3 Hz, 1H), 3.15 (dd, J 14.1, 7.3 Hz, 1H), 2.98 (s, 6H). LCMS (ES^+) 438 ($M+H$) $^+$.
212	3- $\{(S)$ -4-[4-(Dimethylamino)-3-fluorobenzoyl]morpholin-3-ylmethyl}-1-methyl-1 <i>H</i> -indole-5-	δ_H (d_6 -DMSO at 110°C) 7.53 (s, 1H), 7.37 (d, J 8.3 Hz, 1H), 7.18 (dd, J 8.6, 1.3 Hz, 1H), 7.07 (s, 1H), 6.85-6.74 (m, 3H), 4.30-4.26 (m, 1H),

	carboxylic acid dimethylamide	3.92-3.85 (m, 1H), 3.78 (d, <i>J</i> 11.6 Hz, 1H), 3.77-3.75 (m, 1H), 3.75 (s, 3H), 3.54 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.50-3.41 (m, 2H), 3.19 (dd, <i>J</i> 14.4, 7.8 Hz, 1H), 3.09 (dd, <i>J</i> 14.4, 7.1 Hz, 1H), 2.96 (s, 6H), 2.83 (s, 6H). LCMS (ES ⁺) 467 (M+H) ⁺ .
213	3-[(<i>S</i>)-4-(2,6-Dichloropyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.74 (br s, 1H), 7.55 (br s, 1H), 7.41 (d, <i>J</i> 8.6 Hz, 1H), 7.23 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.17 (br s, 2H), 4.72 (br s, 1H), 4.31 (br s, 1H), 3.92 (br s, 1H), 3.84 (d, <i>J</i> 11.6 Hz, 1H), 3.78 (s, 3H), 3.64-3.50 (m, 3H), 3.23-3.17 (m, 2H), 3.00 (s, 6H). LCMS (ES ⁺) 475 (M+H) ⁺ .
214	3-[(<i>S</i>)-4-(6-Isopropoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.96 (d, <i>J</i> 2.3 Hz, 1H), 7.57 (s, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.38 (dd, <i>J</i> 8.6, 2.5 Hz, 1H), 7.20 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.09 (s, 1H), 6.59 (d, <i>J</i> 8.6 Hz, 1H), 4.32-4.29 (m, 1H), 3.96-3.89 (m, 1H), 3.82 (d, <i>J</i> 11.6 Hz, 1H), 3.79-3.76 (m, 2H), 3.76 (s, 3H), 3.59 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.56-3.45 (m, 2H), 3.22 (dd, <i>J</i> 14.4, 7.8 Hz, 1H), 3.13 (dd, <i>J</i> 14.4, 7.3 Hz, 1H), 2.99 (s, 6H), 1.31 (d, <i>J</i> 6.1 Hz, 6H). LCMS (ES ⁺) 465 (M+H) ⁺ .
215	3-[(<i>S</i>)-4-(3-Chloro-4-methoxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.49 (s, 1H), 7.39 (dd, <i>J</i> 8.6, 0.8 Hz, 1H), 7.19 (dd, <i>J</i> 8.6, 1.8 Hz, 1H), 7.10-7.09 (m, 2H), 7.06 (dd, <i>J</i> 8.6, 2.0 Hz, 1H), 7.00 (d, <i>J</i> 8.3 Hz, 1H), 4.27-4.24 (m, 1H), 3.96-3.91 (m, 1H), 3.87 (s, 3H), 3.80 (d, <i>J</i> 11.4 Hz, 1H), 3.79-3.77 (m, 1H), 3.77 (s, 3H), 3.58 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.53-3.44 (m, 2H), 3.20 (dd, <i>J</i> 14.1, 7.6 Hz, 1H), 3.13 (dd, <i>J</i> 14.4, 7.3 Hz, 1H), 2.97 (s, 6H). LCMS (ES ⁺) 470 (M+H) ⁺ .
216	3-[(<i>S</i>)-4-(4-Methoxy-3-methylbenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.50 (s, 1H), 7.39 (dd, <i>J</i> 8.3, 0.5 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.09 (s, 1H), 6.99 (dd, <i>J</i> 8.3, 2.3 Hz, 1H), 6.90 (d, <i>J</i> 1.3 Hz, 1H), 6.83 (d, <i>J</i> 8.3 Hz, 1H), 4.31-4.28 (m, 1H), 3.94-3.85 (m, 1H), 3.81 (s, 3H), 3.81-3.79 (m, 1H), 3.77 (s, 3H), 3.77-3.75 (m, 1H), 3.54 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.50-3.42 (m, 2H), 3.23 (dd, <i>J</i> 14.4, 8.3 Hz, 1H), 3.09 (dd, <i>J</i> 14.4, 6.8 Hz, 1H), 2.97 (s, 6H), 2.09 (s, 3H). LCMS (ES ⁺) 450 (M+H) ⁺ .

217	3-[(S)-4-(3-Chloro-4-methyl-benzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d_6 -DMSO at 110°C) 7.49 (s, 1H), 7.39 (d, <i>J</i> 8.3 Hz, 1H), 7.22 (d, <i>J</i> 7.8 Hz, 1H), 7.19 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.09 (s, 1H), 7.05 (s, 1H), 6.97 (dd, <i>J</i> 7.6, 1.0 Hz, 1H), 4.30-4.24 (m, 1H), 3.95-3.87 (m, 1H), 3.80 (d, <i>J</i> 11.6 Hz, 1H), 3.79-3.77 (m, 1H), 3.77 (s, 3H), 3.58 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.52-3.44 (m, 2H), 3.20 (dd, <i>J</i> 14.4, 7.8 Hz, 1H), 3.13 (dd, <i>J</i> 14.4, 7.3 Hz, 1H), 2.98 (s, 6H), 2.31 (s, 3H). LCMS (ES^+) 454 ($\text{M}+\text{H}$) ⁺ .
218	3-[(S)-4-(5-Chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d_6 -DMSO at 110°C) 7.59 (s, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.27 (d, <i>J</i> 2.0 Hz, 1H), 7.25 (d, <i>J</i> 2.3 Hz, 1H), 7.20 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.11 (s, 1H), 4.31-4.27 (m, 1H), 3.96-3.89 (m, 2H), 3.83 (d, <i>J</i> 11.6 Hz, 1H), 3.79-3.74 (m, 1H), 3.77 (s, 3H), 3.61 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.55-3.45 (m, 2H), 3.19 (dd, <i>J</i> 14.7, 7.6 Hz, 1H), 3.14 (dd, <i>J</i> 14.4, 7.6 Hz, 1H), 2.99 (s, 6H). LCMS (ES^+) 457 ($\text{M}+\text{H}$) ⁺ .
219	3-[(S)-4-(5-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d_6 -DMSO at 110°C) 8.23 (d, <i>J</i> 3.0 Hz, 1H), 7.95 (d, <i>J</i> 5.1 Hz, 1H), 7.46 (s, 1H), 7.39 (dd, <i>J</i> 8.3, 0.5 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.10 (s, 1H), 6.99 (s, 1H), 4.26 (s, 1H), 3.97-3.89 (m, 1H), 3.82-3.80 (m, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 3.61 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.55-3.47 (m, 2H), 3.22 (dd, <i>J</i> 14.4, 7.8 Hz, 1H), 3.13 (dd, <i>J</i> 14.4, 7.1 Hz, 1H), 2.98 (s, 6H). LCMS (ES^+) 437 ($\text{M}+\text{H}$) ⁺ .
220	3-[(S)-4-(5-Chloropyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d_6 -DMSO at 110°C) 8.49 (d, <i>J</i> 2.0 Hz, 1H), 8.22 (s, 1H), 7.46 (s, 1H), 7.40-7.38 (m, 2H), 7.19 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.10 (s, 1H), 4.30-4.20 (m, 1H), 3.98-3.90 (m, 1H), 3.84 (d, <i>J</i> 11.4 Hz, 1H), 3.80-3.78 (m, 1H), 3.78 (s, 3H), 3.67 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.62-3.49 (m, 2H), 3.22-3.13 (m, 2H), 2.98 (s, 6H). LCMS (ES^+) 441 ($\text{M}+\text{H}$) ⁺ .
221	3-[(S)-4-(4-Chloropyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d_6 -DMSO at 110°C) 8.48 (s, 1H), 7.73 (br s, 1H), 7.49 (s, 1H), 7.40 (d, <i>J</i> 8.6 Hz, 1H), 7.20 (d, <i>J</i> 8.3 Hz, 1H), 7.13 (br s, 2H), 4.75 (br s, 1H), 4.31 (br s, 1H), 3.94-3.87 (m, 1H), 3.81 (d, <i>J</i> 11.4 Hz, 1H), 3.78 (s, 3H), 3.65-3.46 (m, 3H), 3.32-3.26 (m, 1H), 3.12 (dd, <i>J</i> 14.4, 6.6 Hz, 1H), 2.99 (s, 6H). LCMS (ES^+) 441

		(M+H) ⁺ .
222	3-[(S)-4-(2-Chloro-6-methoxy-pyridine-4-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 7.51 (s, 1H), 7.40 (d, <i>J</i> 8.3, Hz, 1H), 7.20 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.11 (s, 1H), 6.60 (s, 1H), 6.37 (s, 1H), 4.17 (s, 1H), 3.95-3.91 (m, 1H), 3.85 (s, 3H), 3.83 (d, <i>J</i> 11.9 Hz, 1H), 3.78 (s, 3H), 3.80-3.78 (m, 2H), 3.62 (dd, <i>J</i> 11.6, 2.8 Hz, 1H), 3.54-3.44 (m, 1H), 3.18-3.16 (m, 2H), 2.98 (s, 6H). LCMS (ES ⁺) 471 (M+H) ⁺ .
223	3-[(S)-4-(3-Hydroxybenzoyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 7.48 (s, 1H), 7.37 (dd, <i>J</i> 8.3, 0.5 Hz, 1H), 7.17 (s, 1H), 7.14-7.10 (m, 3H), 6.80-6.77 (m, 1H), 6.68-6.67 (m, 1H), 6.61-6.59 (m, 1H), 4.32 (s, 1H), 3.94-3.86 (m, 1H), 3.77-3.72 (m, 2H), 3.49 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.49-3.40 (m, 3H), 3.31 (dd, <i>J</i> 14.1, 8.8 Hz, 1H), 3.03 (dd, <i>J</i> 14.1, 8.8 Hz, 1H), 2.99 (s, 6H). LCMS (ES ⁺) 408 (M+H) ⁺ .
224	3-[(S)-4-(5-Cyano-6-methoxy-pyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 8.09 (s, 1H), 7.68-7.60 (m, 1H), 7.46 (s, 1H), 7.39 (dd, <i>J</i> 8.3, 0.5 Hz, 1H), 7.19 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.09 (s, 1H), 4.21-4.19 (m, 1H), 4.01 (s, 3H), 3.98-3.91 (m, 1H), 3.86 (d, <i>J</i> 11.6 Hz, 1H), 3.82-3.78 (m, 1H), 3.78 (s, 3H), 3.70 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.57-3.47 (m, 2H), 3.21 (dd, <i>J</i> 14.4, 7.8 Hz, 1H), 3.11 (dd, <i>J</i> 14.4, 6.8 Hz, 1H), 2.98 (s, 6H). LCMS (ES ⁺) 462 (M+H) ⁺ .
225	3-[(S)-4-(4-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 8.40 (s, 1H), 7.95 (br s, 1H), 7.64 (br s, 1H), 7.39 (d, <i>J</i> 8.3 Hz, 1H), 7.19 (d, <i>J</i> 7.8 Hz, 1H), 7.08 (s, 1H), 7.04-7.03 (m, 1H), 4.24 (br s, 1H), 3.90-3.89 (m, 1H), 3.86 (s, 3H), 3.78-3.75 (m, 5H), 3.56-3.43 (m, 3H), 3.29-3.23 (m, 2H), 2.99 (s, 6H). LCMS (ES ⁺) 437 (M+H) ⁺ .
226	3-[(S)-4-(2,5-Dichloropyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 8.45 (br s, 1H), 8.32 (br s, 1H), 7.80 (br s, 1H), 7.42 (d, <i>J</i> 8.6 Hz, 1H), 7.21-7.20 (m, 1H), 7.09 (br s, 1H), 4.71 (br s, 1H), 4.33 (br s, 1H), 4.00 (br s, 1H), 3.84 (d, <i>J</i> 12.1 Hz, 1H), 3.79 (s, 3H), 3.64-3.52 (m, 3H), 3.16-3.18 (m, 2H), 2.98 (s, 6H). LCMS (ES ⁺) 475 (M+H) ⁺ .
227	3-[(S)-4-(4-Hydroxybenzoyl)-morpholin-3-ylmethyl]-1-methyl-	δ_H (d ₆ -DMSO at 110°C) 7.54 (s, 1H), 7.38 (d, <i>J</i> 8.3 Hz, 1H), 7.19 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.08-7.02 (m, 3H),

	1 <i>H</i> -indole-5-carboxylic acid dimethylamide	6.72-6.69 (m, 2H), 4.35-4.30 (m, 1H), 3.93-3.84 (m, 1H), 3.78-3.75 (m, 6H), 3.52 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.49-3.41 (m, 2H), 3.25 (dd, <i>J</i> 14.1, 8.3 Hz, 1H), 3.05 (dd, <i>J</i> 14.1, 6.6 Hz, 1H), 2.99 (s, 6H). LCMS (ES ⁺) 422 (M+H) ⁺ .
228	1-Methyl-3-[(<i>S</i>)-4-[4-(methylsulfanyl)benzoyl]morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.55 (s, 1H), 7.39 (d, <i>J</i> 8.6 Hz, 1H), 7.21-7.18 (m, 3H), 7.09-7.06 (m, 3H), 4.29-4.25 (m, 1H), 3.94-3.86 (m, 1H), 3.80-3.76 (m, 5H), 3.55 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.51-3.43 (m, 2H), 3.23 (dd, <i>J</i> 14.4, 8.1 Hz, 1H), 3.11 (dd, <i>J</i> 14.4, 6.8 Hz, 1H), 2.99 (s, 6H), 2.48 (s, 3H). LCMS (ES ⁺) 452 (M+H) ⁺ .
229	1-Methyl-3-[(<i>S</i>)-4-(2-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 8.41-8.40 (m, 1H), 7.49 (br s, 1H), 7.39 (d, <i>J</i> 8.6 Hz, 1H), 7.20 (dd, <i>J</i> 8.3, 1.0 Hz, 1H), 7.21 (br s, 2H), 7.12-7.08 (m, 1H), 4.25 (br s, 1H), 3.93-3.90 (m, 1H), 3.80-3.76 (m, 5H), 3.54 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.51-3.43 (m, 2H), 3.26 (dd, <i>J</i> 14.4, 8.6 Hz, 1H), 3.09 (dd, <i>J</i> 14.1, 6.8 Hz, 1H), 2.98 (s, 6H), 2.28 (s, 3H). LCMS (ES ⁺) 421 (M+H) ⁺ .
230	3-[(<i>S</i>)-4-(2-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 8.12 (s, 1H), 7.40 (br s, 1H), 7.39 (d, <i>J</i> 8.6 Hz, 1H), 7.19 (d, <i>J</i> 8.1 Hz, 1H), 7.08 (br s, 1H), 6.85 (br s, 2H), 4.25 (br s, 1H), 3.89-3.86 (m, 5H), 3.79-3.76 (m, 4H), 3.52 (dd, <i>J</i> 11.4, 2.5 Hz, 1H), 3.49-3.40 (m, 2H), 3.26-3.21 (m, 1H), 3.06-3.01 (m, 1H), 2.98 (s, 6H). LCMS (ES ⁺) 437 (M+H) ⁺ .
231	3-[(<i>S</i>)-4-[5-Chloro-6-(methylsulfanyl)pyridine-3-carbonyl]-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 8.13 (s, 1H), 7.54 (s, 1H), 7.39 (d, <i>J</i> 8.6 Hz, 1H), 7.27 (s, 1H), 7.19 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.09 (s, 1H), 4.24 (s, 1H), 3.97-3.90 (m, 1H), 3.85 (d, <i>J</i> 11.6 Hz, 1H), 3.83-3.79 (m, 1H), 3.77 (s, 3H), 3.66 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.60-3.48 (m, 2H), 3.21 (dd, <i>J</i> 14.4, 7.6 Hz, 1H), 3.14 (dd, <i>J</i> 14.4, 7.1 Hz, 1H), 2.98 (s, 6H), 2.53 (s, 3H). LCMS (ES ⁺) 487 (M+H) ⁺ .
232	3-[(<i>S</i>)-4-(2-Chloropyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 8.36 (br s, 1H), 7.76 (br s, 1H), 7.41 (d, <i>J</i> 8.3 Hz, 1H), 7.21-7.19 (m, 2H), 7.14 (br s, 2H), 4.73 (br s, 1H), 4.32 (br s, 1H), 3.95 (br s, 1H), 3.82-3.78 (m, 4H), 3.65-3.49 (m, 3H), 3.27 (br s, 1H), 3.14-3.09 (m, 1H), 2.99 (s, 6H).

		LCMS (ES ⁺) 441 (M+H) ⁺ .
233	3-[(S)-4-(5-Bromo-6-chloropyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 8.07 (s, 1H), 7.66 (s, 1H), 7.53 (s, 1H), 7.40 (d, <i>J</i> 8.3 Hz, 1H), 7.20 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.10 (s, 1H), 4.20 (s, 1H), 3.98-3.90 (m, 1H), 3.86 (d, <i>J</i> 11.6 Hz, 1H), 3.84-3.78 (m, 1H), 3.78 (s, 3H), 3.68 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.61-3.49 (m, 2H), 3.23 (dd, <i>J</i> 14.1, 6.6 Hz, 1H), 3.14 (dd, <i>J</i> 14.1, 6.6 Hz, 1H), 2.98 (s, 6H). LCMS (ES ⁺) 521 (M+H) ⁺ .
234	3-[(S)-4-(5-Hydroxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 8.11 (d, <i>J</i> 2.5 Hz, 1H), 7.81 (s, 1H), 7.50 (s, 1H), 7.38 (d, <i>J</i> 8.3 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.09 (s, 1H), 6.90 (s, 1H), 4.29 (s, 1H), 3.96-3.88 (m, 1H), 3.80 (d, <i>J</i> 11.6 Hz, 1H), 3.76 (s, 3H), 3.76-3.73 (m, 2H), 3.57 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.53-3.45 (m, 2H), 3.24 (dd, <i>J</i> 14.4, 8.1 Hz, 1H), 3.09 (dd, <i>J</i> 14.4, 7.1 Hz, 1H), 2.99 (s, 6H). LCMS (ES ⁺) 424 (M+H) ⁺ .
235	3-[(S)-4-(5-Cyanopyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 8.81 (s, 1H), 8.45 (s, 1H), 7.74 (s, 1H), 7.40 (s, 1H), 7.39 (d, <i>J</i> 8.6 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.10 (s, 1H), 4.17-4.13 (m, 1H), 3.99-3.90 (m, 1H), 3.85 (d, <i>J</i> 11.4 Hz, 1H), 3.83-3.78 (m, 2H), 3.78 (s, 3H), 3.71 (dd, <i>J</i> 11.6, 2.8 Hz, 1H), 3.58-3.48 (m, 2H), 3.24-3.09 (m, 2H), 2.98 (s, 6H). LCMS (ES ⁺) 432 (M+H) ⁺ .
236	3-[(S)-4-(6-Methoxy-5-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 7.81 (d, <i>J</i> 1.8 Hz, 1H), 7.49 (s, 1H), 7.39 (d, <i>J</i> 8.3 Hz, 1H), 7.19 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.10 (s, 1H), 7.09 (s, 1H), 4.28-4.23 (m, 1H), 3.97-3.90 (m, 1H), 3.90 (s, 3H), 3.83-3.80 (m, 2H), 3.77 (s, 3H), 3.61 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.54-3.45 (m, 2H), 3.19 (dd, <i>J</i> 14.4, 7.3 Hz, 1H), 3.13 (dd, <i>J</i> 13.6, 6.6 Hz, 1H), 2.96 (s, 6H), 2.04 (s, 3H). LCMS (ES ⁺) 451 (M+H) ⁺ .
237	3-[(S)-4-(6-Methoxy-5-nitropyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 8.16 (d, <i>J</i> 1.8 Hz, 1H), 7.48 (s, 1H), 7.49 (s, 1H), 7.34 (d, <i>J</i> 8.3 Hz, 1H), 7.16 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.11 (s, 1H), 4.25-4.23 (m, 1H), 4.04 (s, 3H), 4.00-3.92 (m, 1H), 3.87 (d, <i>J</i> 11.6 Hz, 1H), 3.83-3.81 (m, 1H), 3.77 (s, 3H), 3.72 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.59-3.50 (m, 2H), 3.23 (dd, <i>J</i> 14.4, 8.1 Hz, 1H), 3.12 (dd, <i>J</i> 14.4, 6.6 Hz, 1H),

		2.96 (s, 6H). LCMS (ES ⁺) 482 (M+H) ⁺ .
238	3-[(S)-4-(5,6-Dimethoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.55 (d, <i>J</i> 1.8 Hz, 1H), 7.53 (s, 1H), 7.39 (dd, <i>J</i> 8.3, 0.5 Hz, 1H), 7.19 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.11 (s, 1H), 6.93 (d, <i>J</i> 1.8 Hz, 1H), 4.37-4.32 (m, 1H), 3.96-3.88 (m, 1H), 3.90 (s, 3H), 3.82 (d, <i>J</i> 11.6 Hz, 1H), 3.81-3.78 (m, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.61 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.56-3.46 (m, 2H), 3.23 (dd, <i>J</i> 14.4, 8.1 Hz, 1H), 3.13 (dd, <i>J</i> 14.4, 7.1 Hz, 1H), 2.97 (s, 6H). LCMS (ES ⁺) 467 (M+H) ⁺ .
239	3-[(S)-4-(2,6-Dimethoxypyrimidine-4-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.47 (br s, 1H), 7.36 (d, <i>J</i> 8.3 Hz, 1H), 7.19 (d, <i>J</i> 8.3 Hz, 1H), 7.08 (br s, 1H), 6.08 (br s, 1H), 4.39 (br s, 1H), 3.94-3.89 (m, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.89-3.84 (m, 1H), 3.83 (d, <i>J</i> 11.6 Hz, 1H), 3.76 (s, 3H), 3.60-3.57 (m, 1H), 3.54-3.42 (m, 2H), 3.16 (m, 2H), 2.99 (s, 6H). LCMS (ES ⁺) 468 (M+H) ⁺ .
240	1-Methyl-3-[(S)-4-(5-methyl-1 <i>H</i> -pyrazole-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.66 (s, 1H), 7.37 (d, <i>J</i> 8.6 Hz, 1H), 7.21 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.12 (s, 1H), 6.15 (s, 1H), 4.76-4.74 (m, 1H), 4.38-4.32 (m, 1H), 3.97-3.90 (m, 1H), 3.77-3.74 (m, 2H), 3.75 (s, 3H), 3.50-3.39 (m, 3H), 3.33 (dd, <i>J</i> 14.1, 9.6 Hz, 1H), 3.01 (s, 6H), 3.01-2.96 (m, 1H), 2.23 (s, 3H). LCMS (ES ⁺) 410 (M+H) ⁺ .
241	3-[(S)-4-(1 <i>H</i> -Imidazole-4-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.76 (d, <i>J</i> 1.0 Hz, 1H), 7.61 (d, <i>J</i> 1.0 Hz, 1H), 7.45 (d, <i>J</i> 1.0 Hz, 1H), 7.37 (dd, <i>J</i> 8.3, 0.5 Hz, 1H), 7.20 (dd, <i>J</i> 8.6, 1.8 Hz, 1H), 7.13 (s, 1H), 5.07 (s, 1H), 4.62-4.56 (m, 1H), 3.98-3.90 (m, 1H), 3.75-3.72 (m, 2H), 3.75 (s, 3H), 3.51-3.40 (m, 3H), 3.35 (dd, <i>J</i> 13.9, 9.9 Hz, 1H), 3.01 (s, 6H), 3.01-2.97 (m, 1H). LCMS (ES ⁺) 468 (M+H) ⁺ .
242	1-Methyl-3-[(S)-4-(1-methyl-1 <i>H</i> -imidazole-4-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.52 (s, 1H), 7.48 (s, 1H), 7.35 (d, <i>J</i> 8.3 Hz, 1H), 7.18 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.11 (s, 1H), 7.00 (d, <i>J</i> 0.5 Hz, 1H), 4.57-4.53 (m, 1H), 3.98-3.88 (m, 2H), 3.81 (d, <i>J</i> 11.6 Hz, 1H), 3.72 (s, 3H), 3.57 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.54-3.42 (m, 2H), 3.20 (dd, <i>J</i> 14.4, 8.1 Hz, 1H), 3.39 (s, 3H), 3.09 (dd, <i>J</i> 14.4, 7.3 Hz, 1H), 2.97 (s, 6H).

		LCMS (ES ⁺) 410 (M+H) ⁺ .
243	3-[(S)-4-(3-Hydroxybenzoyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid <i>N</i> -(2-hydroxyethyl)- <i>N</i> -methanamide	δ_H (d ₆ -DMSO at 110°C) 9.07 (s, 1H), 7.50 (s, 1H), 7.36 (d, <i>J</i> 8.3 Hz, 1H), 7.20-7.00 (m, 3H), 6.78-6.75 (m, 1H), 6.62-6.57 (m, 2H), 4.37-4.20 (m, 2H), 3.88 (d, <i>J</i> 7.3 Hz, 1H), 3.78-3.68 (m, 4H), 3.62-3.56 (m, 2H), 3.51-3.37 (m, 5H), 3.25 (dd, <i>J</i> 14.4, 8.8 Hz, 1H), 3.06-2.95 (m, 4H), 1.07 (d, <i>J</i> 5.8 Hz, 1H). LCMS (ES ⁺) 452 (M+H) ⁺ .
244	1-{3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carbonyl}-azetidine-3-carbonitrile	δ_H (d ₆ -DMSO at 110°C) 7.96 (d, <i>J</i> 2.0 Hz, 1H), 7.78 (s, 1H), 7.49-7.40 (m, 2H), 7.36 (dd, <i>J</i> 8.6, 2.3 Hz, 1H), 7.14 (s, 1H), 6.64 (d, <i>J</i> 8.6 Hz, 1H), 4.49 (td, <i>J</i> 9.1, 2.3 Hz, 2H), 4.39-4.29 (m, 3H), 3.94 (d, <i>J</i> 7.8 Hz, 1H), 3.90-3.74 (m, 7H), 3.63 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.54-3.49 (m, 2H), 3.20-3.13 (m, 2H), 2.97 (2H, s). LCMS (ES ⁺) 474 (M+H) ⁺ .
245	1-{3-[(S)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carbonyl}azetidine-3-carbonitrile	δ_H (d ₆ -DMSO at 110°C) 7.87 (d, <i>J</i> 1.8 Hz, 1H), 7.77 (s, 1H), 7.48-7.39 (m, 2H), 7.34 (s, 1H), 7.14 (s, 1H), 4.49 (td, <i>J</i> 9.1, 2.5 Hz, 2H), 4.39-4.30 (m, 3H), 3.98-3.92 (m, 4H), 3.90-3.75 (m, 6H), 3.69 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.53 (d, <i>J</i> 8.8 Hz, 2H), 3.25-3.12 (m, 2H). LCMS (ES ⁺) 508 (M+H) ⁺ .
246	1-{3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carbonyl}-azetidine-3-carboxylic acid amide	δ_H (d ₆ -DMSO at 110°C) 7.97 (d, <i>J</i> 2.3 Hz, 1H), 7.77 (s, 1H), 7.46-7.44 (m, 1H), 7.38-7.34 (m, 2H), 7.11 (s, 1H), 6.81 (s, 1H), 6.65 (d, <i>J</i> 8.3 Hz, 1H), 4.36-4.18 (m, 4H), 3.94 (d, <i>J</i> 7.8 Hz, 1H), 3.89 (s, 3H), 3.84-3.77 (m, 5H), 3.62 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.54-3.49 (m, 2H), 3.42-3.36 (m, 1H), 3.25-3.12 (m, 2H), 1.31 (s, 2H). LCMS (ES ⁺) 492 (M+H) ⁺ .
247	1-{3-[(S)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carbonyl}azetidine-3-carboxylic acid amide	δ_H (d ₆ -DMSO at 110°C) 7.87 (d, <i>J</i> 2.0 Hz, 1H), 7.76 (s, 1H), 7.45-7.43 (m, 1H), 7.40-7.38 (m, 1H), 7.33 (d, <i>J</i> 0.5 Hz, 1H), 7.11 (s, 1H), 6.81 (s, 1H), 4.34-4.18 (m, 6H), 3.96-3.93 (m, 4H), 3.87-3.81 (m, 1H), 3.78 (s, 5H), 3.68 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.53 (d, <i>J</i> 9.1 Hz, 2H), 3.25-3.11 (m, 2H). LCMS (ES ⁺) 526 (M+H) ⁺ .
248	1-{3-[(S)-4-(4-Chloro-3-hydroxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carbonyl}-	δ_H (d ₆ -DMSO at 110°C) 9.75 (br s, 1H), 7.83 (s, 1H), 7.50-7.39 (m, 2H), 7.23 (d, <i>J</i> 8.1 Hz, 1H), 7.13 (s, 1H), 6.81 (d, <i>J</i> 1.8 Hz, 1H), 6.56 (dd, <i>J</i> 8.1, 1.3 Hz, 1H), 4.52-4.46 (m, 2H),

	azetidine-3-carbonitrile	4.40-4.30 (m, 3H), 3.95-3.90 (m, 1H), 3.86-3.70 (m, 6H), 3.55 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.50-3.44 (m, 2H), 3.26 (dd, <i>J</i> 14.4, 8.6 Hz, 1H), 3.10 (dd, <i>J</i> 14.1, 6.8 Hz, 1H). LCMS (ES ⁺) 493 (M+H) ⁺ .
249	{(S)-3-[5-(Azetidine-1-carbonyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]-morpholin-4-yl}-(4-chloro-3-hydroxyphenyl)-methanone	δ _H (d ₆ -DMSO at 110°C) 7.79 (s, 1H), 7.45-7.43 (m, 1H), 7.39-7.37 (m, 1H), 7.22 (d, <i>J</i> 8.1 Hz, 1H), 7.10 (s, 1H), 6.82 (d, <i>J</i> 1.8 Hz, 1H), 6.55 (dd, <i>J</i> 7.8, 1.5 Hz, 1H), 4.35-4.27 (m, 1H), 4.22-4.15 (m, 3H), 3.91 (d, <i>J</i> 7.8 Hz, 1H), 3.81-3.68 (m, 5H), 3.53 (dd, <i>J</i> 11.4, 3.0 Hz, 2H), 3.49-3.43 (m, 2H), 3.26 (dd, <i>J</i> 14.4, 8.3 Hz, 1H), 3.12-2.79 (m, 1H), 2.29 (m, 3H). LCMS (ES ⁺) 468 (M+H) ⁺ .
250	3-[(S)-4-(5-Chloropyrazine-2-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ _H (d ₆ -DMSO at 110°C) 8.56 (s, 1H), 7.53 (s, 1H), 7.36-7.34 (m, 1H), 7.19 (d, <i>J</i> 8.6 Hz, 1H), 7.08 (s, 1H), 4.55-4.40 (m, 1H), 4.07-3.94 (m, 2H), 3.88 (d, <i>J</i> 11.4 Hz, 2H), 3.76 (s, 3H), 3.64-3.62 (m, 1H), 3.54-3.51 (m, 2H), 3.27-3.09 (m, 2H), 3.00 (m, 6H). LCMS (ES ⁺) 442 (M+H) ⁺ .

EXAMPLES 251 TO 261

The following compounds were prepared from the relevant carboxylic acid and the appropriate amine according to *Method F*, heating the reaction mixture to 40°C.

Example No.	Compound Name	¹ H NMR/LCMS
251	4-{3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carbonyl}-piperazine-1-carboxylic acid ethyl ester	δ _H (d ₆ -DMSO at 110°C) 7.94 (d, <i>J</i> 2.1 Hz, 1H), 7.54 (s, 1H), 7.41 (d, <i>J</i> 8.4 Hz, 1H), 7.34 (dd, <i>J</i> 8.4, 2.1 Hz, 1H), 7.21 (dd, <i>J</i> 8.4, 1.4 Hz, 1H), 7.11 (s, 1H), 6.65-6.60 (m, 1H), 4.30-4.25 (m, 1H), 4.11 (q, <i>J</i> 7.1 Hz, 2H), 3.94-3.92 (m, 1H), 3.88 (s, 3H), 3.84-3.77 (m, 4H), 3.61 (dd, <i>J</i> 11.5, 3.1 Hz, 1H), 3.56-3.44 (m, 8H), 3.18-3.15 (m, 2H), 2.11 (s, 3H), 1.23 (t, <i>J</i> 6.6 Hz, 3H). LCMS (ES ⁺) 550 (M+H) ⁺ .
252	4-{3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carbonyl}-	δ _H (d ₆ -DMSO at 110°C) 7.96 (s, 1H), 7.63 (br s, 1H), 7.57 (s, 1H), 7.42 (d, <i>J</i> 8.4 Hz, 1H), 7.39 (d, <i>J</i> 8.6 Hz, 1H), 7.23 (d, <i>J</i> 8.4 Hz, 1H), 7.13 (s, 1H), 6.66 (d, <i>J</i> 8.5 Hz, 1H), 4.30-4.21 (m, 1H), 4.07 (s, 2H), 3.93 (d, <i>J</i> 7.9 Hz,

	piperazin-2-one	1H), 3.88 (s, 3H), 3.82 (d, <i>J</i> 11.6 Hz, 1H), 3.78 (s, 3H), 3.67-3.58 (m, 4H), 3.55-3.46 (m, 2H), 3.30-3.27 (m, 2H), 3.23-3.11 (m, 2H). LCMS (ES ⁺) 492 (M+H) ⁺ .
253	[2-(<i>N</i> -{3-[(<i>S</i>)-4-(6-Methoxy-pyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carbonyl}- <i>N</i> -methylamino)ethyl]-carbamic acid <i>tert</i> -butyl ester	δ_{H} (d ₆ -DMSO at 110°C) 7.97 (d, <i>J</i> 2.2 Hz, 1H), 7.51 (s, 1H), 7.39-7.36 (m, 2H), 7.18 (dd, <i>J</i> 8.4, 1.5 Hz, 1H), 7.09 (s, 1H), 6.66 (d, <i>J</i> 8.5 Hz, 1H), 6.32 (s, 1H), 4.32-4.30 (m, 1H), 3.92-3.90 (m, 1H), 3.88 (s, 3H), 3.82 (d, <i>J</i> 11.6 Hz, 1H), 3.76 (s, 3H), 3.60 (dd, <i>J</i> 11.5, 3.1 Hz, 1H), 3.52-3.44 (m, 4H), 3.21-3.14 (m, 4H), 2.97 (s, 3H), 2.96 (s, 9H), 1.80 (s, 1H). LCMS (ES ⁺) 566 (M+H) ⁺ .
254	3-[(<i>S</i>)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid (2-hydroxyethyl)amide	δ_{H} (d ₆ -DMSO at 110°C) 7.99 (s, 1H), 7.90 (s, 1H), 7.74-7.69 (m, 1H), 7.67 (dd, <i>J</i> 8.6, 1.0 Hz, 1H), 7.37 (d, <i>J</i> 8.6 Hz, 1H), 7.28 (d, <i>J</i> 8.3 Hz, 1H), 7.09 (s, 1H), 6.60 (d, <i>J</i> 8.6 Hz, 1H), 4.39-4.32 (m, 1H), 3.94 (d, <i>J</i> 7.3 Hz, 1H), 3.89-3.79 (m, 5H), 3.76 (s, 3H), 3.66 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.64-3.59 (m, 2H), 3.54-3.49 (m, 2H), 3.45-3.39 (m, 2H), 3.24 (m, 1H), 3.16 (m, 1H). LCMS (ES ⁺) 453 (M+H) ⁺ .
255	{3-[(<i>S</i>)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}-(morpholin-4-yl)-methanone	δ_{H} (d ₆ -DMSO at 110°C) 7.94 (s, 1H), 7.54 (s, 1H), 7.41 (d, <i>J</i> 8.3 Hz, 1H), 7.37 (d, <i>J</i> 8.3 Hz, 1H), 7.20 (d, <i>J</i> 8.3 Hz, 1H), 7.11 (s, 1H), 6.65 (d, <i>J</i> 8.3 Hz, 1H), 4.27 (s, 1H), 3.96-3.92 (m, 1H), 3.88 (s, 3H), 3.85-3.75 (m, 5H), 3.66-3.58 (m, 5H), 3.56-3.47 (m, 6H), 3.19 (m, 2H). LCMS (ES ⁺) 479 (M+H) ⁺ .
256	(<i>R</i>)-3-({1-Methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carbonyl}amino)pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester	δ_{H} (d ₆ -DMSO at 110°C) 8.14 (s, 1H), 7.97 (s, 1H), 7.88 (s, 1H), 7.68 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.20-7.19 (m, 1H), 7.10 (s, 1H), 7.03 (d, <i>J</i> 8.1 Hz, 1H), 4.52-4.44 (m, 1H), 4.32-4.28 (m, 1H), 3.97-3.90 (m, 1H), 3.85 (d, <i>J</i> 11.4 Hz, 1H), 3.83-3.76 (m, 1H), 3.76 (s, 3H), 3.67-3.61 (m, 2H), 3.55-3.47 (m, 3H), 3.37-3.31 (m, 1H), 3.29-3.20 (m, 2H), 3.16 (dd, <i>J</i> 14.4, 7.1 Hz, 1H), 2.42 (s, 3H), 2.21-2.13 (m, 1H), 2.02-1.93 (m, 1H), 1.44 (s, 9H). LCMS (ES ⁺) 562 (M+H) ⁺ .
257	(<i>S</i>)-3-({1-Methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)-	δ_{H} (d ₆ -DMSO at 110°C) 8.14 (s, 1H), 7.96 (s, 1H), 7.86 (s, 1H), 7.68 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.20-7.19 (m, 1H), 7.09 (s, 1H),

	morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carbonyl}amino)pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester	7.04 (d, <i>J</i> 7.6 Hz, 1H), 4.52-4.44 (m, 1H), 4.30 (s, 1H), 3.97-3.89 (m, 1H), 3.85 (d, <i>J</i> 11.6 Hz, 1H), 3.83-3.76 (m, 1H), 3.76 (s, 3H), 3.67-3.61 (m, 2H), 3.55-3.47 (m, 3H), 3.37-3.31 (m, 1H), 3.28-3.20 (m, 2H), 3.16 (dd, <i>J</i> 14.4, 7.3 Hz, 1H), 2.42 (s, 3H), 2.22-2.13 (m, 1H), 2.02-1.94 (m, 1H), 1.44 (s, 9H). LCMS (ES ⁺) 562 (M+H) ⁺ .
258	{(S)-3-[5-(3-Aminoazetidine-1-carbonyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholin-4-yl}-(6-methylpyridin-3-yl)-methanone	δ _H (d ₆ -DMSO at 110°C) 8.20 (s, 1H), 7.72 (s, 1H), 7.45 (dd, <i>J</i> 8.6, 1.3 Hz, 1H), 7.39 (d, <i>J</i> 8.6 Hz, 1H), 7.31-7.29 (m, 1H), 7.10-7.09 (m, 2H), 4.33-4.27 (m, 2H), 3.97-3.89 (m, 1H), 3.83-3.76 (m, 3H), 3.76 (s, 3H), 3.61 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.55-3.46 (m, 2H), 3.23-3.12 (m, 5H), 2.45 (s, 3H). LCMS (ES ⁺) 448 (M+H) ⁺ .
259	[(S)-3-{5-[3-(Aminomethyl)-azetidine-1-carbonyl]-1-methyl-1 <i>H</i> -indol-3-ylmethyl}morpholin-4-yl]-(6-methylpyridin-3-yl)-methanone	δ _H (d ₆ -DMSO at 110°C) 8.21 (s, 1H), 7.75 (s, 1H), 7.46 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.39 (d, <i>J</i> 8.6 Hz, 1H), 7.32-7.30 (m, 1H), 7.11-7.09 (m, 2H), 4.33-4.28 (m, 1H), 4.23-4.17 (m, 2H), 3.93-3.87 (m, 3H), 3.78-3.76 (m, 2H), 3.76 (s, 3H), 3.61 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.55-3.46 (m, 2H), 3.22 (dd, <i>J</i> 14.4, 7.8 Hz, 1H), 3.14 (dd, <i>J</i> 14.4, 7.3 Hz, 1H), 2.83-2.82 (m, 2H), 2.68-2.60 (m, 1H), 2.45 (s, 3H). LCMS (ES ⁺) 462 (M+H) ⁺ .
260	[(S)-3-{5-[3-(Hydroxymethyl)-azetidine-1-carbonyl]-1-methyl-1 <i>H</i> -indol-3-ylmethyl}morpholin-4-yl]-(6-methylpyridin-3-yl)-methanone	δ _H (d ₆ -DMSO at 110°C) 8.21 (s, 1H), 7.74 (s, 1H), 7.45 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.39 (d, <i>J</i> 8.6 Hz, 1H), 7.32-7.30 (m, 1H), 7.11-7.09 (m, 2H), 4.30-4.26 (m, 1H), 4.27-4.17 (m, 2H), 3.94-3.90 (m, 3H), 3.82 (d, <i>J</i> 11.6 Hz, 1H), 3.81-3.76 (m, 1H), 3.76 (s, 3H), 3.62-3.59 (m, 3H), 3.55-3.46 (m, 2H), 3.24-3.11 (m, 2H), 2.79-2.69 (m, 1H), 2.45 (s, 3H). LCMS (ES ⁺) 463 (M+H) ⁺ .
261	1-Methyl-3-[(S)-4-[6-(2,2,2-trifluoroethoxy)pyridine-3-carbonyl]morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ _H (d ₆ -DMSO at 110°C) 7.95 (d, <i>J</i> 1.8 Hz, 1H), 7.51 (s, 1H), 7.48-7.43 (m, 1H), 7.41-7.36 (m, 1H), 7.19 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.10 (s, 1H), 6.80 (d, <i>J</i> 8.3 Hz, 1H), 4.94 (q, <i>J</i> 9.1 Hz, 2H), 4.28-4.21 (m, 1H), 3.94 (d, <i>J</i> 7.3 Hz, 1H), 3.85-3.74 (m, 5H), 3.62 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.54-3.47 (m, 2H), 3.20-3.13 (m, 2H), 2.98 (s, 6H). LCMS (ES ⁺) 505 (M+H) ⁺ .

EXAMPLE 262 (METHOD G)

3-[(S)-4-(2-Chloro-6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

- 5 To a stirred solution of *Intermediate 3* (684 mg, 2.3 mmol) and DIPEA (494 μ L, 3.0 mmol) in THF (25 mL) was added 2-chloro-6-methylnicotinoyl chloride (2.53 mmol). The reaction mixture was stirred at r.t. for 3 h. The reaction was partitioned between water (25 mL) and DCM (25 mL). The organic layer was washed with brine, separated, dried (magnesium sulphate) and concentrated *in vacuo*. The crude mixture was
- 10 chromatographed (SiO₂, DCM $\rightarrow$ 10% MeOH/DCM), yielding the *title compound*. δ_{H} (d₆-DMSO) 7.85-7.77 (m, 0.7H), 7.49-6.98 (m, 4.3H), 6.52 (d, *J* 7.8 Hz, 0.5H), 6.14 (d, *J* 7.8 Hz, 0.5H), 4.69-4.63 (m, 0.5H), 4.35-4.25 (m, 0.6H), 4.05-3.96 (m, 0.6H), 3.88-3.68 (m, 4.8H), 3.62-3.18 (m, 4.9H), 3.08-2.86 (m, 7.3H), 2.50-2.45 (m, 0.9H), 2.35-2.26 (m, 1.4H). LCMS (ES⁺) 455 (M+H)⁺.

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EXAMPLE 263

3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid methyl ester

- 20 Prepared from the relevant acyl chloride and the appropriate amine according to *Method G*. δ_{H} (d₆-DMSO) 7.91 (d, *J* 8.3 Hz, 1H), 7.87-7.75 (m, 1H), 7.34-7.25 (m, 3H), 7.01-6.89 (m, 1H), 6.50-6.33 (m, 1H), 4.19-4.10 (m, 1H), 4.10-4.02 (m, 1H), 3.97-3.86 (m, 6H), 3.80 (m, 3H), 3.76-3.69 (m, 1H), 3.66-3.55 (m, 1H), 3.54-3.44 (m, 1H), 3.43-3.31 (m, 1H), 3.23-3.02 (m, 1H), 2.09-2.05 (m, 1H), 1.33-1.22 (m, 1H). LCMS (ES⁺) 424
- 25 (M+H)⁺.

EXAMPLES 264 TO 270 (METHOD H)

- 30 To a stirred solution of *Intermediate 14* (300 mg, 0.76 mmol) in DMF (5 mL) were added the relevant substituted 2-iodoaniline (0.76 mmol), Pd(OAc)₂ (9 mg, 0.038 mmol), LiCl (32 mg, 0.76 mmol) and sodium carbonate (160 mg, 1.52 mmol). The reaction mixture was heated at 100°C for 2 h and then partitioned between brine (10 mL) and ethyl acetate (10 mL). The organic layer was separated, dried (magnesium sulphate),

concentrated *in vacuo* and chromatographed (SiO₂, 25% EtOAc/hexanes). To the resulting solid was added HCl (4M in 1,4-dioxane, 10 mL) and the reaction mixture was stirred at r.t. for 1 h. The reaction mixture was concentrated *in vacuo* and the residue partitioned between saturated sodium hydrogencarbonate solution (10 mL) and ethyl acetate (10 mL). The organic layer was washed with brine (10 mL), dried (magnesium sulphate) and concentrated *in vacuo*. The residue was chromatographed (SiO₂, 50% EtOAc/hexanes), yielding the *title compound*.

Example No.	Compound Name	¹ H NMR/LCMS
264	5-Chloro-3-[(<i>S</i>)-4-(6-chloropyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-7-carboxylic acid methyl ester	δ _H (d ₆ -DMSO at 110°C) 10.73 (s, 1H), 7.95 (s, 1H), 7.57-7.55 (m, 2H), 7.25 (s, 1H), 7.18-7.12 (m, 2H), 4.21-4.05 (m, 1H), 3.88 (s, 3H), 3.84 (d, <i>J</i> 7.2 Hz, 1H), 3.74-3.67 (m, 2H), 3.58 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.47-3.36 (m, 2H), 3.14 (dd, <i>J</i> 14.5, 8.3 Hz, 1H), 3.01 (dd, <i>J</i> 14.5, 6.6 Hz, 1H). LCMS (ES ⁺) 448 (M+H) ⁺ .
265	(6-Chloropyridin-3-yl)-[(<i>S</i>)-3-(5-fluoro-1 <i>H</i> -indol-3-ylmethyl)-morpholin-4-yl]-methanone	δ _H (d ₆ -DMSO at 110°C) 10.66 (s, 1H), 8.09 (s, 1H), 7.35-7.25 (m, 3H), 7.14 (s, 1H), 7.03-6.98 (m, 1H), 6.86 (dt, <i>J</i> 9.2, 2.5 Hz, 1H), 4.23-4.18 (m, 1H), 3.94 (d, <i>J</i> 7.2 Hz, 1H), 3.82-3.78 (m, 2H), 3.65 (dd, <i>J</i> 11.5, 3.1 Hz, 1H), 3.55-3.45 (m, 2H), 3.19-3.05 (m, 2H). LCMS (ES ⁺) 374 (M+H) ⁺ .
266	(6-Chloropyridin-3-yl)-[(<i>S</i>)-3-(5-trifluoromethyl-1 <i>H</i> -indol-3-ylmethyl)morpholin-4-yl]-methanone	δ _H (d ₆ -DMSO at 110°C) 11.05 (s, 1H), 8.05 (s, 1H), 7.73 (s, 1H), 7.53 (d, <i>J</i> 8.5 Hz, 1H), 7.35-7.19 (m, 4H), 4.29-4.20 (m, 1H), 3.95 (d, <i>J</i> 7.9 Hz, 1H), 3.85-3.80 (m, 2H), 3.68 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.57-3.47 (m, 2H), 3.29-3.14 (m, 2H). LCMS (ES ⁺) 424 (M+H) ⁺ .
267	3-[(<i>S</i>)-4-(6-Chloropyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carbonitrile	δ _H (d ₆ -DMSO at 110°C) 11.28-11.10 (m, 1H), 8.01 (s, 1H), 7.85 (s, 1H), 7.53-7.49 (m, 1H), 7.36 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.34-7.27 (m, 2H), 7.26-7.20 (m, 1H), 4.31-4.21 (m, 1H), 3.98-3.92 (m, 1H), 3.84 (m, 1H), 3.81-3.74 (m, 1H), 3.69 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.56-3.49 (m, 2H), 3.27 (dd, <i>J</i> 14.7, 8.6 Hz, 1H), 3.16-3.08 (m, 1H). LCMS (ES ⁺) 381 (M+H) ⁺ .
268	(6-Chloropyridin-3-yl)-[(<i>S</i>)-3-(1 <i>H</i> -indol-3-ylmethyl)morpholin-4-yl]-	δ _H (d ₆ -DMSO at 110°C) 10.61-10.51 (m, 1H), 8.13 (d, <i>J</i> 1.8 Hz, 1H), 7.40-7.33 (m, 2H), 7.30-7.24 (m, 2H),

	methanone	7.09-7.03 (m, 3H), 6.89 (t, <i>J</i> 7.6 Hz, 1H), 4.25-4.17 (m, 1H), 3.97-3.91 (m, 1H), 3.84-3.78 (m, 2H), 3.63 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.53-3.48 (m, 2H), 3.16 (d, <i>J</i> 7.3 Hz, 2H). LCMS (ES ⁺) 356 (M+H) ⁺ .
269	(6-Chloropyridin-3-yl)-[(<i>S</i>)-3-(5-nitro-1 <i>H</i> -indol-3-ylmethyl)-morpholin-4-yl]-methanone	δ_{H} (d ₆ -DMSO at 110°C) 11.40-11.30 (m, 1H), 8.38-8.30 (m, 1H), 8.02-7.92 (m, 2H), 7.51 (d, <i>J</i> 9.1 Hz, 1H), 7.36 (s, 2H), 7.26-7.18 (m, 1H), 4.37-4.24 (m, 1H), 3.98-3.93 (m, 1H), 3.90-3.85 (m, 1H), 3.84-3.77 (m, 1H), 3.72 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.55-3.50 (m, 2H), 3.32 (dd, <i>J</i> 14.4, 8.6 Hz, 1H), 3.13-3.20 (m, 1H). LCMS (ES ⁺) 401 (M+H) ⁺ .
270	(6-Chloropyridin-3-yl)-[(<i>S</i>)-3-(5-trifluoromethoxy-1 <i>H</i> -indol-3-ylmethyl)morpholin-4-yl]-methanone	δ_{H} (d ₆ -DMSO at 110°C) 10.87 (s, 1H), 8.08 (s, 1H), 7.42 (d, <i>J</i> 8.8 Hz, 1H), 7.39-7.33 (m, 1H), 7.31-7.20 (m, 3H), 7.00 (d, <i>J</i> 8.6 Hz, 1H), 4.24-4.16 (m, 1H), 3.97-3.92 (m, 1H), 3.84-3.76 (m, 2H), 3.66 (dd, <i>J</i> 11.4, 2.8 Hz, 1H), 3.54-3.48 (m, 2H), 3.24-3.09 (m, 2H). LCMS (ES ⁺) 440 (M+H) ⁺ .

EXAMPLES 271 TO 275

The following compounds were prepared from the relevant substituted {(*S*)-3-[3-(trimethylsilanyl)prop-2-ynyl]morpholin-4-yl}methanone (1.00 mmol) and the appropriate substituted 2-iodoaniline according to *Method H*.

Example No.	Compound Name	¹ H NMR/LCMS
271	(6-Methoxypyridin-3-yl)-[(<i>S</i>)-3-(5-methyl-1 <i>H</i> -indol-3-ylmethyl)-morpholin-4-yl]-methanone	δ_{H} (d ₆ -DMSO at 110°C) 10.40 (s, 1H), 8.02 (d, <i>J</i> 2.3 Hz, 1H), 7.38 (dd, <i>J</i> 8.6, 2.3 Hz, 1H), 7.21 (d, <i>J</i> 8.3 Hz, 1H), 7.03-6.96 (m, 2H), 6.87 (d, <i>J</i> 8.3 Hz, 1H), 6.65 (d, <i>J</i> 8.6 Hz, 1H), 4.30-4.22 (m, 1H), 3.98-3.92 (m, 1H), 3.90 (s, 3H), 3.85 (d, <i>J</i> 10.6 Hz, 1H), 3.79-3.73 (m, 1H), 3.59 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.55-3.40 (m, 2H), 3.17 (m, 1H), 3.05 (dd, <i>J</i> 14.4, 7.1 Hz, 1H), 2.30 (s, 3H). LCMS (ES ⁺) 366 (M+H) ⁺ .
272	3-[(<i>S</i>)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-	δ_{H} (d ₆ -DMSO at 110°C) 10.95 (d, <i>J</i> 0.5 Hz, 1H), 8.05 (s, 1H), 7.88 (s, 1H), 7.70 (d, <i>J</i> 8.6 Hz, 1H), 7.41 (d, <i>J</i> 8.6 Hz, 1H), 7.30-7.25 (m, 1H), 7.19

	1 <i>H</i> -indole-5-carboxylic acid methyl ester	(s, 1H), 6.56 (d, <i>J</i> 8.3 Hz, 1H), 4.39-4.32 (m, 1H), 3.94 (m, 1H), 3.88-3.78 (m, 8H), 3.64-3.70 (m, 1H), 3.47-3.53 (m, 2H), 3.25 (m, 1H), 3.17 (m, 1H). LCMS (ES ⁺) 410 (M+H) ⁺ .
273	3-[(<i>S</i>)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-sulfonic acid amide	δ_{H} (d ₆ -DMSO at 110°C) 11.00 (m, 1H), 8.03 (s, 1H), 7.97 (d, <i>J</i> 2.3 Hz, 1H), 7.59 (dd, <i>J</i> 8.6, 1.8 Hz, 1H), 7.47 (d, <i>J</i> 8.6 Hz, 1H), 7.37 (dd, <i>J</i> 8.6, 2.3 Hz, 1H), 7.23 (s, 1H), 6.69-6.61 (m, 3H), 4.44-4.33 (m, 1H), 3.92 (m, 1H), 3.88 (s, 3H), 3.83 (m, 1H), 3.80-3.73 (m, 1H), 3.63 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.59-3.46 (m, 2H), 3.22 (d, <i>J</i> 7.6 Hz, 2H). LCMS (ES ⁺) 431 (M+H) ⁺ .
274	1-Methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid (<i>R</i>)-pyrrolidin-3-ylamide	δ_{H} (d ₆ -DMSO at 110°C) 8.15 (s, 1H), 7.98 (s, 1H), 7.74-7.73 (m, 1H), 7.67 (dd, <i>J</i> 8.6, 1.8 Hz, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.23-7.21 (m, 1H), 7.09 (s, 1H), 7.05 (d, <i>J</i> 7.8 Hz, 1H), 4.46-4.38 (m, 1H), 4.32-4.28 (m, 1H), 3.97-3.89 (m, 1H), 3.85 (d, <i>J</i> 11.6 Hz, 1H), 3.80-3.78 (m, 1H), 3.76 (s, 3H), 3.65 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.55-3.47 (m, 2H), 3.25-3.08 (m, 4H), 2.96-2.87 (m, 2H), 2.43 (s, 3H), 2.15-2.06 (m, 1H), 1.86-1.78 (m, 1H). LCMS (ES ⁺) 462 (M+H) ⁺ .
275	1-Methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid (<i>S</i>)-pyrrolidin-3-ylamide	δ_{H} (d ₆ -DMSO at 110°C) 8.15 (s, 1H), 7.98 (s, 1H), 7.75-7.74 (m, 1H), 7.67 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.22-7.21 (m, 1H), 7.09 (s, 1H), 7.05 (d, <i>J</i> 7.8 Hz, 1H), 4.46-4.38 (m, 1H), 4.32-4.28 (m, 1H), 3.97-3.89 (m, 1H), 3.85 (d, <i>J</i> 11.6 Hz, 1H), 3.80-3.78 (m, 1H), 3.76 (s, 3H), 3.65 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.55-3.47 (m, 2H), 3.25-3.07 (m, 4H), 2.95-2.87 (m, 2H), 2.43 (s, 3H), 2.15-2.06 (m, 1H), 1.87-1.78 (m, 1H). LCMS (ES ⁺) 462 (M+H) ⁺ .

PREPARATIVE EXAMPLES 276 TO 278 (METHOD I)

To the relevant substituted {(*S*)-3-[3-(trimethylsilanyl)prop-2-ynyl]morpholin-4-yl}methanone (1.00mmol) and the appropriate substituted 2-iodoaniline (1.00 mmol) in DMF (5 mL) were added Pd(OAc)₂ (0.05 mmol), LiCl (1.00 mmol) and sodium carbonate (2.00 mmol). The reaction mixture was heated at 100°C for 2 h and then partitioned between brine (10 mL) and ethyl acetate (10 mL). The organic layer was separated, dried

(magnesium sulphate), concentrated *in vacuo* and chromatographed (SiO₂, 75% EtOAc/hexanes), yielding the *title compound*.

Example No.	Compound Name	¹ H NMR/LCMS
276	{(S)-3-[6-Chloro-2-(trimethylsilanyl)-1 <i>H</i> -indol-3-ylmethyl]-morpholin-4-yl}-(6-methoxypyridin-3-yl)-methanone	δ _H (d ₆ -DMSO at 110°C) 10.40 (s, 1H), 8.05 (s, 1H), 7.50 (d, <i>J</i> 6.5 Hz, 1H), 7.38-7.28 (m, 2H), 6.85 (d, <i>J</i> 8.5 Hz, 1H), 6.75 (d, <i>J</i> 8.5 Hz, 1H), 4.35-4.28 (m, 1H), 3.95-3.92 (m, 4H), 3.82-3.80 (m, 1H), 3.66 (d, <i>J</i> 11.5 Hz, 1H), 3.53-3.48 (m, 3H), 3.38 (dd, <i>J</i> 14.0, 9.2 Hz, 1H), 3.02 (dd, <i>J</i> 14.0, 5.7 Hz, 1H), 0.37 (s, 9H). LCMS (ES ⁺) 458 (M+H) ⁺ .
277	3-[(S)-4-(6-Methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-2-(trimethylsilanyl)-1 <i>H</i> -indole-5-carboxylic acid methyl ester	δ _H (d ₆ -DMSO at 110°C) 10.65 (s, 1H), 8.22-8.20 (m, 2H), 7.70 (d, <i>J</i> 8.6 Hz, 1H), 7.43 (d, <i>J</i> 8.6 Hz, 1H), 7.36-7.34 (m, 1H), 7.14 (d, <i>J</i> 7.8 Hz, 1H), 4.41 (m, 1H), 3.95-3.92 (m, 1H), 3.85 (s, 3H), 3.77-3.74 (m, 1H), 3.70 (d, <i>J</i> 11.6 Hz, 1H), 3.61-3.46 (m, 3H), 3.38 (dd, <i>J</i> 13.9, 8.8 Hz, 1H), 3.22-3.14 (m, 1H), 2.46 (s, 3H), 0.37 (s, 9H). LCMS (ES ⁺) 466 (M+H) ⁺ .
278	{(S)-3-[5-Chloro-2-(trimethylsilanyl)-1 <i>H</i> -indol-3-ylmethyl]-morpholin-4-yl}-(6-methylpyridin-3-yl)-methanone	δ _H (d ₆ -DMSO at 110°C) 10.45 (s, 1H), 8.31 (s, 1H), 7.48-7.46 (m, 1H), 7.36 (d, <i>J</i> 8.6 Hz, 1H), 7.33 (m, 1H), 7.21 (d, <i>J</i> 8.1 Hz, 1H), 7.02 (dd, <i>J</i> 8.6, 1.8 Hz, 1H), 4.34-4.32 (m, 1H), 3.97-3.90 (m, 1H), 3.64 (d, <i>J</i> 11.6 Hz, 1H), 3.55-3.46 (m, 4H), 3.39 (dd, <i>J</i> 14.1, 9.6 Hz, 1H), 3.01 (dd, <i>J</i> 14.1, 5.8 Hz, 1H), 2.90 (s, 3H), 0.37 (s, 9H). LCMS (ES ⁺) 442 (M+H) ⁺ .

5

EXAMPLES 279 TO 287 (METHOD J)

To the relevant precursor compound was added HCl (4M in 1,4-dioxane, 10 mL) and the reaction mixture was stirred at r.t. for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between saturated sodium hydrogencarbonate solution (10 mL) and ethyl acetate (10 mL). The organic layer was washed with brine (10 mL), dried (magnesium sulphate) and concentrated *in vacuo*. The residue was chromatographed (SiO₂, 50% EtOAc/hexanes), yielding the *title compound*.

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Example No.	Compound Name	¹ H NMR/LCMS
279	[(<i>S</i>)-3-(6-Chloro-1 <i>H</i> -indol-3-ylmethyl)morpholin-4-yl]-(6-methoxypyridin-3-yl)-methanone	δ_{H} (d_6 -DMSO at 110°C) 10.70 (s, 1H), 7.94 (d, <i>J</i> 2.2 Hz, 1H), 7.38-7.28 (m, 3H), 7.11 (s, 1H), 6.87 (dd, <i>J</i> 8.4, 1.8 Hz, 1H), 6.64 (d, <i>J</i> 8.5 Hz, 1H), 4.28-4.25 (m, 1H), 3.93-3.89 (m, 4H), 3.82-3.77 (m, 2H), 3.61 (dd, <i>J</i> 11.5, 3.2 Hz, 1H), 3.53-3.46 (m, 2H), 3.14-3.12 (m, 2H). LCMS (ES^+) 386 ($\text{M}+\text{H}$) ⁺ .
280	1-Methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid methyl ester	δ_{H} (d_6 -DMSO at 110°C) 8.14 (s, 1H), 8.07 (s, 1H), 7.77 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.44 (d, <i>J</i> 8.6 Hz, 1H), 7.24-7.22 (m, 1H), 7.16 (s, 1H), 7.03 (d, <i>J</i> 7.8 Hz, 1H), 4.31 (s, 1H), 3.94-3.92 (m, 1H), 3.86 (s, 3H), 3.87-3.85 (m, 1H), 3.84-3.82 (m, 1H), 3.78 (s, 3H), 3.65 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.54-3.45 (m, 2H), 3.22 (dd, <i>J</i> 14.4, 7.8 Hz, 1H), 3.17 (dd, <i>J</i> 14.4, 7.3 Hz, 1H), 2.41 (s, 3H). LCMS (ES^+) 408 ($\text{M}+\text{H}$) ⁺ .
281	[(<i>S</i>)-3-(5-Chloro-1 <i>H</i> -indol-3-ylmethyl)morpholin-4-yl]-(6-methylpyridin-3-yl)-methanone	δ_{H} (d_6 -DMSO at 110°C) 10.76 (s, 1H), 8.21 (d, <i>J</i> 2.0 Hz, 1H), 7.34 (dd, <i>J</i> 8.6, 0.5 Hz, 1H), 7.27-7.26 (m, 2H), 7.14 (s, 1H), 7.08 (d, <i>J</i> 7.8 Hz, 1H), 7.03 (dd, <i>J</i> 8.6, 2.0 Hz, 1H), 4.24 (s, 1H), 3.95-3.89 (m, 1H), 3.83-3.81 (m, 1H), 3.78 (d, <i>J</i> 11.4 Hz, 1H), 3.61 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.54-3.42 (m, 2H), 3.15 (dd, <i>J</i> 14.7, 7.6 Hz, 1H), 3.10 (dd, <i>J</i> 14.4, 7.6 Hz, 1H), 2.47 (s, 3H). LCMS (ES^+) 370 ($\text{M}+\text{H}$) ⁺ .
282	[(<i>S</i>)-3-(5-Methanesulfonyl-1 <i>H</i> -indol-3-ylmethyl)morpholin-4-yl]-(6-methoxypyridin-3-yl)-methanone	δ_{H} (d_6 -DMSO at 110°C) 11.16 (d, <i>J</i> 0.8 Hz, 1H), 8.03 (s, 1H), 7.85 (s, 1H), 7.62-7.51 (m, 2H), 7.30 (s, 1H), 7.26 (d, <i>J</i> 8.3 Hz, 1H), 6.57 (d, <i>J</i> 8.3 Hz, 1H), 4.39-4.28 (m, 1H), 3.98-3.91 (m, 1H), 3.90-3.77 (m, 5H), 3.67 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.58-3.46 (m, 2H), 3.28 (m, 1H), 3.19 (m, 1H), 3.07 (s, 3H). LCMS (ES^+) 430 ($\text{M}+\text{H}$) ⁺ .
283	3-[(<i>S</i>)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-sulfonic acid dimethylamide	δ_{H} (d_6 -DMSO at 110°C) 7.91 (d, <i>J</i> 7.1 Hz, 2H), 7.54 (m, 1H), 7.45 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.31 (m, 1H), 7.28 (s, 1H), 6.61 (d, <i>J</i> 8.6 Hz, 1H), 4.37-4.29 (m, 1H), 3.96-3.90 (m, 1H), 3.87 (s, 3H), 3.84 (d, <i>J</i> 11.6 Hz, 1H), 3.80-3.74 (m, 1H), 3.64 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.52 (m, 2H), 3.26-3.20 (m, 2H), 2.62 (s, 6H). LCMS (ES^+) 459

		(M+H) ⁺ .
284	[(<i>S</i>)-3-(5-Chloro-1-methyl-1 <i>H</i> -indol-3-ylmethyl)morpholin-4-yl]-(6-methylpyridin-3-yl)-methanone	δ_H (d ₆ -DMSO at 110°C) 8.16 (s, 1H), 8.06 (s, 1H), 7.71 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.44-7.35 (m, 1H), 7.28-7.13 (m, 2H), 7.07-6.80 (m, 1H), 4.38-4.26 (m, 1H), 3.94 (d, <i>J</i> 7.6 Hz, 1H), 3.89-3.75 (m, 2H), 3.69-3.60 (m, 1H), 3.55-3.47 (m, 2H), 3.26-3.14 (m, 2H), 2.51 (s, 3H), 2.46-2.38 (m, 3H). LCMS (ES ⁺) 384 (M+H) ⁺ .
285	[(<i>S</i>)-3-{5-[(<i>S</i>)-3-(Aminomethyl)pyrrolidine-1-carbonyl]-1-methyl-1 <i>H</i> -indol-3-ylmethyl}morpholin-4-yl]-(6-methylpyridin-3-yl)-methanone	δ_H (d ₆ -DMSO at 110°C) 8.21 (s, 1H), 7.61 (s, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.33-7.29 (m, 2H), 7.11-7.09 (m, 2H), 4.30-4.20 (m, 1H), 3.96-3.89 (m, 1H), 3.82 (d, <i>J</i> 11.6 Hz, 1H), 3.80-3.76 (m, 1H), 3.76 (s, 3H), 3.63-3.45 (m, 6H), 3.26 (dd, <i>J</i> 11.4, 7.3 Hz, 1H), 3.22 (dd, <i>J</i> 13.9, 7.6 Hz, 1H), 3.13 (dd, <i>J</i> 14.4, 7.1 Hz, 1H), 2.67 (dd, <i>J</i> 12.4, 6.8 Hz, 1H), 2.62 (dd, <i>J</i> 11.4, 5.8 Hz, 1H), 2.45 (s, 3H), 2.26-2.17 (m, 1H), 2.04-1.92 (m, 1H), 1.68-1.59 (m, 1H). LCMS (ES ⁺) 476 (M+H) ⁺ .
286	[(<i>S</i>)-3-{5-[(<i>R</i>)-3-(Aminomethyl)pyrrolidine-1-carbonyl]-1-methyl-1 <i>H</i> -indol-3-ylmethyl}morpholin-4-yl]-(6-methylpyridin-3-yl)-methanone	δ_H (d ₆ -DMSO at 110°C) 8.21 (s, 1H), 7.64 (s, 1H), 7.39 (d, <i>J</i> 8.3 Hz, 1H), 7.33 (d, <i>J</i> 8.3 Hz, 1H), 7.34-7.30 (m, 1H), 7.12-7.10 (m, 2H), 4.30-4.20 (m, 1H), 3.96-3.89 (m, 1H), 3.82 (d, <i>J</i> 11.6 Hz, 1H), 3.76 (s, 3H), 3.73 (dd, <i>J</i> 11.9, 7.8 Hz, 1H), 3.60 (dd, <i>J</i> 11.1, 3.3 Hz, 1H), 3.57-3.46 (m, 5H), 3.32 (dd, <i>J</i> 11.4, 7.6 Hz, 1H), 3.22 (dd, <i>J</i> 14.4, 7.8 Hz, 1H), 3.14 (dd, <i>J</i> 14.4, 7.1 Hz, 1H), 2.87-2.85 (m, 2H), 2.50-2.46 (m, 1H), 2.46 (s, 3H), 2.12-2.04 (m, 1H), 1.76-1.66 (m, 1H). LCMS (ES ⁺) 476 (M+H) ⁺ .
287	{(<i>S</i>)-3-[5-(4-Aminopiperidine-1-carbonyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]morpholin-4-yl}-(6-methylpyridin-3-yl)-methanone	δ_H (d ₆ -DMSO at 110°C) 8.19 (s, 1H), 7.48 (s, 1H), 7.40 (d, <i>J</i> 8.6 Hz, 1H), 7.31 (d, <i>J</i> 7.3 Hz, 1H), 7.17 (d, <i>J</i> 8.3 Hz, 1H), 7.11-7.09 (m, 2H), 4.66 (br s, 2H), 4.30-4.20 (m, 1H), 4.05-3.99 (m, 2H), 3.93-3.89 (m, 1H), 3.82 (d, <i>J</i> 11.6 Hz, 1H), 3.80-3.78 (m, 1H), 3.77 (s, 3H), 3.60 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.54-3.46 (m, 2H), 3.20 (dd, <i>J</i> 14.4, 7.6 Hz, 1H), 3.13 (dd, <i>J</i> 14.4, 7.6 Hz, 1H), 3.09-3.00 (m, 3H), 2.45 (s, 3H), 1.86-1.79 (m, 2H), 1.42-1.32 (m, 2H). LCMS (ES ⁺) 476 (M+H) ⁺ .

EXAMPLE 288 (METHOD K)

(6-Methoxypyridin-3-yl)-{(S)-3-[1-methyl-5-(piperidin-1-ylmethyl)-1H-indol-3-ylmethyl]morpholin-4-yl}-methanone

- 5 To a stirred solution of *Intermediate 19* (200 mg, 0.50 mmol) in 10:1 DCM:AcOH (4 mL) were added piperidine (99 μ L, 1.00 mmol) and PS-BH₃CN (428 mg, 1.50 mmol). The reaction mixture was stirred for 16 h, then the resin was filtered. The filtrate was concentrated *in vacuo* to give an oil, which was purified by preparative HPLC to afford the *title compound* (45 mg, 16%) as an off-white solid. δ_{H} (d₆-DMSO at 110°C) 7.98 (d, *J* 2.0 Hz, 1H), 7.37 (dd, *J* 8.3, 2.0 Hz, 1H), 7.27 (d, *J* 8.3 Hz, 1H), 7.19 (s, 1H), 7.10 (d, *J* 8.6 Hz, 1H), 6.98 (s, 1H), 6.65 (d, *J* 8.6 Hz, 1H), 4.29-4.21 (m, 1H), 3.96-3.91 (m, 1H), 3.89 (s, 3H), 3.85-3.77 (m, 2H), 3.72 (s, 3H), 3.60 (dd, *J* 11.4, 3.0 Hz, 1H), 3.52-3.43 (m, 4H), 3.18 (dd, *J* 14.1, 7.8 Hz, 1H), 3.07 (dd, *J* 14.1, 7.1 Hz, 1H), 2.40-2.33 (m, 4H), 1.56-1.48 (m, 4H), 1.46-1.38 (m, 2H). LCMS (ES⁺) 463 (M+H)⁺.

15

EXAMPLES 289 TO 291

The following compounds were prepared from the relevant aldehyde and the appropriate amine according to *Method K*.

20

Example No.	Compound Name	¹ H NMR/LCMS
289	(6-Methoxypyridin-3-yl)-{(S)-3-[1-methyl-5-(morpholin-4-ylmethyl)-1H-indol-3-ylmethyl]morpholin-4-yl}-methanone	δ_{H} (d ₆ -DMSO at 110°C) 7.96 (s, 1H), 7.36 (m, 1H), 7.28 (d, <i>J</i> 8.3 Hz, 1H), 7.21 (s, 1H), 7.11 (d, <i>J</i> 8.3 Hz, 1H), 6.99 (s, 1H), 6.64 (d, <i>J</i> 8.6 Hz, 1H), 4.29-4.19 (m, 1H), 3.97-3.91 (m, 1H), 3.89 (s, 3H), 3.86-3.77 (m, 2H), 3.72 (s, 3H), 3.64-3.55 (m, 5H), 3.52-3.43 (m, 4H), 3.17 (dd, <i>J</i> 14.4, 7.8 Hz, 1H), 3.08 (dd, <i>J</i> 14.1, 7.1 Hz, 1H), 2.40-2.35 (m, 4H). LCMS (ES ⁺) 465 (M+H) ⁺ .
290	(6-Methoxypyridin-3-yl)-{(S)-3-[1-methyl-5-(pyrrolidin-1-ylmethyl)-1H-indol-3-ylmethyl]morpholin-4-yl}-methanone	δ_{H} (d ₆ -DMSO at 110°C) 7.96 (d, <i>J</i> 2.0 Hz, 1H), 7.36 (dd, <i>J</i> 8.3, 2.3 Hz, 1H), 7.30 (d, <i>J</i> 8.3 Hz, 1H), 7.23 (s, 1H), 7.11 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.00 (s, 1H), 6.65 (d, <i>J</i> 8.6 Hz, 1H), 4.29-4.22 (m, 1H), 3.97-3.92 (m, 1H), 3.89 (s, 3H), 3.86-3.77 (m, 2H), 3.72 (s, 3H), 3.60 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.57-3.53 (m, 2H), 3.52-3.46

		(m, 2H), 3.21-3.12 (m, 5H), 2.84 (s, 3H), 2.53-2.45 (m, 2H). LCMS (ES ⁺) 449 (M+H) ⁺ .
291	4-{3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-ylmethyl}-piperazin-2-one	δ_H (d ₆ -DMSO at 110°C) 7.97 (d, <i>J</i> 2.3 Hz, 1H), 7.37 (dd, <i>J</i> 8.3, 2.3 Hz, 1H), 7.30 (d, <i>J</i> 8.3 Hz, 1H), 7.23 (s, 2H), 7.11 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.00 (s, 1H), 6.66 (d, <i>J</i> 8.6 Hz, 1H), 4.31-4.21 (m, 1H), 3.97-3.92 (m, 1H), 3.89 (s, 3H), 3.86-3.78 (m, 2H), 3.73 (s, 3H), 3.64-3.43 (m, 5H), 3.23-3.14 (m, 3H), 3.09 (dd, <i>J</i> 14.4, 7.1 Hz, 1H), 2.96-2.91 (m, 2H), 2.61-2.54 (m, 2H). LCMS (ES ⁺) 478 (M+H) ⁺ .

EXAMPLE 292 (METHOD L)

3-[(S)-4-(4-Cyanobenzoyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carboxylic acid dimethylamide

To a stirred solution of 4-cyanobenzoic acid (63 mg, 0.4 mmol) and *Intermediate 3* (151 mg, 0.5 mmol) in DCM was added PS-CDI (1 g, 1 mmol). The reaction mixture was stirred at r.t. for 16 h prior to filtration. The resin was washed with MeOH (5 mL) then DCM (5 mL) and the filtrate was concentrated *in vacuo* to yield a yellow oil. To a solution of the yellow oil in DCM (5 mL) were added PS-NCO (0.5 g, 1.5 mmol) and TEA (one drop). The reaction mixture was stirred for 5 h, then filtered and concentrated *in vacuo*. The resulting oil was partitioned between EtOAc (5 mL) and water (5 mL). The organic layer was separated, dried (phase separator) and concentrated *in vacuo*. The residue was purified by preparative HPLC to yield the *title compound* (90 mg, 52%) as a white solid. δ_H (d₆-DMSO at 110°C) 7.65 (d, *J* 7.6 Hz, 2H), 7.47-7.37 (m, 2H), 7.25-7.17 (m, 3H), 7.11 (s, 1H), 4.20-4.09 (m, 1H), 3.96-3.90 (m, 1H), 3.83-3.73 (m, 5H), 3.63-3.57 (m, 1H), 3.55-3.43 (m, 2H), 3.23-3.09 (m, 2H), 2.99 (s, 6H). LCMS (ES⁺) 431 (M+H)⁺.

EXAMPLES 293 TO 305

The following compounds were prepared from *Intermediate 3* and the appropriate substituted carboxylic acid according to *Method L*.

Example No.	Compound Name	¹ H NMR/LCMS
293	3-[(<i>S</i>)-4-(3-Fluoro-4-nitrobenzoyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.99-7.90 (m, 1H), 7.42 (m, 2H), 7.19 (d, <i>J</i> 8.6 Hz, 1H), 7.15-7.00 (m, 3H), 4.20-4.10 (m, 1H), 3.99-3.92 (m, 1H), 3.83 (m, 1H), 3.79 (s, 4H), 3.70-3.63 (m, 1H), 3.59-3.45 (m, 2H), 3.25-3.10 (m, 2H), 2.96 (s, 6H). LCMS (ES ⁺) 469 (M+H) ⁺ .
294	3-[(<i>S</i>)-4-(4-Fluorobenzoyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.45 (s, 1H), 7.39 (d, <i>J</i> 8.3 Hz, 1H), 7.22-7.15 (m, 3H), 7.11-7.03 (m, 3H), 4.25-4.18 (m, 1H), 3.95-3.90 (m, 1H), 3.81-3.75 (m, 5H), 3.56 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.51-3.45 (m, 2H), 3.22 (dd, <i>J</i> 14.1, 8.1 Hz, 1H), 3.09 (dd, <i>J</i> 14.4, 7.1 Hz, 1H), 2.98 (s, 6H). LCMS (ES ⁺) 424 (M+H) ⁺ .
295	3-[(<i>S</i>)-4-(4-Methanesulfonylbenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.90 (d, <i>J</i> 7.8 Hz, 1H), 7.72 (s, 1H), 7.55 (t, <i>J</i> 7.6 Hz, 1H), 7.48-7.37 (m, 3H), 7.18 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.13 (s, 1H), 4.30-4.20 (m, 1H), 3.93 (d, <i>J</i> 7.3 Hz, 1H), 3.81 (m, 1H), 3.79-3.76 (m, 3H), 3.61 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.53 (d, <i>J</i> 8.8 Hz, 2H), 3.24 (m, 1H), 3.18-3.10 (m, 5H), 2.98 (s, 6H). LCMS (ES ⁺) 484 (M+H) ⁺ .
296	3-[(<i>S</i>)-4-(3,4-Difluorobenzoyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.45 (s, 1H), 7.39 (d, <i>J</i> 8.3 Hz, 1H), 7.28-7.21 (m, 1H), 7.19 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.11 (s, 1H), 7.07-7.00 (m, 1H), 6.98-6.91 (m, 1H), 4.24-4.15 (m, 1H), 3.96-3.90 (m, 1H), 3.83-3.75 (m, 5H), 3.61 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.52-3.46 (m, 2H), 3.22-3.09 (m, 2H), 3.01-2.95 (m, 6H). LCMS (ES ⁺) 442 (M+H) ⁺ .
297	1-Methyl-3-[(<i>S</i>)-4-[3-(trifluoromethoxy)benzoyl]morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.47 (s, 1H), 7.44-7.37 (m, 2H), 7.31-7.26 (m, 1H), 7.19 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.14-7.08 (m, 2H), 7.02 (s, 1H), 4.28-4.19 (m, 1H), 3.95-3.90 (m, 1H), 3.80 (m, 1H), 3.77 (s, 3H), 3.74-3.70 (m, 1H), 3.59 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.50 (d, <i>J</i> 8.8 Hz, 2H), 3.22 (dd, <i>J</i> 14.4, 7.8 Hz, 1H), 3.12 (dd, <i>J</i> 14.4, 7.1 Hz, 1H), 2.98 (s, 6H). LCMS (ES ⁺) 490 (M+H) ⁺ .
298	1-Methyl-3-[(<i>S</i>)-4-[4-(trifluoromethoxy)benzoyl]morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic	δ_{H} (d ₆ -DMSO at 110°C) 7.54 (s, 1H), 7.39 (d, <i>J</i> 8.4 Hz, 1H), 7.24 (s, 4H), 7.20 (dd, <i>J</i> 8.4, 1.4 Hz, 1H), 7.09 (s, 1H), 4.27-4.20 (m, 1H), 3.94-3.88

	acid dimethylamide	(m, 1H), 3.80 (d, <i>J</i> 11.6 Hz, 1H), 3.79-3.76 (m, 4H), 3.59-3.48 (m, 3H), 3.23 (dd, <i>J</i> 14.4, 8.0 Hz, 1H), 3.11 (dd, <i>J</i> 14.3, 7.0 Hz, 1H), 2.98 (s, 6H). LCMS (ES ⁺) 490 (M+H) ⁺ .
299	3-[(<i>S</i>)-4-(3,5-Dimethoxybenzoyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.51-7.45 (m, 1H), 7.38 (d, <i>J</i> 8.3 Hz, 1H), 7.18 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.11 (s, 1H), 6.48 (t, <i>J</i> 2.3 Hz, 1H), 6.29 (d, <i>J</i> 2.0 Hz, 2H), 4.29 (m, 1H), 3.94-3.87 (m, 1H), 3.80-3.74 (m, 4H), 3.72 (s, 6H), 3.54 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.49-3.42 (m, 2H), 3.25 (dd, <i>J</i> 14.4, 8.6 Hz, 1H), 3.07 (dd, <i>J</i> 14.1, 6.6 Hz, 2H), 2.98 (s, 6H). LCMS (ES ⁺) 466 (M+H) ⁺ .
300	3-[(<i>S</i>)-4-(Benzo[1,3]dioxole-5-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.46 (s, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.18 (m, 1H), 7.10 (s, 1H), 6.77 (m, 1H), 6.67 (d, <i>J</i> 8.1 Hz, 1H), 6.62 (s, 1H), 5.99 (m, 2H), 4.31-4.23 (m, 1H), 3.94-3.88 (m, 1H), 3.83-3.72 (m, 5H), 3.55 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.49-3.42 (m, 2H), 3.21 (dd, <i>J</i> 14.1, 8.1 Hz, 1H), 3.07 (dd, <i>J</i> 14.1, 6.8 Hz, 1H), 2.98 (s, 6H). LCMS (ES ⁺) 450 (M+H) ⁺ .
301	3-[(<i>S</i>)-4-(3-Fluoro-4-methylbenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.48 (s, 1H), 7.39 (d, <i>J</i> 8.6 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 7.16 (m, 1H), 7.10 (s, 1H), 6.84 (d, <i>J</i> 7.6 Hz, 1H), 6.79 (d, <i>J</i> 10.1 Hz, 1H), 4.29-4.18 (m, 1H), 3.91 (d, <i>J</i> 7.3 Hz, 1H), 3.82-3.74 (m, 4H), 3.57 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.50-3.43 (m, 3H), 3.20 (dd, <i>J</i> 14.1, 7.8 Hz, 1H), 3.11 (dd, <i>J</i> 14.4, 7.3 Hz, 1H), 2.98 (s, 6H), 2.21 (s, 3H). LCMS (ES ⁺) 438 (M+H) ⁺ .
302	3-[(<i>S</i>)-4-(3-Fluoro-4-methoxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 7.49 (s, 1H), 7.39 (dd, <i>J</i> 8.6, 0.5 Hz, 1H), 7.19 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.10 (s, 1H), 7.02 (t, <i>J</i> 8.8 Hz, 1H), 6.92-6.87 (m, 2H), 4.29-4.22 (m, 1H), 3.92 (d, <i>J</i> 7.3 Hz, 1H), 3.86 (s, 3H), 3.82-3.75 (m, 5H), 3.57 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.48 (d, <i>J</i> 8.8 Hz, 2H), 3.23-3.17 (m, 1H), 3.11 (dd, <i>J</i> 14.4, 7.3 Hz, 1H), 2.98 (s, 6H). LCMS (ES ⁺) 454 (M+H) ⁺ .
303	1-Methyl-3-[(<i>S</i>)-4-(thieno[2,3- <i>b</i>]pyridine-2-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 8.57 (dd, <i>J</i> 4.5, 1.8 Hz, 1H), 8.15 (dd, <i>J</i> 8.1, 1.8 Hz, 1H), 7.58 (s, 1H), 7.41 (dd, <i>J</i> 8.1, 4.8 Hz, 1H), 7.37 (d, <i>J</i> 8.1 Hz, 1H), 7.33 (s, 1H), 7.18-7.14 (m, 2H), 4.56-4.48 (m, 1H), 4.07-3.95 (m, 2H), 3.87 (d, <i>J</i> 11.6 Hz, 1H), 3.76 (s, 3H), 3.68-

		3.59 (m, 2H), 3.58-3.50 (m, 1H), 3.33-3.20 (m, 2H), 2.91 (s, 6H). LCMS (ES ⁺) 463 (M+H) ⁺ .
304	3-[(S)-4-(1 <i>H</i> -Indole-5-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 10.93-10.82 (m, 1H), 7.54 (s, 1H), 7.42-7.31 (m, 4H), 7.18 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.09 (s, 1H), 6.97-6.93 (m, 1H), 6.44-6.41 (m, 1H), 4.44-4.37 (m, 1H), 3.92-3.87 (m, 1H), 3.86-3.80 (m, 1H), 3.80-3.74 (m, 4H), 3.55 (dd, <i>J</i> 11.4, 3.3 Hz, 1H), 3.51-3.46 (m, 2H), 3.28 (dd, <i>J</i> 14.4, 8.8 Hz, 1H), 3.10 (m, 1H), 2.93 (s, 6H). LCMS (ES ⁺) 445 (M+H) ⁺ .
305	3-[(S)-4-[3-Chloro-4-(trifluoromethyl)benzoyl]morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d ₆ -DMSO at 110°C) 7.67 (d, <i>J</i> 7.6 Hz, 1H), 7.55 (s, 1H), 7.41 (d, <i>J</i> 8.3 Hz, 1H), 7.23-7.17 (m, 3H), 7.11 (s, 1H), 4.23-4.14 (m, 1H), 3.93 (d, <i>J</i> 7.3 Hz, 1H), 3.85 (d, <i>J</i> 11.6 Hz, 1H), 3.79 (s, 4H), 3.65 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.53 (d, <i>J</i> 8.8 Hz, 2H), 3.23-3.12 (m, 2H), 2.97 (s, 6H). LCMS (ES ⁺) 508 (M+H) ⁺ .

EXAMPLES 306 TO 322

The following compounds were prepared from the relevant precursor amine and the appropriate acyl chloride according to *Method D*.

Example No.	Compound Name	¹ H NMR/LCMS
306	(6-Methoxypyridin-3-yl)-[(S)-3-(1-methyl-5-nitro-1 <i>H</i> -indol-3-yl-methyl)morpholin-4-yl]-methanone	δ_H (d ₆ -DMSO at 110°C) 8.33 (s, 1H), 7.99 (dd, <i>J</i> 9.1, 2.3 Hz, 1H), 7.83 (s, 1H), 7.54 (d, <i>J</i> 9.1 Hz, 1H), 7.32 (s, 1H), 7.30-7.26 (m, 1H), 6.57 (d, <i>J</i> 8.6 Hz, 1H), 4.40-4.29 (m, 1H), 3.99-3.92 (m, 1H), 3.89-3.80 (m, 7H), 3.69 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.54-3.46 (m, 3H), 3.27 (dd, <i>J</i> 14.4, 8.3 Hz, 1H), 3.17 (dd, <i>J</i> 14.7, 6.8 Hz, 1H). LCMS (ES ⁺) 411 (M+H) ⁺ .
307	<i>N</i> -{3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}acetamide	δ_H (d ₆ -DMSO at 110°C) 9.24 (s, 1H), 7.96 (d, <i>J</i> 2.2 Hz, 1H), 7.57 (s, 1H), 7.35-7.24 (m, 3H), 6.98 (s, 1H), 6.64 (d, <i>J</i> 8.5 Hz, 1H), 4.30-4.25 (m, 1H), 3.92 (d, <i>J</i> 7.5 Hz, 1H), 3.89 (s, 3H), 3.86-3.74 (m, 2H), 3.71 (s, 3H), 3.61 (dd, <i>J</i> 11.5, 3.2 Hz, 1H), 3.53-3.47 (m, 2H), 3.11 (d, <i>J</i> 7.5 Hz, 2H), 2.03 (s, 3H). LCMS (ES ⁺) 423 (M+H) ⁺ .

308	1,1-Dimethyl-3-{3-[(<i>S</i>)-4-(6-methoxypyridine-3-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}urea	δ_H (d_6 -DMSO at 110°C) 8.00 (d, <i>J</i> 2.2 Hz, 1H), 7.66 (s, 1H), 7.43 (s, 1H), 7.37 (dd, <i>J</i> 8.5, 2.2 Hz, 1H), 7.21-7.18 (m, 2H), 6.94 (s, 1H), 6.67 (d, <i>J</i> 8.5 Hz, 1H), 4.30-4.28 (m, 1H), 3.92 (d, <i>J</i> 7.6 Hz, 1H), 3.89 (s, 3H), 3.82-3.78 (m, 2H), 3.70 (s, 3H), 3.60 (dd, <i>J</i> 11.5, 3.2 Hz, 1H), 3.51-3.46 (m, 2H), 3.12-3.08 (m, 2H), 2.96 (s, 6H). LCMS (ES^+) 452 (M+H) ⁺ .
309	{3-[(<i>S</i>)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}carbamic acid ethyl ester	δ_H (d_6 -DMSO at 110°C) 8.70 (d, <i>J</i> 0.8 Hz, 1H), 7.95 (d, <i>J</i> 2.3 Hz, 1H), 7.48 (d, <i>J</i> 1.0 Hz, 1H), 7.33 (dd, <i>J</i> 8.6, 2.3 Hz, 1H), 7.24 (m, 1H), 7.19 (m, 1H), 6.97 (s, 1H), 6.64 (d, <i>J</i> 8.3 Hz, 1H), 4.32-4.25 (m, 1H), 4.15 (q, <i>J</i> 7.1 Hz, 2H), 3.95-3.90 (m, 1H), 3.88 (s, 3H), 3.86-3.77 (m, 2H), 3.70 (s, 3H), 3.62 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.53-3.43 (m, 2H), 3.10 (d, <i>J</i> 7.6 Hz, 2H), 1.28 (t, <i>J</i> 7.1 Hz, 3H). LCMS (ES^+) 453 (M+H) ⁺ .
310	Cyclobutanecarboxylic acid {3-[(<i>S</i>)-4-(6-methoxypyridine-3-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}amide	δ_H (d_6 -DMSO at 110°C) 9.00 (d, <i>J</i> 0.8 Hz, 1H), 7.95 (d, <i>J</i> 1.8 Hz, 1H), 7.63 (s, 1H), 7.37-7.29 (m, 2H), 7.25 (m, 1H), 6.98 (s, 1H), 6.63 (d, <i>J</i> 8.6 Hz, 1H), 4.34-4.25 (m, 1H), 3.93 (d, <i>J</i> 7.6 Hz, 1H), 3.88 (s, 3H), 3.81 (t, <i>J</i> 11.6 Hz, 2H), 3.71 (s, 3H), 3.62 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.50 (d, <i>J</i> 8.8 Hz, 2H), 3.30-3.17 (m, 1H), 3.11 (d, <i>J</i> 7.3 Hz, 2H), 2.37-2.23 (m, 2H), 2.22-2.10 (m, 2H), 2.01-1.85 (m, 2H). LCMS (ES^+) 463 (M+H) ⁺ .
311	{3-[(<i>S</i>)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}carbamic acid methyl ester	δ_H (d_6 -DMSO at 110°C) 8.75 (s, 1H), 7.95 (s, 1H), 7.46 (s, 1H), 7.33 (d, <i>J</i> 8.3 Hz, 1H), 7.25 (m, 1H), 7.18 (m, 1H), 6.98 (s, 1H), 6.64 (d, <i>J</i> 8.6 Hz, 1H), 4.32-4.24 (m, 1H), 3.92 (m, 1H), 3.88 (s, 3H), 3.84-3.77 (m, 2H), 3.70 (s, 3H), 3.68 (s, 3H), 3.62 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.53-3.43 (m, 2H), 3.10 (d, <i>J</i> 7.6 Hz, 2H). LCMS (ES^+) 439 (M+H) ⁺ .
312	<i>N</i> -{3-[(<i>S</i>)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}-3,3,3-trifluoropropionamide	δ_H (d_6 -DMSO at 110°C) 9.71 (s, 1H), 7.95 (s, 1H), 7.61 (s, 1H), 7.34 (d, <i>J</i> 8.3 Hz, 1H), 7.30 (s, 2H), 7.02 (s, 1H), 6.64 (d, <i>J</i> 8.6 Hz, 1H), 4.35-4.26 (m, 1H), 3.95-3.90 (m, 1H), 3.88 (s, 3H), 3.86-3.75 (m, 2H), 3.73 (s, 3H), 3.62 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.52-3.47 (m, 2H), 3.42 (q, <i>J</i> 11.1 Hz, 2H), 3.12 (d, <i>J</i> 7.6 Hz, 2H). LCMS (ES^+) 491 (M+H) ⁺ .

313	Acetic acid {3-[(<i>S</i>)-4-(6-methoxy-pyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-ylcarbamoyl}methyl ester	δ_{H} (d_6 -DMSO at 110°C) 9.41 (s, 1H), 7.96 (s, 1H), 7.61 (s, 1H), 7.34 (d, <i>J</i> 8.1 Hz, 1H), 7.30 (s, 2H), 7.01 (s, 1H), 6.65 (d, <i>J</i> 8.3 Hz, 1H), 4.64 (s, 2H), 4.36-4.26 (m, 1H), 3.92 (d, <i>J</i> 7.6 Hz, 1H), 3.88 (s, 3H), 3.85-3.76 (m, 2H), 3.72 (s, 3H), 3.62 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.55-3.43 (m, 2H), 3.12 (d, <i>J</i> 7.6 Hz, 2H), 2.15 (s, 3H). LCMS (ES^+) 481 ($\text{M}+\text{H}$) ⁺ .
314	{3-[(<i>S</i>)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}carbamic acid isobutyl ester	δ_{H} (d_6 -DMSO at 110°C) 8.70 (s, 1H), 7.95 (s, 1H), 7.48 (s, 1H), 7.32 (d, <i>J</i> 8.3 Hz, 1H), 7.27-7.18 (m, 2H), 6.97 (s, 1H), 6.63 (d, <i>J</i> 8.3 Hz, 1H), 4.33-4.24 (m, 1H), 3.95-3.86 (m, 6H), 3.84-3.78 (m, 2H), 3.70 (s, 3H), 3.62 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.54-3.44 (m, 2H), 3.10 (d, <i>J</i> 7.3 Hz, 2H), 1.96 (m, 1H), 0.99 (s, 3H), 0.97 (s, 3H). LCMS (ES^+) 481 ($\text{M}+\text{H}$) ⁺ .
315	2-(Dimethylamino)- <i>N</i> -{3-[(<i>S</i>)-4-(6-methoxypyridine-3-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}acetamide	δ_{H} (d_6 -DMSO at 110°C) 9.10 (s, 1H), 7.92 (s, 1H), 7.58 (s, 1H), 7.37 (dd, <i>J</i> 8.6, 1.8 Hz, 1H), 7.33-7.26 (m, 2H), 6.99 (s, 1H), 6.62 (d, <i>J</i> 8.6 Hz, 1H), 4.35-4.24 (m, 1H), 3.93 (d, <i>J</i> 7.3 Hz, 1H), 3.87 (s, 3H), 3.85-3.77 (m, 2H), 3.72 (s, 3H), 3.63 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.54-3.44 (m, 2H), 3.18-3.08 (m, 2H), 2.36 (s, 6H), 2.13 (s, 1H), 1.80 (s, 1H). LCMS (ES^+) 466 ($\text{M}+\text{H}$) ⁺ .
316	<i>N</i> -{3-[(<i>S</i>)-4-(5-Chloro-6-methoxy-pyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}-acetamide	δ_{H} (d_6 -DMSO at 110°C) 9.19 (s, 1H), 7.85 (d, <i>J</i> 2.0 Hz, 1H), 7.59 (s, 1H), 7.34-7.18 (m, 3H), 6.98 (s, 1H), 4.33-4.24 (m, 1H), 3.97 (s, 3H), 3.93 (d, <i>J</i> 8.3 Hz, 1H), 3.85-3.81 (m, 1H), 3.80-3.79 (m, 1H), 3.71 (s, 3H), 3.68 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.53-3.46 (m, 2H), 3.17 (dd, <i>J</i> 14.4, 8.1 Hz, 1H), 3.05 (dd, <i>J</i> 14.4, 6.8 Hz, 1H), 2.03 (s, 3 H). LCMS (ES^+) 457 ($\text{M}+\text{H}$) ⁺ .
317	Cyclopropanecarboxylic acid {3-[(<i>S</i>)-4-(5-chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}amide	δ_{H} (d_6 -DMSO at 110°C) 9.41 (s, 1H), 7.83 (d, <i>J</i> 2.0 Hz, 1H), 7.63 (s, 1H), 7.32-7.28 (m, 2H), 7.25-7.23 (m, 1H), 6.97 (s, 1H), 4.32-4.27 (m, 1H), 3.96 (s, 3H), 3.95-3.91 (m, 1H), 3.85-3.83 (m, 1H), 3.82-3.77 (m, 1H), 3.72 (s, 3H), 3.69-3.66 (m, 1H), 3.53-3.46 (m, 2H), 3.18 (dd, <i>J</i> 14.7, 8.3 Hz, 1H), 3.04 (dd, <i>J</i> 14.7, 6.8 Hz, 1H), 1.83-1.75 (m, 1H), 0.87-0.81 (m, 2H), 0.75-0.72 (m, 2H). LCMS (ES^+) 483 ($\text{M}+\text{H}$) ⁺ .

318	{3-[(S)-4-(5-Chloro-6-methoxy-pyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}-carbamic acid methyl ester	δ_H (d_6 -DMSO at 110°C) 8.70 (s, 1H), 7.84 (d, <i>J</i> 2.0 Hz, 1H), 7.48 (d, <i>J</i> 1.5 Hz, 1H), 7.31 (d, <i>J</i> 1.3 Hz, 1H), 7.25-7.23 (m, 1H), 7.17 (dd, <i>J</i> 8.6, 1.8 Hz, 1H), 6.97 (s, 1H), 4.32-4.24 (m, 1H), 3.96 (s, 3H), 3.95-3.92 (m, 1H), 3.87-3.78 (m, 1H), 3.71 (s, 3H), 3.70-3.68 (m, 1H), 3.68 (s, 3H), 3.66 (d, <i>J</i> 3.3 Hz, 1H), 3.53-3.48 (m, 2H), 3.17 (dd, <i>J</i> 14.7, 8.3 Hz, 1H), 3.04 (dd, <i>J</i> 14.7, 6.8 Hz, 1H). LCMS (ES^+) 473 ($M+H$) ⁺ .
319	<i>N</i> -{3-[(S)-4-(2-Chloro-5-fluoro-6-methoxypyridine-3-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}acetamide	δ_H (d_6 -DMSO at 110°C) 9.23 (br s, 1H), 7.78-7.39 (m, 1H), 7.27-7.25 (m, 2H), 7.03 (br s, 2H), 4.02-3.90 (m, 4H), 3.84 (d, <i>J</i> 11.4 Hz, 2H), 3.72 (s, 5H), 3.49-3.47 (m, 2H), 3.13-3.10 (m, 2H), 2.03 (s, 3H). LCMS (ES^+) 475 ($M+H$) ⁺ .
320	Cyclopropanecarboxylic acid {3-[(S)-4-(2-chloro-5-fluoro-6-methoxypyridine-3-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}amide	δ_H (d_6 -DMSO at 110°C) 9.46 (d, <i>J</i> 0.8 Hz, 1H), 7.68-7.64 (m, 1H), 7.32-7.29 (m, 3H), 7.03 (br s, 1H), 3.97 (s, 4H), 3.85 (d, <i>J</i> 11.4 Hz, 1H), 3.72-3.69 (m, 4H), 3.67-3.59 (m, 2H), 3.50 (d, <i>J</i> 7.1 Hz, 2H), 3.14-3.10 (m, 2H), 1.81-1.77 (m, 1H), 0.85-0.80 (m, 2H), 0.75-0.72 (m, 2H). LCMS (ES^+) 501 ($M+H$) ⁺ .
321	{3-[(S)-4-(2-Chloro-5-fluoro-6-methoxypyridine-3-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}carbamic acid methyl ester	δ_H (d_6 -DMSO at 110°C) 8.75 (d, <i>J</i> 1.3 Hz, 1H), 7.64-7.39 (m, 2H), 7.27-7.25 (m, 1H), 7.19-7.17 (m, 1H), 7.09-6.98 (m, 1H), 3.96 (s, 5H), 3.85 (d, <i>J</i> 11.6 Hz, 2H), 3.70 (d, <i>J</i> 14.7 Hz, 6H), 3.55-3.44 (m, 3H), 3.18-3.05 (m, 2H). LCMS (ES^+) 491 ($M+H$) ⁺ .
322	3-[(S)-4-(5-Acetylamino-6-methoxy-pyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d_6 -DMSO at 110°C) 8.81 (s, 1H), 8.09 (d, <i>J</i> 2.0 Hz, 1H), 7.66 (d, <i>J</i> 2.0 Hz, 1H), 7.49 (s, 1H), 7.35 (d, <i>J</i> 8.3 Hz, 1H), 7.18 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.08 (s, 1H), 4.34-4.31 (m, 1H), 3.96 (s, 3H), 3.93-3.89 (m, 1H), 3.83-3.76 (m, 2H), 3.76 (s, 3H), 3.60 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.56-3.45 (m, 2H), 3.20 (dd, <i>J</i> 14.7, 8.1 Hz, 1H), 3.12 (dd, <i>J</i> 14.4, 7.3 Hz, 1H), 2.97 (s, 6H), 2.13 (s, 3H). LCMS (ES^+) 494 ($M+H$) ⁺ .

EXAMPLE 323 (METHOD M)

{(S)-3-[5-(4-Methoxyphenyl)-1-methyl-1*H*-indol-3-ylmethyl]morpholin-4-yl}-(6-methoxypyridin-3-yl)-methanone

- 5 To a stirred solution of *Example 365* (193 mg, 0.48 mmol) in *n*-BuOH (4 mL) were added 4-methoxybenzeneboronic acid (109 mg, 0.72 mmol), potassium phosphate (212 mg, 1.0 mmol), XPhos (9 mg, 0.019 mmol) and Pd₂(dba)₃ (4.4 mg, 0.005 mmol). The reaction mixture was heated to reflux for 4 h, then partitioned between EtOAc (10 mL) and brine (10 mL). The organic layer was separated, dried (magnesium sulphate)
- 10 and concentrated *in vacuo*. The resulting brown oil was purified by preparative HPLC, yielding the *title compound* (40 mg, 18%) as an off-white solid. δ_{H} (d₆-DMSO at 110°C) 7.95 (d, *J* 2.0 Hz, 1H), 7.56 (s, 1H), 7.51 (d, *J* 8.6 Hz, 2H), 7.42-7.34 (m, 2H), 7.30 (dd, *J* 8.1, 1.3 Hz, 1H), 7.05 (s, 1H), 7.01 (d, *J* 8.6 Hz, 2H), 6.57 (d, *J* 8.6 Hz, 1H), 4.38-4.30 (m, 1H), 3.97-3.92 (m, 1H), 3.88-3.81 (m, 5H), 3.80 (s, 3H), 3.76 (s, 3H), 3.63 (dd, *J*
- 15 11.6, 3.0 Hz, 1H), 3.51 (d, *J* 8.8 Hz, 2H), 3.22-3.15 (m, 2H). LCMS (ES⁺) 472 (M+H)⁺.

EXAMPLES 324 TO 326

- The following compounds were prepared from *Example 365* and the appropriate
- 20 boronic acid according to *Method M*.

Example No.	Compound Name	¹ H NMR/LCMS
324	(6-Methoxypyridin-3-yl)-{(S)-3-[1-methyl-5-(pyridin-3-yl)-1 <i>H</i> -indol-3-ylmethyl]morpholin-4-yl}-methanone	δ_{H} (d ₆ -DMSO at 110°C) 8.83 (d, <i>J</i> 2.0 Hz, 1H), 8.50 (m, 1H), 7.95 (d, <i>J</i> 7.8 Hz, 1H), 7.91 (s, 1H), 7.68 (s, 1H), 7.51-7.39 (m, 3H), 7.24 (d, <i>J</i> 8.3 Hz, 1H), 7.10 (s, 1H), 6.52 (d, <i>J</i> 8.6 Hz, 1H), 4.40-4.32 (m, 1H), 3.97-3.93 (m, 1H), 3.90-3.82 (m, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.66 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.55-3.48 (m, 2H), 3.27-3.12 (m, 2H). LCMS (ES ⁺) 443 (M+H) ⁺ .
325	(6-Methoxypyridin-3-yl)-{(S)-3-[1-methyl-5-(6-methylpyridin-3-yl)-1 <i>H</i> -indol-3-ylmethyl]morpholin-4-yl}-methanone	δ_{H} (d ₆ -DMSO at 110°C) 8.69 (d, <i>J</i> 2.2 Hz, 1H), 7.92 (d, <i>J</i> 1.9 Hz, 1H), 7.83 (dd, <i>J</i> 8.0, 2.4 Hz, 1H), 7.64 (s, 1H), 7.45 (d, <i>J</i> 8.5 Hz, 1H), 7.40 (dd, <i>J</i> 8.5, 1.6 Hz, 1H), 7.28-7.25 (m, 2H), 7.08 (s, 1H), 6.53 (d, <i>J</i> 8.5 Hz, 1H), 4.35-4.30 (m, 1H), 4.10-3.91

		(m, 4H), 3.86-3.82 (m, 2H), 3.77 (s, 6H), 3.65 (dd, <i>J</i> 11.5, 3.1 Hz, 1H), 3.55-3.49 (m, 2H), 3.21-3.18 (m, 2H). LCMS (ES ⁺) 457 (M+H) ⁺ .
326	{(S)-3-[5-(Benzo[1,3]dioxol-5-yl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]-morpholin-4-yl}-(6-methoxypyridin-3-yl)-methanone	δ_{H} (d ₆ -DMSO at 110°C) 7.93 (s, 1H), 7.55 (s, 1H), 7.41-7.31 (m, 2H), 7.30-7.23 (m, 1H), 7.15-7.02 (m, 3H), 6.93 (m, 1H), 6.55 (d, <i>J</i> 8.3 Hz, 1H), 6.02 (s, 2H), 4.39-4.29 (m, 1H), 4.00-3.91 (m, 1H), 3.89-3.73 (m, 7H), 3.68-3.61 (m, 1H), 3.56-3.47 (m, 3H), 3.18 (d, <i>J</i> 7.6 Hz, 2H). LCMS (ES ⁺) 486 (M+H) ⁺ .

EXAMPLE 327 (METHOD N)

Di(1-propanesulfonic acid) {3-[(S)-4-(6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indol-5-yl}amide

To a stirred solution of *Intermediate 21* (100 mg, 0.26 mmol) in DCM (3 mL) was added TEA (54 μ L, 0.39 mmol), followed by 1-propanesulfonyl chloride (29 μ L, 0.26 mmol). The reaction mixture was stirred at r.t. for 2 h, then diluted with DCM (10 mL) and washed with brine (2 x 10 mL). The aqueous layer was extracted with DCM (20 mL). The combined organic layers were dried (phase separator) and concentrated *in vacuo*. The residue was purified by preparative HPLC, yielding the *title compound* (4 mg, 3%) as an off-white solid. δ_{H} (d₆-DMSO at 110°C) 8.03 (d, *J* 2.0 Hz, 1H), 7.66 (d, *J* 1.8 Hz, 1H), 7.46-7.41 (m, 2H), 7.18-7.14 (m, 2H), 6.71 (d, *J* 8.6 Hz, 1H), 4.38-4.29 (m, 1H), 3.94-3.87 (m, 4H), 3.83-3.78 (m, 1H), 3.78 (s, 3H), 3.75-3.68 (m, 1H), 3.64-3.57 (m, 5H), 3.57-3.48 (m, 2H), 3.29-3.21 (m, 1H), 3.15-3.07 (m, 1H), 1.94-1.83 (m, 4H), 1.04 (t, *J* 7.6 Hz, 6H). LCMS (ES⁺) 593 (M+H)⁺.

EXAMPLES 328 TO 333

The following compounds were prepared from the relevant precursor amine and the appropriate sulfonyl chloride according to *Method N*.

Example No.	Compound Name	¹ H NMR/LCMS
328	<i>N</i> -{3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-	δ_{H} (d ₆ -DMSO at 110°C) 7.91 (d, <i>J</i> 2.0 Hz, 1H), 7.37 (d, <i>J</i> 1.5 Hz, 1H), 7.32 (d, <i>J</i> 8.6 Hz, 2H), 7.08 (dd, <i>J</i> 8.6, 1.8

	methyl-1 <i>H</i> -indol-5-yl}methanesulfonamide	Hz, 1H), 7.03 (s, 1H), 6.66 (d, <i>J</i> 8.3 Hz, 1H), 4.33-4.24 (m, 1H), 3.95-3.90 (m, 1H), 3.89 (s, 3H), 3.83 (m, 1H), 3.80-3.75 (m, 1H), 3.73 (s, 3H), 3.62 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.55-3.45 (m, 2H), 3.12 (d, <i>J</i> 7.6 Hz, 2H), 2.89 (s, 3H). LCMS (ES ⁺) 459 (M+H) ⁺ .
329	<i>N</i> -{3-[(<i>S</i>)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}-4-methylbenzenesulfonamide	δ_{H} (d ₆ -DMSO at 110°C) 7.97 (d, <i>J</i> 2.0 Hz, 1H), 7.60 (d, <i>J</i> 8.3 Hz, 2H), 7.37 (dd, <i>J</i> 8.6, 2.3 Hz, 1H), 7.26 (d, <i>J</i> 7.8 Hz, 2H), 7.21-7.17 (m, 2H), 6.97 (s, 1H), 6.87 (dd, <i>J</i> 8.8, 2.0 Hz, 1H), 6.68 (dd, <i>J</i> 8.3, 0.5 Hz, 1H), 4.28-4.20 (m, 1H), 3.93-3.87 (m, 4H), 3.73 (m, 2H), 3.67 (s, 3H), 3.56 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.51-3.42 (m, 2H), 3.12-3.00 (m, 2H), 2.33 (s, 3H). LCMS (ES ⁺) 535 (M+H) ⁺ .
330	<i>N,N</i> -Dimethyl- <i>N'</i> -{3-[(<i>S</i>)-4-(6-methoxypyridine-3-carbonyl)-morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indol-5-yl}sulfuric diamide	δ_{H} (d ₆ -DMSO at 110°C) 7.97 (d, <i>J</i> 2.3 Hz, 1H), 7.41-7.36 (m, 2H), 7.29 (d, <i>J</i> 8.3 Hz, 1H), 7.10 (dd, <i>J</i> 8.6, 2.0 Hz, 1H), 7.01 (s, 1H), 6.69 (d, <i>J</i> 8.6 Hz, 1H), 4.34-4.27 (m, 1H), 3.94-3.87 (m, 4H), 3.84-3.74 (m, 2H), 3.72 (s, 3H), 3.60 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.54-3.47 (m, 2H), 3.19-3.05 (m, 2H), 2.71 (s, 6H). LCMS (ES ⁺) 488 (M+H) ⁺ .
331	<i>N</i> -(1-{1-Methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carbonyl}-piperidin-4-yl)methanesulfonamide	δ_{H} (d ₆ -DMSO at 110°C) 8.18 (s, 1H), 7.47 (s, 1H), 7.40 (dd, <i>J</i> 8.3, 0.5 Hz, 1H), 7.31-7.29 (m, 1H), 7.17 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.11-7.09 (m, 2H), 6.78 (s, 1H), 4.30-4.20 (m, 1H), 4.00-3.89 (m, 3H), 3.82 (d, <i>J</i> 11.6 Hz, 1H), 3.80-3.76 (m, 1H), 3.76 (s, 3H), 3.61 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.54-3.44 (m, 3H), 3.22-3.07 (m, 4H), 2.93 (s, 3H), 2.45 (s, 3H), 1.92-1.87 (m, 2H), 1.55-1.44 (m, 2H). LCMS (ES ⁺) 554 (M+H) ⁺ .
332	3-{(<i>S</i>)-4-[5-(Methanesulfonylamino)pyridine-3-carbonyl]-morpholin-3-ylmethyl}-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_{H} (d ₆ -DMSO at 110°C) 9.80-9.49 (m, 1H), 8.43 (d, <i>J</i> 2.3 Hz, 1H), 8.06 (d, <i>J</i> 1.0 Hz, 1H), 7.51 (s, 1H), 7.44 (t, <i>J</i> 2.0 Hz, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.19 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.10 (s, 1H), 4.37-4.24 (m, 1H), 3.99-3.87 (m, 1H), 3.84-3.70 (m, 5H), 3.60 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.55-3.49 (m, 2H), 3.25 (dd, <i>J</i> 14.4, 8.1 Hz, 1H), 3.12 (dd, <i>J</i> 14.4, 7.1 Hz, 1H), 3.02 (s, 3H), 3.00 (s, 6H). LCMS (ES ⁺) 500 (M+H) ⁺ .

333	3-[(S)-4-(6-Methoxypyridine-3-sulfonyl)morpholin-3-ylmethyl]-1-methyl-1 <i>H</i> -indole-5-carboxylic acid dimethylamide	δ_H (d_6 -DMSO at 110°C) 7.47-7.42 (m, 1H), 7.41 (d, <i>J</i> 1.1 Hz, 1H), 7.21 (d, <i>J</i> 8.5 Hz, 1H), 7.00 (dd, <i>J</i> 8.5, 1.5 Hz, 1H), 7.00 (s, 1H), 6.84-6.79 (m, 2H), 3.74-3.68 (m, 1H), 3.61 (s, 3H), 3.59-3.58 (m, 1H), 3.53 (s, 3H), 3.37 (d, <i>J</i> 11.6 Hz, 1H), 3.30-3.26 (m, 1H), 3.21-3.12 (m, 1H), 3.06-2.94 (m, 3H), 2.79 (s, 6H), 2.55 (dd, <i>J</i> 14.4, 5.3 Hz, 1H). LCMS (ES^+) 472 ($M+H$) ⁺ .
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EXAMPLES 334 TO 337 (METHOD O)

To a stirred solution of the relevant amine precursor (0.07 mmol) and TEA (0.14 mmol) in DCM (5 mL) was added acetic anhydride (0.14 mmol). The reaction mixture was stirred at r.t. for 1 h, then partitioned between DCM (10 mL) and water (10 mL). The aqueous layer was extracted with DCM (2 x 10 mL) and the combined organic layers were dried (sodium sulphate) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 20-50% MeOH/EtOAc), yielding the *title compound*.

10

Example No.	Compound Name	¹ H NMR/LCMS
334	1-(4-{1-Methyl-3-[(S)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carbonyl}-piperazin-1-yl)ethanone	δ_H (d_6 -DMSO at 110°C) 8.18 (s, 1H), 7.54 (s, 1H), 7.42 (d, <i>J</i> 8.3 Hz, 1H), 7.31 (m, 1H), 7.22 (d, <i>J</i> 8.6 Hz, 1H), 7.13-7.08 (m, 2H), 4.32-4.23 (m, 1H), 3.93 (d, <i>J</i> 7.6 Hz, 1H), 3.82 (m, 1H), 3.79-3.73 (m, 4H), 3.61 (dd, <i>J</i> 11.6, 3.0 Hz, 1H), 3.57-3.47 (m, 7H), 3.25-3.10 (m, 3H), 2.46 (s, 4H), 2.04 (m, 4H). LCMS (ES^+) 504 ($M+H$) ⁺ .
335	<i>N</i> -[(S)-1-{1-Methyl-3-[(S)-4-(6-methylpyridine-3-carbonyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carbonyl}pyrrolidin-3-ylmethyl]-acetamide	δ_H (d_6 -DMSO at 110°C) 8.21 (s, 1H), 7.61 (s, 1H), 7.54 (s, 1H), 7.38 (d, <i>J</i> 8.3 Hz, 1H), 7.31-7.29 (m, 2H), 7.10-7.09 (m, 2H), 4.30-4.20 (m, 1H), 3.96-3.89 (m, 1H), 3.82 (d, <i>J</i> 11.6 Hz, 1H), 3.80-3.76 (m, 1H), 3.76 (s, 3H), 3.61-3.58 (m, 2H), 3.55-3.44 (m, 4H), 3.25-3.05 (m, 5H), 2.45 (s, 3H), 2.39-2.32 (m, 1H), 2.00-1.93 (m, 1H), 1.81 (s, 3H), 1.68-1.58 (m, 1H). LCMS (ES^+) 518 ($M+H$) ⁺ .
336	<i>N</i> -[(<i>R</i>)-1-{1-Methyl-3-[(S)-4-(6-methylpyridine-3-carbonyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-	δ_H (d_6 -DMSO at 110°C) 8.20 (s, 1H), 7.61 (s, 1H), 7.54 (s, 1H), 7.38 (d, <i>J</i> 8.6 Hz, 1H), 7.32-7.29 (m, 2H), 7.11-7.09 (m, 2H), 4.30-4.20 (m, 1H), 3.96-3.89 (m, 1H), 3.82 (d, <i>J</i> 11.6 Hz,

	carbonyl}pyrrolidin-3-ylmethyl]-acetamide	1H), 3.80-3.76 (m, 1H), 3.76 (s, 3H), 3.63-3.58 (m, 2H), 3.55-3.45 (m, 4H), 3.26-3.05 (m, 5H), 2.45 (s, 3H), 2.39-2.32 (m, 1H), 2.00-1.93 (m, 1H), 1.80 (s, 3H), 1.67-1.58 (m, 1H). LCMS (ES ⁺) 518 (M+H) ⁺ .
337	<i>N</i> -(1-{1-Methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indole-5-carbonyl}-piperidin-4-yl)acetamide	δ_{H} (d ₆ -DMSO at 110°C) 8.19 (s, 1H), 7.47 (s, 1H), 7.42 (s, 1H), 7.40 (d, <i>J</i> 8.3 Hz, 1H), 7.18-7.15 (m, 1H), 7.10-7.09 (m, 2H), 4.30-4.20 (m, 1H), 3.99-3.91 (m, 3H), 3.88-3.76 (m, 3H), 3.76 (s, 3H), 3.60 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.54-3.46 (m, 2H), 3.22-3.06 (m, 4H), 2.44 (s, 3H), 1.82 (s, 3H), 1.78-1.76 (m, 2H), 1.44-1.36 (m, 2H). LCMS (ES ⁺) 518 (M+H) ⁺ .

EXAMPLE 338 (METHOD P)

N-Methyl-*N*-(1-methyl-3-[(*S*)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1*H*-indol-5-ylmethyl)acetamide

5 To a stirred solution of *Intermediate 37* (240 mg, 0.64 mmol) in 10:1 DCM:AcOH (10 mL) were added methylamine (33% in EtOH; 0.15 mL, 1.28 mmol) and PS-BH₃CN (428 mg, 1.5 mmol). The reaction mixture was stirred for 72 h, then filtered. The filtrate was concentrated *in vacuo*. The residue was treated with acetic anhydride (0.5 mL, 6.4 mmol) and DMAP (10 mg). The reaction mixture was stirred at r.t. for 30 minutes, then
10 partitioned between DCM (25 mL) and water (50 mL). The organic layer was dried (phase separator) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (81 mg, 29%) as a white solid. δ_{H} (d₆-DMSO at 110°C) 8.19 (s, 1H), 7.33-7.25 (m, 3H), 7.11 (d, *J* 7.9 Hz, 1H), 7.02-7.00 (m, 2H), 4.54 (s, 2H),
15 4.28-4.24 (m, 1H), 3.94-3.91 (m, 1H), 3.81-3.79 (m, 2H), 3.72 (s, 3H), 3.60 (dd, *J* 11.5, 3.2 Hz, 1H), 3.54-3.47 (m, 2H), 3.20-3.07 (m, 2H), 2.84 (s, 3H), 2.46 (s, 3H), 2.08 (s, 3H). LCMS (ES⁺) 435 (M+H)⁺.

EXAMPLES 339 TO 343

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The following compounds were prepared from *Intermediate 37* and the appropriate amine according to *Method P*.

Example No.	Compound Name	¹ H NMR/LCMS
339	4-(<i>N</i> -Acetyl- <i>N</i> -{1-methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indol-5-ylmethyl}amino)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	δ_H (d ₆ -DMSO at 110°C) 8.20 (m, 1H), 7.35-7.25 (m, 3H), 7.13 (d, <i>J</i> 7.8 Hz, 1H), 7.03 (dd, <i>J</i> 8.1, 0.8 Hz, 1H), 7.00 (s, 1H), 4.54 (s, 2H), 4.29-4.21 (m, 1H), 4.18-4.09 (m, 1H), 4.00-3.89 (m, 3H), 3.82-3.76 (m, 2H), 3.72 (s, 3H), 3.58 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.49 (m, 2H), 3.21-3.13 (m, 1H), 3.12-3.04 (m, 1H), 2.98-2.96 (m, 2H), 2.78-2.65 (m, 3H), 2.07 (s, 3H), 1.63-1.55 (m, 4H), 1.38 (s, 9H). LCMS (ES ⁺) 604 (M+H) ⁺ .
340	<i>N</i> -Cyclobutyl- <i>N</i> -{1-methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indol-5-ylmethyl}acetamide	δ_H (d ₆ -DMSO at 110°C) 8.21 (d, <i>J</i> 1.5 Hz, 1H), 7.35-7.27 (m, 2H), 7.23 (s, 1H), 7.13 (d, <i>J</i> 8.1 Hz, 1H), 7.01-6.96 (m, 2H), 4.64 (s, 2H), 4.57-4.44 (m, 1H), 4.29-4.19 (m, 1H), 3.92 (m, 1H), 3.83-3.74 (m, 2H), 3.72 (s, 3H), 3.58 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.52-3.47 (m, 2H), 3.22-3.13 (m, 1H), 3.09-3.03 (m, 1H), 2.48 (s, 3H), 2.15-2.01 (m, 7H), 1.62-1.48 (m, 2H). LCMS (ES ⁺) 475 (M+H) ⁺ .
341	<i>N</i> -Cyclopentyl- <i>N</i> -{1-methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indol-5-ylmethyl}acetamide	δ_H (d ₆ -DMSO at 110°C) 8.26-8.18 (m, 1H), 7.35-7.23 (m, 3H), 7.13 (d, <i>J</i> 7.8 Hz, 1H), 7.05-6.94 (m, 2H), 4.54 (s, 2H), 4.50-4.39 (m, 1H), 4.30-4.19 (m, 1H), 3.97-3.89 (m, 1H), 3.76 (m, 5H), 3.58 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.54-3.45 (m, 2H), 3.15-3.01 (m, 3H), 2.47 (s, 2H), 2.04 (s, 3H), 1.79-1.70 (m, 2H), 1.67-1.42 (m, 6H). LCMS (ES ⁺) 489 (M+H) ⁺ .
342	<i>N</i> -Cyclohexyl- <i>N</i> -{1-methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)-morpholin-3-ylmethyl]-1 <i>H</i> -indol-5-ylmethyl}acetamide	δ_H (d ₆ -DMSO at 110°C) 8.24-8.18 (m, 1H), 7.36-7.24 (m, 3H), 7.13 (d, <i>J</i> 7.8 Hz, 1H), 7.04 (dd, <i>J</i> 8.6, 1.3 Hz, 1H), 6.99 (s, 1H), 4.55 (s, 2H), 4.29-4.20 (m, 1H), 3.92 (m, 1H), 3.81-3.74 (m, 2H), 3.72 (s, 3H), 3.58 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.52-3.47 (m, 2H), 3.24-3.15 (m, 2H), 3.10-3.03 (m, 1H), 2.48 (s, 3H), 2.04 (s, 3H), 1.73-1.60 (m, 4H), 1.60-1.52 (m, 1H), 1.51-1.36 (m, 2H), 1.35-1.20 (m, 2H), 1.11-0.97 (m, 1H). LCMS (ES ⁺) 502 (M+H) ⁺ .
343	<i>N</i> -{1-Methyl-3-[(<i>S</i>)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1 <i>H</i> -indol-5-ylmethyl}- <i>N</i> -(tetrahydropyran-4-yl)acetamide	δ_H (d ₆ -DMSO at 110°C) 8.24-8.17 (m, 1H), 7.35-7.26 (m, 3H), 7.13 (d, <i>J</i> 7.8 Hz, 1H), 7.04 (dd, <i>J</i> 8.3, 1.3 Hz, 1H), 6.99 (s, 1H), 4.57 (s, 2H), 4.30-4.17 (m, 2H), 3.92 (m, 1H), 3.87-3.74 (m, 4H), 3.72 (s, 3H), 3.58

		(dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.52-3.44 (m, 2H), 3.38-3.26 (m, 2H), 3.18 (m, 1H), 3.09 (m, 1H), 2.48 (s, 3H), 2.07 (s, 3H), 1.82-1.66 (m, 2H), 1.59-1.50 (m, 2H). LCMS (ES ⁺) 505 (M+H) ⁺ .
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EXAMPLE 344 (METHOD Q)

(6-Methylpyridin-3-yl)-{(S)-3-[1-methyl-5-(thiophene-2-carbonyl)-1*H*-indol-3-ylmethyl]-morpholin-4-yl}-methanone

To a stirred solution of *Example 376* (190 mg, 0.44 mmol) in THF (1 mL) at -70°C under nitrogen was added 2-thienylmagnesium bromide (1M solution in THF; 874 μL, 0.087 mmol) dropwise. The reaction mixture was allowed to warm to r.t. and stirred for 16 h, then partitioned between DCM (10 mL) and brine (10 mL). The aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were dried (sodium sulphate), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-3% MeOH/DCM), and further purified by preparative HPLC, yielding the *title compound* (145 mg, 72%) as a yellow solid. δ_H (d₆-DMSO at 110°C) 8.14 (s, 1H), 8.02 (s, 1H), 7.96 (dd, *J* 5.1, 0.8 Hz, 1H), 7.73 (dd, *J* 3.5, 0.8 Hz, 1H), 7.70 (dd, *J* 8.6, 1.5 Hz, 1H), 7.52 (d, *J* 8.6 Hz, 1H), 7.28-7.18 (m, 3H), 7.02 (d, *J* 7.8 Hz, 1H), 4.33-4.26 (m, 1H), 3.96-3.90 (m, 1H), 3.87-3.77 (m, 5H), 3.65 (dd, *J* 11.6, 3.3 Hz, 1H), 3.53-3.47 (m, 2H), 3.21 (d, *J* 7.6 Hz, 2H), 2.38 (s, 3H). LCMS (ES⁺) 460 (M+H)⁺.

EXAMPLES 345 TO 347

The following compounds were prepared from *Example 376* and the appropriate Grignard reagent according to *Method Q*.

Example No.	Compound Name	¹ H NMR/LCMS
345	{(S)-3-[5-(3,4-Dimethoxybenzoyl)-1-methyl-1 <i>H</i> -indol-3-ylmethyl]-morpholin-4-yl}-(6-methylpyridin-3-yl)-methanone	δ _H (d ₆ -DMSO at 110°C) 8.13 (s, 1H), 7.88 (s, 1H), 7.60 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.49 (m, 1H), 7.40-7.37 (m, 1H), 7.35 (dd, <i>J</i> 8.1, 2.0 Hz, 1H), 7.23 (d, <i>J</i> 7.3 Hz, 1H), 7.17 (s, 1H), 7.09 (d, <i>J</i> 8.3 Hz, 1H), 7.04 (d, <i>J</i> 7.8 Hz, 1H), 4.33-4.24 (m, 1H), 3.94-3.87 (m, 4H), 3.86-3.75 (m, 8H), 3.63 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.52-3.46 (m, 2H), 3.18 (dd, <i>J</i> 7.6, 3.3 Hz,

		2H), 2.40 (s, 3H). LCMS (ES ⁺) 514 (M+H) ⁺ .
346	{(S)-3-[1-Methyl-5-(3-methylthiophene-2-carbonyl)-1H-indol-3-ylmethyl]morpholin-4-yl}-(6-methylpyridin-3-yl)-methanone	δ_H (d ₆ -DMSO at 110°C) 8.17 (s, 1H), 7.92 (s, 1H), 7.73 (d, <i>J</i> 5.1 Hz, 1H), 7.61 (dd, <i>J</i> 8.3, 1.5 Hz, 1H), 7.48 (m, 1H), 7.28-7.23 (m, 1H), 7.18 (s, 1H), 7.09 (d, <i>J</i> 5.1 Hz, 1H), 7.04 (d, <i>J</i> 7.8 Hz, 1H), 4.31-4.24 (m, 1H), 3.94-3.89 (m, 1H), 3.86-3.75 (m, 5H), 3.63 (dd, <i>J</i> 11.4, 3.0 Hz, 1H), 3.52-3.46 (m, 2H), 3.19 (d, <i>J</i> 7.3 Hz, 2H), 2.41 (s, 3H), 2.36 (s, 3H). LCMS (ES ⁺) 474 (M+H) ⁺ .
347	{(S)-3-[5-(5-Chlorothiophene-2-carbonyl)-1-methyl-1H-indol-3-ylmethyl]morpholin-4-yl}-(6-methylpyridin-3-yl)-methanone	δ_H (d ₆ -DMSO at 110°C) 8.13 (s, 1H), 8.02 (d, <i>J</i> 0.5 Hz, 1H), 7.68 (dd, <i>J</i> 8.6, 1.5 Hz, 1H), 7.61 (d, <i>J</i> 4.0 Hz, 1H), 7.53 (d, <i>J</i> 8.6 Hz, 1H), 7.26-7.19 (m, 3H), 7.04 (d, <i>J</i> 7.8 Hz, 1H), 4.34-4.26 (m, 1H), 3.96-3.91 (m, 1H), 3.87-3.76 (m, 5H), 3.65 (dd, <i>J</i> 11.6, 3.3 Hz, 1H), 3.54-3.48 (m, 2H), 3.21 (dd, <i>J</i> 7.6, 2.3 Hz, 2H), 2.39 (s, 3H). LCMS (ES ⁺) 495 (M+H) ⁺ .

EXAMPLE 348

3-{(S)-4-[6-Methoxy-5-(trifluoromethyl)pyridine-3-carbonyl]morpholin-3-ylmethyl}-1-methyl-1H-indole-5-carboxylic acid dimethylamide

To a stirred solution of *Example 133* (200 mg, 0.4 mmol) in DCM (5 mL) was added a solution of sodium hydroxide (500 mg) in MeOH (5 mL). The resulting mixture was stirred for 0.5 h at r.t. prior to the addition of water (10 mL) and DCM (10 mL). The organic layer was separated, dried (magnesium sulphate), concentrated *in vacuo* and chromatographed (SiO₂, 75% EtOAc/hexanes + 1% MeOH), yielding the *title compound* (95 mg, 50%) as a white solid after freeze-drying with 1:1 MeCN-water. δ_H (d₆-DMSO at 110°C) 8.16 (s, 1H), 7.58-7.49 (m, 2H), 7.37 (d, *J* 8.6 Hz, 1H), 7.18 (dd, *J* 8.3, 1.3 Hz, 1H), 7.11 (s, 1H), 4.31-4.23 (m, 1H), 4.00 (s, 3H), 3.95 (d, *J* 7.8 Hz, 1H), 3.89-3.84 (m, 1H), 3.82-3.78 (m, 1H), 3.76 (s, 3H), 3.69 (dd, *J* 11.4, 3.0 Hz, 1H), 3.60-3.49 (m, 2H), 3.27-3.18 (m, 1H), 3.17-3.10 (m, 1H), 2.96 (s, 6H). LCMS (ES⁺) 505 (M+H)⁺.

EXAMPLE 349**3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid**

5 To a stirred solution of *Example 263* (1.19 g, 2.0 mmol) in MeOH (30 mL) was added sodium hydroxide solution (2M, 2.0 mL, 4.0 mmol). The reaction mixture was heated at reflux for 15 minutes. A further excess of sodium hydroxide solution (2M, 20 mL) was added and the reaction heated under reflux for 0.5 h. The reaction mixture was cooled and concentrated *in vacuo*. The aqueous residue was acidified using HCl (2M, 25
10 mL) to pH 2. The gummy solid was dissolved in DCM, dried (magnesium sulphate) and concentrated *in vacuo*, yielding the *title compound* (690 mg, 84%) as a brown oil. δ_{H} (d_6 -DMSO at 110°C) 11.79-11.34 (m, 1H), 8.10 (s, 1H), 7.89 (s, 1H), 7.76 (d, *J* 8.6 Hz, 1H), 7.41 (d, *J* 8.6 Hz, 1H), 7.31 (d, *J* 8.1 Hz, 1H), 7.14 (s, 1H), 6.59 (d, *J* 8.6 Hz, 1H), 4.37-4.30 (m, 1H), 3.94 (d, *J* 7.6 Hz, 1H), 3.88-3.77 (m, 8H), 3.65 (dd, *J* 11.4, 2.8 Hz, 1H),
15 3.50 (d, *J* 8.6 Hz, 2H), 3.23-3.16 (m, 2H). LCMS (ES^+) 408 ($\text{M}+\text{H}$)⁺.

EXAMPLE 350**3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1H-indole-7-carboxylic acid methyl ester**

20 To a stirred solution of *Intermediate 15* (332 mg, 1.00 mmol) in DMF (5 mL) were added 2-amino-5-chloro-3-iodobenzoic acid methyl ester (311 mg, 1.00 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), LiCl (42 mg, 1.00 mmol) and sodium carbonate (212 mg, 2.00 mmol). The reaction mixture was heated at 100°C for 2 h and then partitioned
25 between brine (10 mL) and ethyl acetate (10 mL). The organic layer was separated, dried (magnesium sulphate), concentrated *in vacuo* and chromatographed (SiO₂, 75% EtOAc/hexanes). To the resulting solid (290 mg, 0.56 mmol) was added HCl (4M in 1,4-dioxane, 10 mL) and the reaction mixture was stirred at r.t. for 1 h, then concentrated *in vacuo*. The residue was partitioned between aqueous sodium hydrogencarbonate solution
30 (10 mL) and ethyl acetate (10 mL). The organic layer was washed with brine (10 mL), dried (magnesium sulphate) and concentrated *in vacuo*. To the resulting residue (200 mg, 0.45 mmol) in EtOH (4 mL) were added ammonium formate (150 mg, 2.3 mmol) and 10% Pd/C (20 mg). The reaction mixture was heated under microwave irradiation at

160°C for 2 h, then filtered through celite. The residue was concentrated *in vacuo*, then chromatographed (SiO₂, 50% EtOAc/hexanes), yielding the *title compound* (70 mg, 17%) as an off-white solid. δ_{H} (d₆-DMSO at 110°C) 10.61 (s, 1H), 7.97 (s, 1H), 7.75 (d, *J* 7.6 Hz, 1H), 7.64 (d, *J* 7.6 Hz, 1H), 7.37 (m, 1H), 7.19 (s, 1H), 7.02 (t, *J* 7.6 Hz, 1H), 6.62 (d, *J* 8.6 Hz, 1H), 4.35-4.27 (m, 1H), 3.98-3.92 (m, 4H), 3.88 (s, 3H), 3.84-3.76 (m, 2H), 3.62 (dd, *J* 11.6, 3.0 Hz, 1H), 3.50 (d, *J* 8.8 Hz, 2H), 3.26-3.13 (m, 2H). LCMS (ES⁺) 410 (M+H)⁺.

EXAMPLE 351

{{(S)-3-[5-(Dimethylaminomethyl)-1-methyl-1*H*-indol-3-ylmethyl]morpholin-4-yl}-(6-methoxypyridin-3-yl)-methanone

Intermediate 16 (402 mg, 1.04 mmol) was dissolved in 4M HCl in 1,4-dioxane (10 mL). After 2 h the solution was concentrated *in vacuo*, and the residue was dissolved in ethyl acetate (10 mL) and shaken with aqueous sodium carbonate solution (10 mL). The organic layer was separated, dried (magnesium sulphate) and cooled at 0°C. TEA (285 μ L, 2 mmol) and 6-methoxynicotinoyl chloride (240 mg, 0.84 mmol) were added to the stirred solution. The reaction mixture was stirred at r.t. for 30 minutes, shaken with water (10 mL) and the organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The resulting oil was purified by preparative HPLC to afford the *title compound* (120 mg, 27%) as an off-white solid. δ_{H} (d₆-DMSO at 110°C) 7.97 (s, 1H), 7.36 (d, *J* 8.3 Hz, 1H), 7.28 (d, *J* 8.3 Hz, 1H), 7.20 (s, 1H), 7.09 (d, *J* 8.3 Hz, 1H), 6.99 (s, 1H), 6.64 (d, *J* 8.3 Hz, 1H), 4.29-4.22 (m, 1H), 3.97-3.92 (m, 1H), 3.90-3.77 (m, 5H), 3.72 (s, 3H), 3.60 (dd, *J* 11.4, 3.0 Hz, 1H), 3.49 (m, 2H), 3.44 (s, 2H), 3.17 (dd, *J* 14.4, 7.8 Hz, 1H), 3.08 (dd, *J* 14.4, 7.3 Hz, 1H), 2.18 (s, 6H). LCMS (ES⁺) 423 (M+H)⁺.

EXAMPLE 352

3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carboxylic acid *tert*-butyl ester

To *Example 349* (95 mg, 0.23 mmol) was added DMF.DBA (0.5mL). The reaction mixture was heated at 100-130°C for 20 minutes. The excess reagent was removed *in vacuo* and the residue was chromatographed (SiO₂, 75% EtOAc/hexanes),

yielding the *title compound* (74 mg, 69%) as an off-white solid. δ_{H} (d_6 -DMSO at 110°C) 8.08 (s, 1H), 7.89 (s, 1H), 7.71 (d, J 8.6 Hz, 1H), 7.39 (d, J 8.6 Hz, 1H), 7.32 (d, J 8.1 Hz, 1H), 7.14 (s, 1H), 6.61 (d, J 8.3 Hz, 1H), 4.38-4.28 (m, 1H), 3.94 (d, J 7.6 Hz, 1H), 3.88-3.76 (m, 8H), 3.65 (dd, J 11.6, 3.0 Hz, 1H), 3.57-3.45 (m, 2H), 3.24-3.13 (m, 2H), 1.59 (s, 9H). LCMS (ES^+) 466 ($\text{M}+\text{H}$)⁺.

EXAMPLE 353

[(S)-3-(5-Chloro-1H-indol-3-ylmethyl)morpholin-4-yl]-(6-methoxypyridin-3-yl)-methanone

Intermediate 6 (100 mg, 237 μmol) was dissolved in 4M HCl in 1,4-dioxane (4 mL). After 1 h the solution was concentrated *in vacuo*, and the residue was dissolved in DCM (5 mL) and shaken with aqueous sodium carbonate solution (5 mL). The organic layer was separated, dried (magnesium sulphate) and cooled at 0°C. TEA (70 μL , 0.47 mmol) and 6-methoxynicotinoyl chloride (45 mg, 261 μmol) were added to the stirred solution. The reaction mixture was stirred at r.t. for 18 h, shaken with water (10 mL) and the organic layer was separated, dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the *title compound* (77 mg, 84%) as a white solid. δ_{H} (d_6 -DMSO at 110°C) 10.75 (m, 1H), 7.96 (s, 1H), 7.38-7.27 (m, 3H), 7.16-7.13 (m, 1H), 7.02 (d, J 8.6 Hz, 1H), 6.63 (d, J 8.3 Hz, 1H), 4.31-4.24 (m, 1H), 3.94 (m, 1H), 3.90 (s, 3H), 3.85-3.75 (m, 2H), 3.62 (dd, J 11.6, 3.0 Hz, 1H), 3.55-3.42 (m, 2H), 3.18-3.07 (m, 2H). LCMS (ES^+) 386 ($\text{M}+\text{H}$)⁺.

EXAMPLES 354 & 355

1-{3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indol-5-yl}-2-methylpropan-1-one and 2,2-Dimethyl-1-{3-[(S)-4-(6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indol-5-yl}propan-1-one

To a stirred solution of *Intermediate 22* (1.1 g, 2.4 mmol) in THF (21 mL) at -78°C was added methyl iodide (3 mL) followed by a solution of LiHMDS (1M solution in hexanes, 10 mL). The reaction mixture was stirred for 20 minutes at -78°C, then allowed to warm to r.t. and stirred for 16 h. The reaction mixture was partitioned between ammonium chloride solution (100 mL) and EtOAc (100 mL). The organic layer was

separated, dried (sodium sulphate), filtered (phase separator) and concentrated *in vacuo*. The residue was treated with DCM (2 mL) and 4M HCl in 1,4-dioxane (10 mL) and stirred for 10 minutes. The reaction mixture was then partitioned between saturated sodium carbonate solution (100 mL) and EtOAc (100 mL). The organic layer was separated, dried (phase separator) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-100% EtOAc/hexanes), yielding 1-{3-[(S)-4-(6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indol-5-yl}-2-methylpropan-1-one (241 mg, 23%) as a white solid. δ_{H} (d₆-DMSO at 110°C) 8.12 (s, 1H), 7.89 (d, *J* 1.8 Hz, 1H), 7.76 (dd, *J* 8.8, 1.8 Hz, 1H), 7.44 (d, *J* 8.6 Hz, 1H), 7.28 (d, *J* 7.6 Hz, 1H), 7.15 (s, 1H), 6.58 (d, *J* 8.6 Hz, 1H), 4.38-4.29 (m, 1H), 3.95 (d, *J* 7.3 Hz, 1H), 3.89-3.77 (m, 8H), 3.72-3.63 (m, 2H), 3.57-3.47 (m, 2H), 3.28-3.14 (m, 2H), 1.16 (dd, *J* 6.6, 4.8 Hz, 6H). LCMS (ES⁺) 436 (M+H)⁺. Further purification by preparative HPLC yielded 2,2-dimethyl-1-{3-[(S)-4-(6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indol-5-yl}propan-1-one (12 mg, 1%) as a white solid. δ_{H} (d₆-DMSO at 110°C) 7.95 (m, 2H), 7.59 (dd, *J* 8.6, 1.8 Hz, 1H), 7.40 (d, *J* 8.6 Hz, 1H), 7.34 (dd, *J* 8.3, 1.8 Hz, 1H), 7.13 (s, 1H), 6.62 (d, *J* 8.3 Hz, 1H), 4.35-4.27 (m, 1H), 3.93 (d, *J* 7.6 Hz, 1H), 3.89-3.75 (m, 8H), 3.62 (dd, *J* 11.6, 3.3 Hz, 1H), 3.55-3.49 (m, 2H), 3.12-3.26 (m, 2H), 1.36 (s, 9H). LCMS (ES⁺) 450 (M+H)⁺.

PREPARATIVE EXAMPLE 356

1-Methyl-3-[(S)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-2-(trimethylsilanyl)-1H-indole-5-carboxylic acid methyl ester

To a stirred solution of *Example 277* (3.71 g, 8.0 mmol) in THF (50 mL) at -78°C was added methyl iodide (1.5 mL, 24 mmol) followed by a solution of LiHMDS (1.06M solution in THF; 15 mL, 16 mmol). The reaction mixture was stirred for 2 h at -78°C, then allowed to warm to r.t. and stirred for 2 h. The reaction mixture was partitioned between brine (100 mL) and EtOAc (100 mL). The organic layer was separated, dried (sodium sulphate) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 80-100% EtOAc/hexanes to 5% MeOH/EtOAc), yielding the *title compound* (3.489 g, 91%) as an off-white solid. δ_{H} (d₆-DMSO at 110°C) 8.25 (s, 1H), 8.11 (s, 1H), 7.79-7.77 (m, 1H), 7.44 (dd, *J* 8.8, 2.3 Hz, 1H), 7.27 (m, 1H), 7.13 (d, *J* 7.6 Hz, 1H), 4.35 (s, 1H), 3.94 (d, *J* 10.9 Hz, 1H), 3.84 (s, 3H), 3.76-3.73 (m, 1H), 3.70 (d, *J*

11.6 Hz, 1H), 3.59-3.45 (m, 3H), 3.39 (dd, *J* 14.4, 8.3 Hz, 1H), 3.23 (dd, *J* 14.4, 7.1 Hz, 1H), 2.90 (s, 3H), 2.46 (s, 3H), 0.44 (s, 9H). LCMS (ES⁺) 480 (M+H)⁺.

EXAMPLE 357

5

3-[(S)-4-(6-Methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1*H*-indole-5-carboxylic acid methyl ester

To a stirred solution of *Example 277* (1 g, 2.15 mmol) in THF (12 mL) was added HCl (4M in 1,4-dioxane, 12 mL). The reaction mixture was stirred at r.t. for 5 h, then
10 partitioned between 2M sodium carbonate solution (50 mL) and EtOAc (50 mL). The aqueous layer was washed with EtOAc (50 mL). The combined organic layers were washed with brine (50 mL), dried (sodium sulphate) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-20% MeOH/EtOAc), yielding the *title compound* (779 mg, 92%) as a yellow solid. δ_H (d₆-DMSO at 110°C) 10.90 (s,
15 1H), 8.14 (s, 1H), 8.07 (s, 1H), 7.71 (dd, *J* 8.6, 1.5 Hz, 1H), 7.41 (d, *J* 8.6 Hz, 1H), 7.21-7.18 (m, 2H), 7.01 (d, *J* 7.8 Hz, 1H), 4.32 (s, 1H), 3.97-3.89 (m, 1H), 3.86 (s, 3H), 3.83-3.81 (m, 1H), 3.79-3.77 (m, 1H), 3.65 (dd, *J* 11.6, 3.3 Hz, 1H), 3.54-3.45 (m, 2H), 3.24 (dd, *J* 14.4, 7.8 Hz, 1H), 3.18 (dd, *J* 14.7, 7.3 Hz, 1H), 2.41 (s, 3H). LCMS (ES⁺) 394 (M+H)⁺.

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EXAMPLE 358

3-[(S)-4-(6-Methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1*H*-indole-5-carboxylic acid

25 To a stirred solution of *Example 357* (769 mg, 1.94 mmol) in MeOH (20 mL) was added 10% NaOH solution (2.5M, 4 mL). The reaction mixture was heated to reflux and stirred for 5 h. The reaction mixture was cooled to r.t., acidified with 1M HCl and then concentrated *in vacuo*. The residue was washed with DCM to give a precipitate, which was washed with water, then filtered. The resulting solid was washed with DCM (10 mL)
30 and hexane (10 mL) and dried in a vacuum oven, yielding the *title compound* (642 mg, 87%) as a brown glassy solid. δ_H (d₆-DMSO at 110°C) 11.76 (br s, 1H), 10.91 (s, 1H), 8.16 (s, 1H), 8.05 (s, 1H), 7.71 (dd, *J* 8.3, 1.3 Hz, 1H), 7.39 (d, *J* 8.6 Hz, 1H), 7.22 (d, *J* 5.1 Hz, 1H), 7.16 (s, 1H), 7.02 (d, *J* 7.6 Hz, 1H), 4.31 (s, 1H), 3.94 (d, *J* 7.6 Hz, 1H), 3.83

(d, J 11.4 Hz, 1H), 3.80-3.78 (m, 1H), 3.64 (dd, J 11.4, 2.8 Hz, 1H), 3.51-3.49 (m, 2H), 3.25-3.15 (m, 2H), 2.42 (s, 3H). LCMS (ES^+) 380 ($M+H$)⁺.

EXAMPLE 359

5

{(S)-3-[5-(1,1-Dioxidoisothiazolidin-2-yl)-1-methyl-1H-indol-3-ylmethyl]morpholin-4-yl}-(6-methoxypyridin-3-yl)-methanone

To a stirred solution of *Intermediate 24* (140 mg, 0.209 mmol) in MeCN (5 mL) was added potassium carbonate (93 mg, 0.673 mmol). The reaction mixture was heated at 80°C for 3 h. The reaction mixture was allowed to cool to r.t. and then concentrated *in vacuo*. The residue was diluted with DCM (15 mL), then washed with brine (2 x 15 mL). The aqueous layer was extracted with DCM (15 mL). The combined organic layers were dried (phase separator) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 2% MeOH:EtOAc), yielding the *title compound* (103 mg, 79%) as a pale pink solid. δ_H (d_6 -DMSO at 110°C) 7.97 (d, J 2.3 Hz, 1H), 7.38-7.33 (m, 2H), 7.31-7.28 (m, 1H), 7.18 (dd, J 8.6, 2.0 Hz, 1H), 7.07 (s, 1H), 6.66 (d, J 8.6 Hz, 1H), 4.34-4.26 (m, 1H), 3.93 (d, J 7.6 Hz, 1H), 3.89 (s, 3H), 3.84-3.76 (m, 2H), 3.74 (s, 3H), 3.70 (t, J 6.6 Hz, 2H), 3.61 (dd, J 11.4, 3.0 Hz, 1H), 3.50 (d, J 9.1 Hz, 2H), 3.41-3.36 (m, 2H), 3.20-3.08 (m, 2H), 2.49-2.40 (m, 2H). LCMS (ES^+) 485 ($M+H$)⁺.

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EXAMPLE 360

7-Acetyl-3-[(S)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide

To a stirred solution of *Intermediate 27* (100 mg, 0.24 mmol), HATU (108 mg, 0.29 mmol) and dimethylamine hydrochloride (25 mg, 0.29 mmol) in DCM (10 mL) was added DIPEA (166 μ L, 0.96 mmol). The reaction mixture was stirred at r.t. for 3 h and then partitioned between water (10 mL) and DCM (5 mL). The organic layer was washed with water (2 x 10 mL), dried (phase separator) and concentrated *in vacuo*. The residue was purified by preparative HPLC, yielding the *title compound* (27 mg, 25%) as a white solid. δ_H (d_6 -DMSO at 110°C) 11.02 (s, 1H), 8.19 (s, 1H), 7.88-7.78 (m, 2H), 7.34-7.23 (m, 2H), 7.06 (d, J 7.8 Hz, 1H), 4.31-4.21 (m, 1H), 3.95-3.89 (m, 1H), 3.84-3.72 (m, 2H),

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3.61 (dd, J 11.6, 2.8 Hz, 1H), 3.57-3.45 (m, 2H), 3.22 (d, J 7.6 Hz, 2H), 3.05 (s, 6H), 2.68 (s, 3H), 2.44 (s, 3H). LCMS (ES⁺) 449 (M+H)⁺.

EXAMPLE 361

[(S)-3-(5-Benzoyl-1-methyl-1*H*-indol-3-ylmethyl)morpholin-4-yl]-(6-methoxypyridin-3-yl)-methanone

To a stirred solution of *Intermediate 29* (190 mg, 0.36 mmol) in THF (3 mL) at 0°C were added LiHMDS (1M solution; 0.5 mL, 0.50 mmol) and MeI (0.05 mL, 0.70 mmol). The solution was warmed to r.t. and stirred for 2 h. The reaction mixture was partitioned between EtOAc (20 mL) and saturated ammonium chloride solution (10 mL). The aqueous layer was separated and extracted with EtOAc (10 mL). The combined organic layers were dried (phase separator) and concentrated *in vacuo* to give a pale yellow oil, which was dissolved in DCM (1 mL) and treated with HCl (4M in 1,4-dioxane, 3 mL). The reaction mixture was stirred at r.t. for 20 minutes prior to being partitioned between EtOAc (50 mL) and saturated sodium carbonate solution (20 mL). The aqueous layer was separated and extracted with EtOAc (10 mL). The combined organic layers were dried (sodium sulphate), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-100% EtOAc/hexanes to 2% MeOH/EtOAc) to give the *title compound* (107 mg, 63%) as a white solid. δ_{H} (d₆-DMSO at 110°C) 7.91 (s, 1H), 7.85 (d, J 2.0 Hz, 1H), 7.71 (m, 2H), 7.62 (m, 2H), 7.56-7.47 (m, 3H), 7.25 (dd, J 8.6, 2.0 Hz, 1H), 7.18 (s, 1H), 6.58 (d, J 8.3 Hz, 1H), 4.32-4.24 (m, 1H), 3.94-3.89 (m, 1H), 3.86-3.77 (m, 8H), 3.65 (dd, J 11.4, 3.0 Hz, 1H), 3.53-3.43 (m, 2H), 3.21 (m, 1H), 3.12 (m, 1H). LCMS (ES⁺) 470 (M+H)⁺.

EXAMPLE 362

[(S)-3-(5-Hydroxy-1-methyl-1*H*-indol-3-ylmethyl)morpholin-4-yl]-(6-methylpyridin-3-yl)-methanone

To a stirred solution of *Intermediate 30* (1.0 g, 2.24 mmol) in EtOH (40 mL) were added NH₄HCO₂ (1.39 g, 22 mmol) and 10% Pd/C (100 mg, 0.11 mmol). The reaction mixture was heated to reflux for 2 h, then cooled and filtered through celite. The filtrate was concentrated *in vacuo*. The residue was partitioned between DCM (50 mL) and

water (50mL). The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The brown foam was purified using preparative HPLC, yielding the *title compound* (32 mg, 4%) as a white solid. δ_{H} (d_6 -DMSO at 110°C) 8.25 (s, 1H), 7.33 (d, J 7.6 Hz, 1H), 7.12 (d, J 8.6 Hz, 2H), 6.89 (s, 1H), 6.73-6.64 (m, 2H), 4.28-4.19 (m, 1H), 3.95-3.88 (m, 1H), 3.83-3.74 (m, 2H), 3.66 (s, 3H), 3.57 (dd, J 11.6, 3.0 Hz, 1H), 3.52-3.41 (m, 2H), 3.16-2.91 (m, 2H), 2.48 (s, 3H). LCMS (ES^+) 366 ($\text{M}+\text{H}$)⁺.

EXAMPLE 363

10 {(S)-3-[5-(2-Methoxyethoxy)-1-methyl-1H-indol-3-ylmethyl]morpholin-4-yl}-(6-methylpyridin-3-yl)-methanone

To a stirred solution of *Example 362* (100 mg, 0.27 mmol) and 1-bromo-2-methoxyethane (52 μL , 0.55 mmol) in THF (10 mL) was added caesium carbonate (62 mg, 0.19 mmol). The reaction mixture was heated to 90°C for 2 h, then cooled and
15 partitioned between DCM (10 mL) and water (10 mL). The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The brown oil was purified using preparative HPLC, yielding the *title compound* (25 mg, 22%) as a white solid. δ_{H} (d_6 -DMSO at 110°C) 8.21 (s, 1H), 7.28-7.21 (m, 2H), 7.08 (d, J 7.8 Hz, 1H), 6.97 (s, 1H), 6.89 (s, 1H), 6.80 (dd, J 8.8, 1.3 Hz, 1H), 4.28-4.20 (m, 1H), 4.10-4.02 (m, 2H), 3.96-3.90
20 (m, 1H), 3.80 (d, J 11.6 Hz, 2H), 3.73-3.66 (m, 5H), 3.60 (dd, J 11.4, 3.0 Hz, 1H), 3.53-3.45 (m, 2H), 3.37 (s, 3H), 3.11 (m, 2H), 2.46 (s, 3H). LCMS (ES^+) 424 ($\text{M}+\text{H}$)⁺.

EXAMPLE 364

25 2-(3-{1-Methyl-3-[(S)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1H-indol-5-yloxy}propyl)isoindole-1,3-dione

To a stirred solution of *Example 362* (100 mg, 0.27 mmol) and 2-(3-bromo-propyl)isoindole-1,3-dione (147 mL, 0.55 mmol) in THF (10 mL) was added caesium carbonate (62 mg, 0.19 mmol). The reaction mixture was heated to 90°C for 2 h, then
30 cooled and partitioned between DCM (10 mL) and water (10mL). The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The brown oil was purified using preparative HPLC, yielding the *title compound* (50 mg, 33%) as a white solid. δ_{H} (d_6 -DMSO at 110°C) 8.18 (s, 1H), 7.88-7.79 (m, 4H), 7.28-7.16 (m, 2H), 7.06

(d, J 7.8 Hz, 1H), 6.95 (s, 1H), 6.83 (s, 1H), 6.69 (d, J 8.6 Hz, 1H), 4.26-4.17 (m, 1H), 4.05-3.98 (m, 2H), 3.95-3.91 (m, 1H), 3.86-3.76 (m, 4H), 3.68 (s, 3H), 3.60 (dd, J 11.6, 3.0 Hz, 1H), 3.52-3.44 (m, 2H), 3.10-3.01 (m, 2H), 2.44 (s, 3H), 2.17-2.05 (m, 2H). LCMS (ES⁺) 553 (M+H)⁺.

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EXAMPLE 365

[(S)-3-(5-Chloro-1-methyl-1H-indol-3-ylmethyl)morpholin-4-yl]-(6-methoxypyridin-3-yl)-methanone

10 To a stirred solution of *Example 353* (1.91 g, 4.95 mmol) in THF (100 mL) at -78°C were added methyl iodide (623 μ L, 10 mmol) and LiHMDS (1M solution; 6 mL, 6 mmol). The reaction mixture was allowed to warm to r.t. prior to quenching with water. The reaction mixture was partitioned between TBME (50 mL) and brine (50 mL). The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*,
15 yielding the *title compound* (1.77 g, 90%) as a yellow oil. δ_{H} (d₆-DMSO at 110°C) 7.95 (d, J 1.8 Hz, 1H), 7.38-7.30 (m, 3H), 7.11 (s, 1H), 7.09 (dd, J 8.8, 2.0 Hz, 1H), 6.65 (d, J 8.3 Hz, 1H), 4.27 (m, 1H), 3.97-3.92 (m, 1H), 3.90 (s, 3H), 3.85-3.77 (m, 2H), 3.74 (s, 3H), 3.62 (dd, J 11.4, 3.0 Hz, 1H), 3.48 (m, 2H), 3.11 (m, 2H). LCMS (ES⁺) 400 (M+H)⁺.

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PREPARATIVE EXAMPLE 366

{(S)-3-[5-Chloro-1-methyl-2-(trimethylsilyl)-1H-indol-3-ylmethyl]morpholin-4-yl}-(6-methylpyridin-3-yl)-methanone

25 To a stirred solution of *Example 278* (218 mg, 0.49 mmol) and methyl iodide (0.09 mL, 1.48 mmol) in THF (5 mL) at -78°C was added LiHMDS (1M solution; 0.93 mL, 0.98 mmol). The reaction mixture was stirred at -78°C before being allowed to warm to r.t. The reaction mixture was partitioned between EtOAc (20 mL) and brine (20 mL). The organic layer was separated, dried (sodium sulphate) and concentrated *in vacuo*. The
30 residue was purified by column chromatography (SiO₂, 50-100% EtOAc/hexanes), yielding the *title compound* (180 mg, 93%) as a cream powder. δ_{H} (d₆-DMSO at 110°C) 8.26 (d, J 1.0 Hz, 1H), 7.47-7.35 (m, 3H), 7.21 (d, J 7.8 Hz, 1H), 7.12 (dd, J 8.8, 2.0 Hz, 1H), 4.34-4.25 (m, 1H), 3.97-3.90 (m, 1H), 3.83-3.75 (m, 4H), 3.64 (m, 1H), 3.56-3.48

(m, 3H), 3.42 (dd, *J* 14.1, 9.1 Hz, 1H), 3.05 (dd, *J* 14.1, 5.8 Hz, 1H), 2.51 (s, 3H), 0.45 (s, 9H). LCMS (ES⁺) 456 (M+H)⁺.

EXAMPLE 367

5

N-{3-[(*S*)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indol-5-yl}-*N*-methylcarbamic acid methyl ester

To a stirred solution of *Example 311* (114 mg, 0.26 mmol) in THF (5 mL) at 0°C was added sodium hydride (16 mg, 0.39 mmol). The reaction mixture was stirred at 0°C for 20 minutes prior to the addition of methyl iodide (41 mg, 0.29 mmol). The reaction mixture was allowed to warm to r.t and stirred for 2 h, then partitioned between DCM (20 mL) and water (20 mL). The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried (phase separator) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, EtOAc) to yield the *title compound* (77 mg, 66%) as a white solid. δ_{H} (d₆-DMSO at 110°C) 7.99-7.97 (m, 1H), 7.36 (dd, *J* 8.6, 2.3 Hz, 1H), 7.32 (d, *J* 8.6 Hz, 1H), 7.23-7.21 (m, 1H), 7.06 (s, 1H), 7.00 (dd, *J* 8.6, 2.0 Hz, 1H), 6.64 (d, *J* 8.3 Hz, 1H), 4.27-4.20 (m, 1H), 3.95-3.91 (m, 1H), 3.88 (s, 3H), 3.84-3.78 (m, 2H), 3.74 (s, 3H), 3.62-3.57 (m, 4H), 3.52-3.47 (m, 2H), 3.21 (s, 3H), 3.17 (dd, *J* 14.4, 7.8 Hz, 1H), 3.07 (dd, *J* 14.4, 7.1 Hz, 1H). LCMS (ES⁺) 453 (M+H)⁺.

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EXAMPLE 368

25

N-{3-[(*S*)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indol-5-yl}-*N*-methylmethanesulfonamide

To a stirred solution of *Example 328* (119 mg, 0.26 mmol) in THF (5 mL) at 0°C was added sodium hydride (16 mg, 0.39 mmol). The reaction mixture was stirred at 0°C for 20 minutes prior to the addition of methyl iodide (41 mg, 0.29 mmol). The reaction mixture was allowed to warm to r.t and stirred for 2 h, then partitioned between DCM (20 mL) and water (20 mL). The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried (phase separator) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 90% EtOAc/hexanes), followed by preparative HPLC, to yield the *title compound* (50 mg, 41%) as a white solid. δ_{H} (d₆-

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DMSO at 110°C) 7.92 (d, *J* 2.3 Hz, 1H), 7.47 (s, 1H), 7.37 (d, *J* 8.8 Hz, 1H), 7.33-7.27 (m, 1H), 7.17 (dd, *J* 8.8, 2.0 Hz, 1H), 7.09 (s, 1H), 6.63 (d, *J* 8.6 Hz, 1H), 4.22-4.32 (m, 1H), 3.96-3.91 (m, 1H), 3.88 (s, 3H), 3.81 (m, 2H), 3.75 (s, 3H), 3.63 (dd, *J* 11.6, 3.3 Hz, 1H), 3.53-3.48 (m, 2H), 3.25 (s, 3H), 3.14 (d, *J* 7.6 Hz, 2H). LCMS (ES⁺) 473 (M+H)⁺.

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EXAMPLE 369

{{(S)-3-[5-(1H-Imidazol-2-yl)-1-methyl-1H-indol-3-ylmethyl]morpholin-4-yl}}-(6-methoxypyridin-3-yl)-methanone

- 10 To a stirred solution of *Intermediate 19* (159 mg, 0.40 mmol) in EtOH (4 mL) at 0°C were added glyoxal (40% wt in water; 27 mg, 0.48 mmol) and conc. ammonia (1 mL). The reaction mixture was stirred at r.t. for 72 h prior to the addition of further glyoxal (27 mg) and ammonia (1 mL). The reaction mixture was stirred at r.t. for a further 16 h, then concentrated *in vacuo*, dissolved in MeOH and captured on a SCX cartridge.
- 15 The crude product was released using methanolic ammonia. The solution was concentrated *in vacuo* to give a brown solid which was purified by preparative HPLC to yield the *title compound* (12 mg, 7%) as a white solid. δ_{H} (d₆-DMSO at 110°C) 7.99-7.88 (m, 2H), 7.75 (dd, *J* 8.6, 1.3 Hz, 1H), 7.39 (d, *J* 8.6 Hz, 1H), 7.29-7.24 (m, 1H), 7.04 (s, 3H), 6.55 (d, *J* 8.3 Hz, 1H), 4.41-4.34 (m, 1H), 3.95 (d, *J* 7.8 Hz, 1H), 3.88 (m, 1H), 3.82
- 20 (dd, *J* 10.1, 0.8 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.68 (dd, *J* 11.6, 3.3 Hz, 1H), 3.56-3.46 (m, 2H), 3.25 (dd, *J* 14.7, 8.3 Hz, 1H), 3.19-3.09 (m, 1H). LCMS (ES⁺) 432 (M+H)⁺.

EXAMPLE 370

25

(6-Methoxypyridin-3-yl)-{{(S)-3-[5-(thiazol-2-yl)-1H-indol-3-ylmethyl]morpholin-4-yl}}-methanone

- To a degassed stirred solution of *Intermediate 35* (81 mg, 0.19 mmol), 2-(tributylstannanyl)thiazole (88 μ L, 0.28 mmol) and lithium chloride (10 mg, 0.23 mmol) in 1,4-dioxane (3 mL) was added Pd(PPh₃)₄ (11 mg, 0.01 mmol). The reaction mixture was
- 30 further degassed and then heated to reflux for 8 h. The reaction mixture was cooled to r.t. and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 60-100% EtOAc/hexanes), and further purified by preparative HPLC, to yield the *title*

compound (8 mg, 10%) as an off-white solid. δ_{H} (d_6 -DMSO at 110°C) 7.97 (s, 1H), 7.92 (d, J 1.8 Hz, 1H), 7.81 (d, J 3.3 Hz, 1H), 7.69 (dd, J 8.6, 1.8 Hz, 1H), 7.54 (d, J 3.3 Hz, 1H), 7.43 (dd, J 8.3, 0.5 Hz, 1H), 7.33-7.28 (m, 1H), 7.16 (d, J 1.5 Hz, 1H), 6.56 (d, J 8.6 Hz, 1H), 4.41-4.33 (m, 1H), 3.95 (d, J 7.6 Hz, 1H), 3.86 (m, 1H), 3.82 (d, J 9.6 Hz, 1H), 3.78 (s, 3H), 3.66 (dd, J 11.6, 3.3 Hz, 1H), 3.51 (m, 2H), 3.28-3.15 (m, 2H). LCMS (ES^+) 435 ($\text{M}+\text{H}$)⁺.

EXAMPLE 371

N-(1-Acetylpiperidin-4-yl)-*N*-{1-methyl-3-[(*S*)-4-(6-methylpyridine-3-carbonyl)-morpholin-3-ylmethyl]-1*H*-indol-5-ylmethyl}acetamide

To a stirred solution of *Example 339* (200 mg, 0.33 mmol) in MeOH (2 mL) was added 4M HCl in 1,4-dioxane (4 mL). The reaction mixture was stirred at r.t. for 16 h prior to being concentrated *in vacuo*. The reaction mixture was partitioned between DCM (25 mL) and sodium carbonate solution (25 mL). The organic layer was dried (phase separator) and concentrated *in vacuo*. To a stirred solution of the residue in acetic acid (2 mL) and acetic anhydride (400 μL) was added DMAP (5 mg). The reaction mixture was heated at 90°C for 1 h, then allowed to cool and concentrated *in vacuo*. The residue was purified by preparative HPLC, yielding the *title compound* (88 mg, 49%) as a white solid. δ_{H} (d_6 -DMSO at 110°C) 8.23-8.17 (m, 1H), 7.36-7.26 (m, 3H), 7.14 (d, J 8.1 Hz, 1H), 7.04 (dd, J 8.6, 1.3 Hz, 1H), 6.99 (s, 1H), 4.55 (d, J 2.5 Hz, 2H), 4.32-4.03 (m, 4H), 3.92 (d, J 7.3 Hz, 1H), 3.83-3.74 (m, 2H), 3.72 (s, 3H), 3.58 (dd, J 11.6, 3.3 Hz, 1H), 3.49 (d, J 8.8 Hz, 2H), 3.47-3.41 (m, 1H), 3.18 (m, 1H), 3.09 (m, 1H), 2.88-2.64 (m, 1H), 2.48 (s, 3H), 2.08 (s, 3H), 1.94 (s, 3H), 1.70-1.54 (m, 4H). LCMS (ES^+) 546 ($\text{M}+\text{H}$)⁺.

EXAMPLE 372

(6-Methoxypyridin-3-yl)-[(*S*)-3-(5-nitro-1*H*-indol-3-ylmethyl)morpholin-4-yl]-methanone

To a stirred solution of 3-[(3*S*)-morpholin-3-ylmethyl]-5-nitro-1*H*-indole (WO 2008/001076, Intermediate 39; 1.20 g, 4.61 mmol) in DCM (30 mL) and DMF (15 mL) was added triethylamine (560 mg, 5.53 mmol) followed by 6-methoxynicotinoyl chloride (867 mg, 5.07 mmol). The reaction mixture was stirred at r.t. for 16 h and then

concentrated *in vacuo*. The residue was partitioned between DCM (25 mL) and water (25 mL). The organic layer was washed with brine (2 x 25 mL), dried (phase separator) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 20-100% EtOAc/hexanes), yielding the *title compound* (1.49 g, 81%) as a yellow foam. δ_{H} (d₆-DMSO at 110°C) 8.31 (s, 1H), 8.08 (s, 1H), 8.00 (dd, *J* 9.1, 2.3 Hz, 1H), 7.55 (d, *J* 8.8 Hz, 1H), 7.32 (s, 1H), 7.26-7.20 (m, 1H), 7.03 (d, *J* 7.6 Hz, 1H), 4.37-4.29 (m, 1H), 3.98-3.91 (m, 1H), 3.88-3.78 (m, 5H), 3.68 (dd, *J* 11.6, 3.0 Hz, 1H), 3.57-3.46 (m, 2H), 3.26 (dd, *J* 14.7, 8.3 Hz, 1H), 3.18 (dd, *J* 14.4, 6.8 Hz, 1H), 2.40 (s, 3H). LCMS (ES⁺) 397 (M+H)⁺.

EXAMPLE 373

{(S)-3-[5-(1,1-Dioxo-1 Λ 6-isothiazolidin-2-yl)-1*H*-indol-3-ylmethyl]morpholin-4-yl}-(6-methoxypyridin-3-yl)-methanone

To a stirred solution of *Intermediate 39* (388 mg, 0.77 mmol) in MeCN (10 mL) was added potassium carbonate (266 mg, 1.93 mmol). The reaction mixture was stirred at 80°C for 2 h, then partitioned between DCM (20 mL) and brine (2 x 20 mL). The combined aqueous layers were extracted with DCM (2 x 30 mL). The combined organic layers were dried (phase separator) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 70-100% EtOAc/hexanes), and further purified by preparative HPLC, to yield the *title compound* (96 mg, 26%) as a white solid. δ_{H} (d₆-DMSO at 110°C) 10.47 (d, *J* 1.0 Hz, 1H), 7.81 (d, *J* 2.0 Hz, 1H), 7.21-7.10 (m, 3H), 6.98-6.93 (m, 2H), 6.48 (d, *J* 8.6 Hz, 1H), 4.19-4.12 (m, 1H), 3.77 (d, *J* 7.6 Hz, 1H), 3.73 (s, 3H), 3.68-3.60 (m, 2H), 3.53 (t, *J* 6.6 Hz, 2H), 3.46 (dd, *J* 11.6, 3.3 Hz, 1H), 3.36-3.31 (m, 2H), 3.22 (t, *J* 7.6 Hz, 2H), 2.99 (dd, *J* 7.3, 1.3 Hz, 2H), 2.32-2.23 (m, 2H). LCMS (ES⁺) 471 (M+H)⁺.

EXAMPLE 374

1-{3-[(S)-4-(6-Methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indol-5-yl}pyrrolidin-2-one

To a stirred solution of *Intermediate 40* (102 mg, 0.21 mmol) in THF (7 mL) at -10°C was added lithium bis(trimethylsilyl)amide (0.50 mL, 0.53 mmol). The reaction

mixture was stirred for 1.5 h, then allowed to warm to r.t. and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 5-20% MeOH/EtOAc), and further purified by preparative HPLC, yielding the *title compound* (30 mg, 32%) as an off-white solid. δ_{H} (d₆-DMSO at 110°C) 7.95 (d, *J* 2.3 Hz, 1H), 7.49 (dd, *J* 8.8, 2.0 Hz, 1H), 7.40 (s, 1H), 7.35-7.27 (m, 2H), 7.03 (s, 1H), 6.63 (d, *J* 8.3 Hz, 1H), 4.32-4.24 (m, 1H), 3.96-3.90 (m, 1H), 3.88 (s, 3H), 3.84-3.77 (m, 4H), 3.73 (s, 3H), 3.62 (dd, *J* 11.6, 3.3 Hz, 1H), 3.53-3.46 (m, 2H), 3.13 (d, *J* 7.6 Hz, 2H), 2.47 (d, *J* 8.3 Hz, 2H), 2.18-2.06 (m, 2H). LCMS (ES⁺) 449 (M+H)⁺.

EXAMPLE 375

3-[(S)-4-(2-Methoxythiazole-5-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

To a stirred solution of *Example 157* (90 mg, 0.2 mmol) in MeOH (1 mL) was added sodium methoxide (12 mg, 0.22 mmol). The reaction mixture was stirred at r.t. for 30 minutes. Sodium methoxide (5 mg, 0.10 mmol) was added and the reaction mixture was heated at 50°C for 1.5 h. The reaction mixture was concentrated *in vacuo* and then partitioned between DCM (5 mL) and saturated ammonium chloride solution (2 mL). The aqueous layer was extracted with DCM (1 mL). The combined organic layers were dried (phase separator) and concentrated *in vacuo*. The white foam was purified using preparative HPLC, yielding the *title compound* (38 mg, 43%) as a white solid. δ_{H} (d₆-DMSO at 110°C) 7.61 (s, 1H), 7.38 (d, *J* 8.3 Hz, 1H), 7.30 (s, 1H), 7.20 (dd, *J* 8.3, 1.5 Hz, 1H), 7.14 (s, 1H), 4.52-4.45 (m, 1H), 4.03-3.93 (m, 5H), 3.84 (d, *J* 11.6 Hz, 1H), 3.75 (s, 3H), 3.59 (dd, *J* 11.6, 3.0 Hz, 1H), 3.56-3.44 (m, 2H), 3.24 (dd, *J* 14.4, 7.8 Hz, 1H), 3.15-3.10 (m, 1H), 3.00 (s, 6H). LCMS (ES⁺) 443 (M+H)⁺.

EXAMPLE 376

1-Methyl-3-[(S)-4-(6-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid N-methoxy-N-methylamide

To a stirred solution of *Intermediate 33* (3.1 g, 7.89 mmol) in THF (30 mL) were added 2-chloro-4,6-dimethoxy-[1,3,5]triazine (1.66 g, 9.46 mmol) and DIPEA (3.9 mL, 23.64 mmol). The reaction mixture was stirred at r.t. for 1 h. *N,O*-Dimethylhydroxyl-

amine hydrochloride (0.77 g, 7.9 mmol) was added and the reaction mixture was stirred for 18 h. The reaction was not complete, so further DIPEA (1 mL, 6.1 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (0.29 g, 2.97 mmol) were added and the reaction mixture was stirred for a further 18 h prior to pouring over ice-water. The solution was extracted with EtOAc (100 mL) and DCM (2 x 100 mL). The combined organic layers were dried (sodium sulphate), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-3% MeOH/DCM), yielding the *title compound* (2.6 g, 76%) as a white solid. δ_{H} (d₆-DMSO at 110°C) 8.21 (d, *J* 1.5 Hz, 1H), 7.77 (s, 1H), 7.45 (dd, *J* 8.3, 1.5 Hz, 1H), 7.42-7.37 (m, 1H), 7.31 (d, *J* 7.3 Hz, 1H), 7.13-7.08 (m, 2H), 4.33-4.24 (m, 1H), 3.93 (d, *J* 7.6 Hz, 1H), 3.82 (d, *J* 11.4 Hz, 1H), 3.77 (s, 4H), 3.64-3.56 (m, 5H), 3.27 (s, 3H), 3.22 (dd, *J* 14.4, 7.6 Hz, 1H), 3.14 (dd, *J* 14.4, 7.3 Hz, 1H), 2.45 (s, 3H). LCMS (ES⁺) 437 (M+H)⁺.

EXAMPLE 377 (METHOD R)

(6-Methylpyridin-3-yl)-{(S)-3-[1-methyl-5-(thiazole-2-carbonyl)-1*H*-indol-3-ylmethyl]-morpholin-4-yl}-methanone

To a stirred solution of *Example 376* (200 mg, 0.46 mmol) and thiazole (40 μ L, 0.56 mmol) in THF (0.2 mL) at -78°C was added *n*-butyllithium (2.5M; 62 μ L, 0.16 mmol) dropwise. The reaction mixture was allowed to warm to r.t. and stirred for 16 h, then partitioned between DCM (10 mL) and water (10 mL). The aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were dried (sodium sulphate), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-3% MeOH/DCM), and further purified by preparative HPLC, yielding the *title compound* (44 mg, 21%) as a yellow solid. δ_{H} (d₆-DMSO at 110°C) 8.66 (s, 1H), 8.29 (dd, *J* 8.8, 1.5 Hz, 1H), 8.17 (d, *J* 3.3 Hz, 1H), 8.11 (d, *J* 2.8 Hz, 2H), 7.52 (d, *J* 8.8 Hz, 1H), 7.23-7.18 (m, 2H), 6.99 (d, *J* 7.8 Hz, 1H), 4.38-4.29 (m, 1H), 3.95 (d, *J* 7.6 Hz, 1H), 3.87 (m, 1H), 3.81 (s, 4H), 3.67 (dd, *J* 11.6, 3.0 Hz, 1H), 3.56-3.46 (m, 2H), 3.27 (dd, *J* 14.7, 8.1 Hz, 1H), 3.18 (dd, *J* 14.4, 6.8 Hz, 1H), 2.35 (s, 3H). LCMS (ES⁺) 461 (M+H)⁺.

EXAMPLE 378

{(S)-3-[1-Methyl-5-(1-methyl-1H-imidazole-2-carbonyl)-1H-indol-3-ylmethyl]-morpholin-4-yl}-(6-methylpyridin-3-yl)-methanone

- 5 The *title compound* was prepared from *Example 376* and 1-methyl-1H-imidazole according to *Method R* and was isolated as an off-white solid (14 mg). δ_{H} (d_6 -DMSO at 110°C) 8.49 (s, 1H), 8.19 (dd, J 8.6, 1.5 Hz, 1H), 8.15 (s, 1H), 7.46-7.41 (m, 2H), 7.23 (d, J 7.6 Hz, 1H), 7.15 (m, 2H), 7.02 (d, J 7.8 Hz, 1H), 4.36-4.27 (m, 1H), 4.02 (s, 3H), 3.97-3.90 (m, 1H), 3.85 (m, 1H), 3.80 (s, 4H), 3.65 (dd, J 11.6, 3.3 Hz, 1H), 3.54-3.45 (m, 2H),
10 3.27-3.12 (m, 2H), 2.39 (s, 3H). LCMS (ES^+) 457 ($\text{M}+\text{H}$)⁺.

EXAMPLE 379

- 15 (5-Chloro-6-methoxypyridin-3-yl)-{(S)-3-[5-(1H-imidazol-2-yl)-1-methyl-1H-indol-3-ylmethyl]morpholin-4-yl}-methanone

- To a stirred solution of *Intermediate 45* (443 mg, 1.03 mmol) in DCM (10 mL) was added manganese dioxide (1.0 g, 12.36 mmol). The reaction mixture was stirred at r.t. for 18 h, then filtered through celite and concentrated *in vacuo*, yielding a colourless oil. LCMS (ES^+) 428 ($\text{M}+\text{H}$)⁺. The resulting material was dissolved in glyoxal (40%
20 aqueous solution; 260 μL) and THF (2 mL) and cooled to 0°C. Concentrated ammonia (2 mL) was added to the reaction mixture, which was stirred at 0°C for 1 h. Repeated addition of glyoxal and ammonia was carried out and the reaction mixture was stirred at r.t. for 72 h, then concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , 0-5% MeOH/DCM), and further purified by preparative HPLC,
25 yielding the *title compound* (86 mg, 19%) as a white solid. δ_{H} (d_6 -DMSO at 100°C) 8.19 (s, 1H), 7.94 (s, 1H), 7.79 (d, J 1.8 Hz, 1H), 7.74 (dd, J 8.6, 1.5 Hz, 1H), 7.38 (d, J 8.6 Hz, 1H), 7.23 (s, 1H), 7.02 (s, 3H), 4.43-4.36 (m, 1H), 3.99-3.89 (m, 2H), 3.85-3.80 (m, 4H), 3.77-3.73 (m, 4H), 3.55-3.49 (m, 2H), 3.30 (dd, J 14.7, 8.8 Hz, 2H). LCMS (ES^+) 466 ($\text{M}+\text{H}$)⁺.

EXAMPLE 380

(5-Chloro-6-methoxypyridin-3-yl)-{(S)-3-[5-(1,1-dioxo-1 Λ 6-isothiazolidin-2-yl)-1-methyl-1*H*-indol-3-ylmethyl]morpholin-4-yl}-methanone

5 To a stirred solution of *Intermediate 56* (150 mg, 0.4 mmol) in DCM (5 mL) at 0°C were added triethylamine (276 μ L, 0.6 mmol) and 3-chloropropanesulfonyl chloride (58 μ L, 0.5 mmol). The reaction mixture was stirred at r.t. for 18 h, then quenched with water. The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The resulting material was dissolved in MeCN (5 mL), potassium carbonate (125
10 mg, 1.0 mmol) was added and the reaction mixture heated at 80°C for 4 h. The reaction mixture was partitioned between DCM (20 mL) and water (20 mL), dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the *title compound* (45 mg, 22%) as a yellow solid. δ_{H} (d_6 -DMSO at 100°C) 7.85 (d, *J* 2.0 Hz, 1H), 7.36-7.34 (m, 2H), 7.29 (s, 1H), 7.17 (dd, *J* 8.8, 2.3 Hz,
15 1H), 7.06 (s, 1H), 4.33-4.26 (m, 1H), 3.97 (s, 3H), 3.94 (d, *J* 8.6 Hz, 1H), 3.87-3.77 (m, 1H), 3.75 (s, 3H), 3.72-3.68 (m, 2H), 3.65 (d, *J* 3.0 Hz, 1H), 3.54-3.48 (m, 2H), 3.39-3.35 (m, 2H), 3.20-3.07 (m, 2H), 2.48-2.40 (m, 3H). LCMS (ES^+) 519 ($\text{M}+\text{H}$)⁺.

EXAMPLE 381

20 3-{3-[(S)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indol-5-yl}oxazolidin-2-one

To a stirred solution of *Intermediate 56* (150 mg, 0.4 mmol) in DCM (5 mL) at 0°C were added triethylamine (276 μ L, 0.6 mmol) and 2-chloroethyl chloroformate (49
25 μ L, 0.5 mmol). The reaction mixture was stirred at r.t. for 18 h, then quenched with water. The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The resulting material was dissolved in MeCN (5 mL), potassium carbonate (125 mg, 1.0 mmol) was added and the reaction mixture heated at 80°C for 4 h. The reaction mixture was partitioned between DCM (20 mL) and water (20 mL), dried (magnesium
30 sulfate), filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the *title compound* (82 mg, 42%) as a white solid. δ_{H} (d_6 -DMSO at 100°C) 7.82 (d, *J* 1.8 Hz, 1H), 7.45-7.39 (m, 2H), 7.37-7.34 (m, 1H), 7.29 (d, *J* 0.8 Hz, 1H), 7.05 (s, 1H), 4.44 (t, *J* 7.8 Hz, 2H), 4.33-4.25 (m, 1H), 4.05-4.00 (m, 2H), 3.95 (s,

3H), 3.95-3.94 (m, 1H), 3.86-3.81 (m, 2H), 3.75 (s, 3H), 3.69 (dd, *J* 11.6, 3.3 Hz, 1H), 3.54-3.49 (m, 2H), 3.20 (dd, *J* 14.7, 8.1 Hz, 1H), 3.07 (dd, *J* 14.4, 6.6 Hz, 1H). LCMS (ES⁺) 485 (M+H)⁺.

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EXAMPLE 382

3-{3-[(*S*)-4-(2-Chloro-5-fluoro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indol-5-yl}oxazolidin-2-one

To a stirred solution of *Intermediate 70* (150 mg, 0.3 mmol) in DCM (5 mL) at 0°C were added triethylamine (76 µL, 0.45 mmol) and 2-chloroethyl chloroformate (34 µL, 0.36 mmol). The reaction mixture was stirred at r.t. for 18 h, then quenched with water. The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The resulting material was dissolved in MeCN (5 mL), potassium carbonate (250 mg, 1.8 mmol) was added and the reaction mixture heated at 80°C for 4 h. The reaction mixture was partitioned between DCM (20 mL) and water (20 mL), dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the *title compound* (3 mg) as a white solid. δ_H (d₆-DMSO at 100°C) 7.45-7.43 (m, 2H), 7.39-7.37 (m, 2H), 7.11 (br s, 1H), 4.44 (t, *J* 8.1 Hz, 3H), 4.09-4.02 (m, 2H), 3.96-3.94 (m, 5H), 3.85 (d, *J* 11.4 Hz, 2H), 3.75 (s, 3H), 3.70-3.59 (m, 1H), 3.51-3.49 (m, 2H), 3.23-3.09 (m, 1H). LCMS (ES⁺) 503 (M+H)⁺.

EXAMPLE 383

(2-Chloro-5-fluoro-6-methoxypyridin-3-yl)-{(S)-3-[5-(1,1-dioxo-1*Λ*6-isothiazolidin-2-yl)-1-methyl-1*H*-indol-3-ylmethyl]morpholin-4-yl}-methanone

To a stirred solution of *Intermediate 70* (150 mg, 0.3 mmol) in DCM (5 mL) at 0°C were added triethylamine (76 µL, 0.45 mmol) and 3-chloropropanesulfonyl chloride (53 µL, 0.36 mmol). The reaction mixture was stirred at r.t. for 18 h, then quenched with water. The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The resulting material was dissolved in MeCN (5 mL), potassium carbonate (250 mg, 1.8 mmol) was added and the reaction mixture heated at 80°C for 4 h. The reaction mixture was partitioned between DCM (20 mL) and water (20 mL), dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by preparative

HPLC to afford the *title compound* (12 mg) as an off-white solid. δ_{H} (d_6 -DMSO at 100°C) 7.63-7.44 (m, 1H), 7.38 (d, J 8.8 Hz, 1H), 7.19 (dd, J 8.8, 1.5 Hz, 1H), 7.12 (br s, 2H), 4.01-3.90 (m, 4H), 3.84 (d, J 11.4 Hz, 1H), 3.78-3.69 (m, 6H), 3.67-3.60 (m, 1H), 3.50 (d, J 7.6 Hz, 2H), 3.39-3.36 (m, 2H), 3.15-3.13 (m, 2H), 2.48-2.41 (m, 3H). LCMS (ES⁺) 537 (M+H)⁺.

EXAMPLE 384

1-{3-[(*S*)-4-(2-Chloro-5-fluoro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indol-5-yl}pyrrolidin-2-one

To a stirred solution of *Intermediate 70* (150 mg, 0.3 mmol) in DCM (5 mL) at 0°C were added triethylamine (76 μ L, 0.45 mmol) and 4-chlorobutyryl chloride (43 μ L, 0.36 mmol). The reaction mixture was stirred at r.t. for 18 h, then quenched with water. The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The resulting material was dissolved in MeCN (5 mL), potassium carbonate (250 mg, 1.8 mmol) was added and the reaction mixture heated at 80°C for 1.5 h. The reaction mixture was partitioned between DCM (20 mL) and water (20 mL), dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-1% MeOH/DCM), yielding the *title compound* (3 mg) as a white solid. δ_{H} (d_6 -DMSO at 100°C) 7.50-7.47 (m, 2H), 7.35 (d, J 9.1 Hz, 1H), 7.09 (br s, 1H), 3.97 (s, 3H), 3.86-3.81 (m, 2H), 3.75 (s, 3H), 3.70-3.63 (m, 1H), 3.51-3.49 (m, 2H), 3.20-3.10 (m, 2H), 2.95-2.84 (m, 5H), 2.49-2.25 (m, 2H), 2.15-2.08 (m, 2H). LCMS (ES⁺) 501 (M+H)⁺.

EXAMPLE 385

3-[(*S*)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-[2-(dimethylamino)ethyl]-1*H*-indole-5-carboxylic acid dimethylamide

To a stirred solution of *Example 99* (150 mg, 0.30 mmol) in DMF (5 mL) at 0°C was added sodium hydride (60% dispersion in oil; 32 mg, 0.78 mmol). The reaction mixture was stirred at r.t. for 1 h and then cooled to 0°C prior to the addition of *N*-(2-chloroethyl)dimethylamine hydrochloride (50 mg, 0.46 mmol). The reaction mixture was heated at 50°C for 18 h, then partitioned between DCM (20 mL) and water (20 mL). The combined organic layers were dried (sodium sulphate), filtered and concentrated *in vacuo*.

The residue was purified by column chromatography (SiO₂, 0-10% MeOH/EtOAc), yielding the *title compound* (40 mg, 25%) as a white solid. δ_{H} (d₆-DMSO at 100°C) 7.88 (d, *J* 2.0 Hz, 1H), 7.48 (s, 1H), 7.43 (d, *J* 8.3 Hz, 1H), 7.39 (s, 1H), 7.19 (s, 1H), 7.17 (dd, *J* 8.6, 1.3 Hz, 1H), 4.26-4.19 (m, 3H), 3.96 (s, 3H), 3.93-3.89 (m, 1H), 3.85-3.80 (m, 2H), 3.66 (dd, *J* 11.4, 3.0 Hz, 1H), 3.52 (d, *J* 9.1 Hz, 2H), 3.17 (m, 2H), 2.97 (s, 6H), 2.68 (t, *J* 6.6 Hz, 2H), 2.24 (s, 6H). LCMS (ES⁺) 528 (M+H)⁺.

EXAMPLE 386

3-[(*S*)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-(2-hydroxyethyl)-1*H*-indole-5-carboxylic acid dimethylamide

To a stirred solution of *Example 99* (150 mg, 0.30 mmol) in DMF (5 mL) at 0°C was added sodium hydride (60% dispersion in oil; 32 mg, 0.78 mmol). The reaction mixture was stirred at r.t. for 1 h and then cooled to 0°C prior to the addition of (2-bromoethoxy)-*tert*-butyldimethylsilane (94 μ L, 0.46 mmol). The reaction mixture was heated at 50°C for 18 h, then partitioned between EtOAc (20 mL) and 10% aqueous NH₄Cl solution (20 mL). The combined organic layers were dried (sodium sulphate), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 70-100% EtOAc/isohehexane), yielding a clear oil. The residue was dissolved in THF (5 mL) and TBAF (5 mL, 1M solution in THF) was added. The reaction mixture was stirred at r.t. for 18 h, then partitioned between EtOAc (20mL) and 10% aqueous NH₄Cl solution (20 mL). The combined organic layers were dried (sodium sulphate), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-10% MeOH/EtOAc), yielding the *title compound* (71 mg, 47%) as a white solid. δ_{H} (d₆-DMSO at 100°C) 7.89 (d, *J* 1.8 Hz, 1H), 7.49 (s, 1H), 7.44-7.42 (m, 2H), 7.18 (s, 1H), 7.16 (dd, *J* 8.6, 1.5 Hz, 1H), 4.47 (t, *J* 5.1 Hz, 1H), 4.30-4.23 (m, 1H), 4.21-4.16 (m, 2H), 3.97 (s, 3H), 3.94 (d, *J* 7.8 Hz, 1H), 3.86-3.81 (m, 1H), 3.79-3.76 (m, 3H), 3.65 (dd, *J* 11.6, 3.3 Hz, 1H), 3.52 (d, *J* 8.8 Hz, 2H), 3.17 (dd, *J* 7.6, 1.3 Hz, 2H), 2.98 (s, 6H). LCMS (ES⁺) 501 (M+H)⁺.

EXAMPLE 387**5-[(S)-3-[5-(3-Aminoazetidine-1-carbonyl)-1-methyl-1H-indol-3-ylmethyl]morpholine-4-carbonyl]-2-methoxynicotinonitrile**

5 To a stirred solution of *Intermediate* 72 (87 mg, 0.20 mmol), azetidin-3-yl-carbamic acid *tert*-butyl ester hydrochloride (42 mg, 0.20 mmol), EDC (58 mg, 0.30mmol) and HOBT (27 mg, 0.20 mmol) in DMF (5 mL) was added DIPEA (1.10 mL, 1.0 mmol). The reaction mixture was heated at 60°C for 2 h. After cooling, the mixture was partitioned between ethyl acetate (10 mL) and water (10 mL). The organic layer was
10 washed with water (3 x 10 mL), dried (phase separator), concentrated *in vacuo* and chromatographed (SiO₂, 0-10% MeOH/EtOAc), yielding an off-white solid. This material was dissolved in DCM (4 mL), trifluoroacetic acid (4 mL) was slowly added dropwise, and the reaction mixture was stirred at r.t. for 2 h, then concentrated *in vacuo*. The residue was purified using preparative HPLC, yielding the *title compound* (7 mg, 7%)
15 as a white solid. δ_H (d₆-DMSO at 100°C) 8.09 (d, *J* 1.5 Hz, 1H), 7.69 (s, 1H), 7.66 (d, *J* 0.8 Hz, 1H), 7.45-7.43 (m, 1H), 7.39-7.37 (m, 1H), 7.12 (s, 1H), 4.37-4.29 (m, 2H), 4.29-4.22 (m, 1H), 4.01 (s, 3H), 3.96 (d, *J* 7.8 Hz, 1H), 3.89-3.81 (m, 1H), 3.79-3.76 (m, 8H), 3.73 (dd, *J* 11.6, 3.0 Hz, 1H), 3.56-3.50 (m, 2H), 3.25-3.22 (m, 2H), 3.11 (dd, *J* 14.4, 6.6 Hz, 1H). LCMS (ES⁺) 489 (M+H)⁺.

20

EXAMPLE 388**3-[(S)-4-(6-Methoxy-5-methylpyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid N-(2-hydroxyethyl)-N-methylamide**

25 To a stirred solution of *Intermediate* 75 (200 mg, 0.40 mmol), 6-methoxy-5-methylnicotinic acid (70 mg, 0.40 mmol), EDC (120 mg, 0.60 mmol) and HOBT (56 mg, 0.40 mmol) in DCM (5 mL) was added DIPEA (233 μ L, 1.60 mmol). The reaction mixture was stirred at r.t. for 18 h, then partitioned between DCM (10 mL) and water (10 mL). The organic layer was washed with water (3 x 10 mL), dried (phase separator) and
30 concentrated *in vacuo*. The resulting material was dissolved in THF (4 mL), 2-(methyl-amino)ethanol (70 μ L, 0.80 mmol) and DIPEA (215 μ L, 1.60 mmol) were added and the reaction mixture was stirred at r.t. for 18 h, then concentrated *in vacuo*. The residue was purified using preparative HPLC, yielding the *title compound* (140 mg, 87%) as a white

solid. δ_{H} (d_6 -DMSO at 100°C) 7.82 (d, J 2.0 Hz, 1H), 7.53 (s, 1H), 7.38 (d, J 8.6 Hz, 1H), 7.19 (dd, J 8.6, 1.5 Hz, 1H), 7.11 (s, 1H), 7.09 (s, 1H), 4.35-4.26 (m, 2H), 3.95-3.88 (m, 3H), 3.84-3.81 (m, 2H), 3.79-3.73 (m, 3H), 3.65-3.58 (m, 3H), 3.52-3.43 (m, 5H), 3.17 (dd, J 7.6, 4.0 Hz, 2H), 3.00 (s, 3H), 2.06 (s, 3H). LCMS (ES^+) 481 ($\text{M}+\text{H}$)⁺.

5

EXAMPLE 389

3-[(*S*)-4-(5-Cyano-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carboxylic acid *N*-(2-hydroxyethyl)-*N*-methylethylamide

10 To a stirred solution of *Intermediate* 75 (200 mg, 0.40 mmol), 5-cyano-6-methoxynicotinic acid (89 mg, 0.50 mmol), EDC (120 mg, 0.60 mmol) and HOBt (56 mg, 0.40 mmol) in DCM (5 mL) was added DIPEA (233 μL , 1.60 mmol). The reaction mixture was stirred at r.t. for 18 h, then partitioned between DCM (10 mL) and water (10 mL). The organic layer was washed with water (3 x 10 mL), dried (phase separator) and
15 concentrated *in vacuo*. The resulting material was dissolved in THF (4 mL), 2-(methylamino)ethanol (70 μL , 0.80 mmol) and DIPEA (215 μL , 1.60 mmol) were added and the reaction mixture was stirred at r.t. for 18 h, then concentrated *in vacuo*. The residue was purified using preparative HPLC, yielding the *title compound* (60 mg, 30%) as a white solid. δ_{H} (d_6 -DMSO at 100°C) 8.07 (d, J 2.0 Hz, 1H), 7.66 (d, J 0.5 Hz, 1H), 7.46 (s, 1H),
20 7.36 (dd, J 8.6, 0.5 Hz, 1H), 7.17 (dd, J 8.3, 1.5 Hz, 1H), 7.07 (s, 1H), 4.24-4.20 (m, 1H), 4.21-4.19 (m, 1H), 3.99 (s, 3H), 3.95-3.90 (m, 1H), 3.85-3.82 (m, 2H), 3.81-3.75 (m, 5H), 3.68 (dd, J 11.6, 3.3 Hz, 1H), 3.52-3.48 (m, 2H), 3.46-3.41 (m, 2H), 3.21-3.10 (m, 1H), 3.08-3.05 (m, 1H), 2.98 (s, 3H). LCMS (ES^+) 492 ($\text{M}+\text{H}$)⁺.

25

EXAMPLE 390

3-[(*S*)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carboxylic acid 2-(methylsulfanyl)ethylamide

30 To a stirred solution of *Intermediate* 76 (250 mg, 0.4 mmol) in THF (5 mL) and *Intermediate* 77 (126 mg, 0.8 mmol) was added DIPEA (106 μL , 0.8 mmol). The reaction mixture was stirred at r.t. for 18 h, then concentrated *in vacuo*. The residue was purified using preparative HPLC, yielding the *title compound* (60 mg, 29%) as a white solid. δ_{H} (d_6 -DMSO at 100°C) 7.97 (s, 1H), 7.84 (s, 1H), 7.79 (d, J 2.0 Hz, 1H), 7.66 (dd,

J 8.6, 1.5 Hz, 1H), 7.38-7.36 (m, 1H), 7.25 (s, 1H), 7.10 (s, 1H), 4.39-4.31 (m, 1H), 3.97-3.92 (m, 4H), 3.89-3.86 (m, 1H), 3.83-3.81 (m, 1H), 3.77 (s, 3H), 3.73 (dd, *J* 11.6, 3.3 Hz, 1H), 3.56-3.47 (m, 4H), 3.29 (dd, *J* 14.7, 8.6 Hz, 1H), 3.10 (dd, *J* 14.7, 6.3 Hz, 1H), 2.73 (t, *J* 7.3 Hz, 2H), 2.15 (s, 3H). LCMS (ES⁺) 517 (M+H)⁺.

5

EXAMPLE 391

3-[(*S*)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carboxylic acid 2-(methanesulfinyl)ethylamide

10 To a stirred solution of *Example 390* (110 mg, 0.2 mmol) in DCM (5 mL) was added 3-chloroperoxybenzoic acid (58 mg, 0.24 mmol). The reaction mixture was stirred at r.t. for 2 h, then partitioned between DCM (10 mL) and saturated sodium bicarbonate solution (10 mL). The organics were separated, dried (sodium sulphate) and concentrated *in vacuo*. The residue was purified using preparative HPLC, yielding the *title compound*
15 (31 mg, 29%) as a white solid. δ_{H} (d₆-DMSO at 100°C) 8.02 (s, 1H), 7.97 (s, 1H), 7.78 (s, 1H), 7.65 (dd, *J* 8.6, 1.8 Hz, 1H), 7.39 (d, *J* 8.6 Hz, 1H), 7.24 (s, 1H), 7.10 (s, 1H), 4.40-4.31 (m, 1H), 3.95-3.94 (m, 1H), 3.94 (s, 3H), 3.88-3.86 (m, 2H), 3.85-3.81 (m, 1H), 3.78 (s, 3H), 3.76-3.70 (m, 2H), 3.55-3.50 (m, 2H), 3.29 (dd, *J* 14.7, 8.6 Hz, 1H), 3.10-3.04 (m, 2H), 2.95-2.89 (m, 1H), 2.61 (s, 3H). LCMS (ES⁺) 533 (M+H)⁺.

20

EXAMPLE 392

3-[(*S*)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carboxylic acid 2-(methanesulfonyl)ethylamide

25 To a stirred solution of *Example 390* (110 mg, 0.2 mmol) in DCM (5 mL) was added 3-chloroperoxybenzoic acid (58 mg, 0.24 mmol). The reaction mixture was stirred at r.t. for 2 h, then partitioned between DCM (10 mL) and saturated sodium bicarbonate solution (10 mL). The organics were separated, dried (sodium sulphate) and concentrated *in vacuo*. The residue was purified using preparative HPLC, yielding the *title compound*
30 (28 mg, 26%) as a white solid. δ_{H} (d₆-DMSO at 100°C) 7.99 (s, 1H), 7.96 (s, 1H), 7.76 (d, *J* 1.8 Hz, 1H), 7.65 (dd, *J* 8.6, 1.8 Hz, 1H), 7.39 (d, *J* 8.6 Hz, 1H), 7.24 (s, 1H), 7.10 (s, 1H), 4.40-4.35 (m, 1H), 3.96-3.94 (m, 1H), 3.94 (s, 3H), 3.87 (d, *J* 11.5 Hz, 1H), 3.84-3.81 (m, 1H), 3.78 (s, 3H), 3.77-3.71 (m, 3H), 3.57-3.50 (m, 2H), 3.40 (t, *J* 6.8 Hz, 2H),

3.29 (dd, *J* 14.7, 8.6 Hz, 1H), 3.09 (dd, *J* 14.5, 6.2 Hz, 1H), 3.01 (s, 3H). LCMS (ES⁺) 549 (M+H)⁺.

EXAMPLE 393

5

3-[(*S*)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carboxylic acid *N*-[2-(methanesulfonyl)ethyl]-*N*-methylamide

To a stirred solution of *Intermediate 76* (110 mg, 0.2 mmol) in THF (5 mL) and *N*-[2-(methanesulfonyl)ethyl]-*N*-methylamine (50 mg, 0.4 mmol) was added DIPEA (60
10 μL, 0.4 mmol). The reaction mixture was stirred at r.t. for 18 h, then concentrated *in vacuo*. The residue was purified using preparative HPLC, yielding the *title compound* (40 mg, 36%) as a white solid. δ_H (d₆-DMSO at 100°C) 7.88 (d, *J* 1.8 Hz, 1H), 7.55 (s, 1H), 7.41 (d, *J* 8.4 Hz, 1H), 7.38 (s, 1H), 7.22 (dd, *J* 8.3, 1.5 Hz, 1H), 7.11 (s, 1H), 4.33-4.25 (m, 1H), 3.97 (s, 3H), 3.94 (d, *J* 7.6 Hz, 1H), 3.86-3.81 (m, 3H), 3.78 (s, 4H), 3.65 (dd, *J*
15 11.6, 3.0 Hz, 1H), 3.56-3.51 (m, 2H), 3.48-3.45 (m, 2H), 3.19-3.15 (m, 2H), 2.99 (d, *J* 7.8 Hz, 6H). LCMS (ES⁺) 563 (M+H)⁺.

EXAMPLE 394

20 {3-[(*S*)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indol-5-yl}-(thiazolidin-3-yl)-methanone

To a stirred solution of *Intermediate 76* (360 mg, 0.7 mmol) in THF (5 mL) and thiazolidine (106 μL, 1.4 mmol) was added DIPEA (170 μL, 1.4 mmol). The reaction mixture was stirred at r.t. for 18 h, then concentrated *in vacuo*. The residue was purified
25 using preparative HPLC, yielding the *title compound* (170 mg, 47%) as a white solid. δ_H (d₆-DMSO at 100°C) 7.84 (d, *J* 1.8 Hz, 1H), 7.67 (s, 1H), 7.43-7.41 (m, 1H), 7.35-7.30 (m, 2H), 7.13 (s, 1H), 4.62 (s, 2H), 4.31-4.24 (m, 1H), 3.96 (s, 3H), 3.94 (s, 1H), 3.87 (s, 1H), 3.84-3.81 (m, 3H), 3.79 (s, 3H), 3.67 (dd, *J* 11.4, 3.0 Hz, 1H), 3.56-3.51 (m, 2H), 3.25-3.11 (m, 2H), 3.03 (t, *J* 6.3 Hz, 2H). LCMS (ES⁺) 515 (M+H)⁺.

30

EXAMPLE 395

{3-[(S)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indol-5-yl}-(1-oxo-1 Λ 4-thiazolidin-3-yl)-methanone

To a stirred solution of *Example 394* (130 mg, 0.25 mmol) in DCM (5 mL) was added 3-chloroperoxybenzoic acid (57 mg, 0.25 mmol). The reaction mixture was stirred at r.t. for 18 h, then partitioned between DCM (10 mL) and saturated sodium bicarbonate solution (10 mL). The organics were separated, dried (sodium sulphate) and concentrated *in vacuo*. The residue was purified using preparative HPLC, yielding the *title compound* (51 mg, 39%) as a white solid. δ_{H} (d_6 -DMSO at 100°C) 7.84 (d, J 1.8 Hz, 1H), 7.71 (d, J 4.8 Hz, 1H), 7.45-7.42 (m, 1H), 7.37-7.30 (m, 2H), 7.14 (d, J 2.3 Hz, 1H), 4.60-4.59 (m, 2H), 4.33-4.24 (m, 2H), 4.03-3.97 (m, 1H), 3.96 (d, J 2.3 Hz, 3H), 3.96-3.93 (m, 2H), 3.86-3.84 (m, 1H), 3.79 (s, 3H), 3.69-3.66 (m, 1H), 3.53-3.48 (m, 2H), 3.25-3.20 (m, 1H), 3.17-3.14 (m, 1H), 3.10-3.08 (m, 1H), 3.07-3.00 (m, 1H). LCMS (ES^+) 531 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 396

[(S)-3-{1-[2-(Dimethylamino)ethyl]-5-(1,1-dioxo-1 Λ 6-isothiazolidin-2-yl)-1H-indol-3-ylmethyl}morpholin-4-yl]-(6-methoxypyridin-3-yl)-methanone

To a stirred solution of *Example 373* (100 mg, 0.21 mmol) in DMF (5 mL) at 0°C was added sodium hydride (60% dispersion in oil; 51 mg, 2.13 mmol). The reaction mixture was stirred at r.t. for 1 h and then cooled to 0°C prior to the addition of *N*-(2-chloroethyl)dimethylamine hydrochloride (92 mg, 0.64 mmol). The reaction mixture was heated at 50°C for 18 h, then partitioned between DCM (20 mL) and water (20 mL). The combined organic layers were dried (sodium sulphate), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , 0-10% MeOH/EtOAc), yielding the *title compound* (32 mg, 28%) as a yellow solid. δ_{H} (d_6 -DMSO at 100°C) 7.98 (d, J 2.3 Hz, 1H), 7.40 (d, J 8.8 Hz, 1H), 7.35 (dd, J 8.6, 2.3 Hz, 1H), 7.28 (s, 1H), 7.18-7.14 (m, 2H), 6.64 (d, J 8.6 Hz, 1H), 4.34-4.27 (m, 1H), 4.17 (t, J 6.6 Hz, 2H), 3.94-3.90 (m, 1H), 3.89 (s, 3H), 3.83-3.76 (m, 2H), 3.70 (t, J 6.6 Hz, 2H), 3.61 (dd, J 11.6, 3.3 Hz, 1H), 3.52-3.47 (m, 2H), 3.41-3.35 (m, 2H), 3.14 (dd, J 7.6, 1.0 Hz, 2H), 2.64 (t, J 6.6 Hz, 2H), 2.47-2.41 (m, 2H), 2.21 (s, 6H). LCMS (ES^+) 542 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 397

3-[(S)-4-(1,6-Dimethyl-2-oxo-1,2-dihydropyridine-4-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

To a stirred solution of *Example 187* (120 mg, 0.27 mmol) in DMF (5 mL) at 0°C were added iodomethane (17 µL, 0.27 mmol) and sodium hydride (11 mg, 0.27 mol). The reaction mixture was stirred at r.t. for 3 h, quenched by the addition of water (20 mL) and extracted with EtOAc (20 mL). The organic layer was washed with brine (20 mL), dried (magnesium sulphate) and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the *title compound* (18 mg, 15%) as a white solid. δ_{H} (d_6 -DMSO at 110°C) 7.59 7.50 (m, 1H), 7.40 (d, *J* 8.3 Hz, 1H), 7.19 (dd, *J* 8.6, 1.5 Hz, 1H), 7.13 (s, 1H), 5.95 (s, 1H), 5.64-5.53 (m, 1H), 4.32-4.19 (m, 1H), 3.97-3.90 (m, 1H), 3.85-3.75 (m, 5H), 3.56 (dd, *J* 11.6, 3.0 Hz, 1H), 3.50-3.42 (m, 2H), 3.37 (s, 3H), 3.18-3.07 (m, 2H), 3.00 (s, 6H), 2.23 (s, 3H). LCMS (ES^+) 451(M+H)⁺.

EXAMPLE 398

3-[(S)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid N-(2-cyanoethyl)-N-methylamide

To a stirred solution of *Intermediate 76* (120 mg, 0.2 mmol) in THF (5 mL) and 3-(methylamino)propionitrile (33 mg, 0.4 mmol) was added DIPEA (60 µL, 0.4 mmol). The reaction mixture was stirred at r.t. for 18 h, then concentrated *in vacuo*. The residue was purified using preparative HPLC, yielding the *title compound* (64 mg, 63%) as a white solid. δ_{H} (d_6 -DMSO at 100°C) 7.86 (d, *J* 2.0 Hz, 1H), 7.54 (s, 1H), 7.42 (dd, *J* 8.6, 0.5 Hz, 1H), 7.35 (s, 1H), 7.21 (dd, *J* 8.3, 1.5 Hz, 1H), 7.11 (s, 1H), 4.34-4.20 (m, 1H), 3.99-3.88 (m, 4H), 3.88-3.71 (m, 6H), 3.73-3.62 (m, 3H), 3.57-3.47 (m, 2H), 3.17 (dd, *J* 14.4, 7.6 Hz, 2H), 3.02 (s, 3H), 2.93-2.76 (m, 1H). LCMS (ES^+) 510 (M+H)⁺.

EXAMPLE 399

3-[(S)-4-[4-(Dimethylamino)-3-(trifluoromethyl)benzoyl]morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

- 5 Dimethylamine hydrochloride (12 mg, 0.15 mmol) was added to a solution of *Example 210* (60 mg, 0.12 mmol) in DMSO (1 mL) in a microwave vial. Potassium carbonate (35 mg, 0.26 mmol) was added and the reaction mixture was then heated to 100°C for 0.5 h. Water (5 mL) was added and the mixture was extracted with DCM (2 x 10 mL). The combined organics were dried (sodium sulphate), filtered and concentrated
10 *in vacuo*. The residue was purified by preparative HPLC to yield the *title compound* as a white solid. δ_{H} (d_6 -DMSO at 80°C) 7.58 (s, 1H), 7.38 (d, J 8.3 Hz, 1H), 7.31-7.24 (m, 3H), 7.20 (dd, J 8.3, 1.5 Hz, 1H), 7.09 (s, 1H), 4.29-4.27 (m, 1H), 3.93-3.90 (m, 1H), 3.82 (d, J 11.6 Hz, 1H), 3.76 (s, 3H), 3.74-3.71 (m, 1H), 3.59 (dd, J 11.6, 3.3 Hz, 1H), 3.56-3.45 (m, 2H), 3.21 (dd, J 14.4, 7.3 Hz, 1H), 3.15 (dd, J 14.7, 7.6 Hz, 1H), 2.98 (s, 6H),
15 2.73 (s, 6H). LCMS (ES⁺) 517 (M+H)⁺.

EXAMPLE 400

1-Methyl-3-[(S)-4-(1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide

- 20 To a stirred solution of *Example 30* (102 mg, 0.24 mmol) in DMF (5 mL) at 0°C was added sodium hydride (12 mg, 0.20 mmol). The reaction mixture was stirred at 0°C for 20 minutes prior to the addition of methyl iodide (20 μ L, 0.36 mmol). The reaction mixture was allowed to warm to r.t and stirred for 18 h, then partitioned between DCM
25 (20 mL) and water (20 mL). The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried (phase separator) and concentrated *in vacuo*. The residue was purified by preparative HPLC to yield the *title compound* as a white solid. δ_{H} (d_6 -DMSO at 110°C) 7.58 (d, J 0.8 Hz, 1H), 7.46 (d, J 2.3 Hz, 1H), 7.39 (d, J 8.3 Hz, 1H), 7.20 (dd, J 8.3, 1.5 Hz, 1H), 7.15 (dd, J 9.3, 2.5 Hz, 1H), 7.12 (s, 1H), 6.21
30 (d, J 9.3 Hz, 1H), 4.29-4.26 (m, 1H), 3.96-3.89 (m, 1H), 3.82 (d, J 11.6 Hz, 1H), 3.82 (d, J 10.9 Hz, 1H), 3.77 (s, 3H), 3.59 (dd, J 11.6, 3.3 Hz, 1H), 3.55-3.45 (m, 2H), 3.34 (s, 3H), 3.20 (dd, J 14.4, 7.6 Hz, 1H), 3.12 (dd, J 14.4, 7.3 Hz, 1H), 2.98 (s, 6H). LCMS (ES⁺) 437 (M+H)⁺.

EXAMPLE 401**1-Methyl-3-[(S)-4-[6-(methylsulfonyl)pyridine-3-carbonyl]morpholin-3-ylmethyl]-1H-indole-5-carboxylic acid dimethylamide**

To a stirred solution of *Example 6* (100 mg, 0.23 mmol) in THF (10 mL) was added sodium thiomethoxide (16 mg, 0.23 mmol). The reaction mixture was heated to reflux for 18 h, then partitioned between DCM (20 mL) and water (20 mL). The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried (phase separator) and concentrated *in vacuo*. The residue was purified by preparative HPLC to yield the *title compound* (12 mg, 11%) as a white solid. δ_{H} (d_6 -DMSO at 110°C) 8.18 (d, *J* 1.8 Hz, 1H), 7.55 (s, 1H), 7.39 (dd, *J* 8.3, 0.5 Hz, 1H), 7.28 (dd, *J* 8.1, 2.0 Hz, 1H), 7.20 (dd, *J* 8.3, 1.5 Hz, 1H), 7.15 (d, *J* 8.1 Hz, 1H), 7.09 (s, 1H), 4.26-4.23 (m, 1H), 3.96-3.89 (m, 1H), 3.83 (d, *J* 11.6 Hz, 1H), 3.79-3.76 (m, 1H), 3.76 (s, 3H), 3.61 (dd, *J* 11.6, 3.3 Hz, 1H), 3.56-3.46 (m, 2H), 3.21 (dd, *J* 14.7, 7.8 Hz, 1H), 3.15 (dd, *J* 14.7, 7.6 Hz, 1H), 2.99 (s, 6H), 2.52 (s, 3H). LCMS (ES^+) 453 ($\text{M}+\text{H}$)⁺.

EXAMPLE 402**3-[(S)-4-(5-Bromo-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide**

To a stirred solution of *Example 233* (149 mg, 0.29 mmol) in MeOH (10 mL) was added lithium hydroxide monohydrate (36 mg, 0.86 mmol). The reaction mixture was heated to reflux for 4.5 h, then cooled and neutralised with 2M HCl. The residue was partitioned with DCM (20 mL) and water (20 mL). The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried (magnesium sulphate) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , 0-10% MeOH/EtOAc), yielding the *title compound* (129 mg, 87%) as a white solid. δ_{H} (d_6 -DMSO at 110°C) 7.91 (d, *J* 2.0 Hz, 1H), 7.53-7.50 (m, 2H), 7.39 (d, *J* 8.3 Hz, 1H), 7.19 (dd, *J* 8.3, 1.5 Hz, 1H), 7.09 (s, 1H), 4.26-4.23 (m, 1H), 3.95 (s, 3H), 3.95-3.90 (m, 1H), 3.85 (d, *J* 11.6 Hz, 1H), 3.83-3.79 (m, 1H), 3.78 (s, 3H), 3.65 (dd, *J* 11.6, 3.3 Hz, 1H), 3.56-3.48 (m, 2H), 3.19 (dd, *J* 14.4, 7.6 Hz, 1H), 3.15 (dd, *J* 14.4, 7.6 Hz, 1H), 2.97 (s, 6H). LCMS (ES^+) 517 ($\text{M}+\text{H}$)⁺.

EXAMPLE 403**3-[(S)-4-(6-Ethoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide**

To a solution of *Example 6* (119 mg, 0.27 mmol) in EtOH (5 mL) in a microwave vial was added lithium hydroxide monohydrate (34 mg, 0.81 mmol). The reaction mixture was heated to 180°C for 1 h, then cooled and neutralised with 2M HCl. The residue was partitioned with DCM (20 mL) and water (20 mL). The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried (magnesium sulphate) and concentrated *in vacuo*. The residue was purified by preparative HPLC to yield the *title compound* (5 mg, 11%) as a pink solid. δ_{H} (d_6 -DMSO at 110°C) 7.96 (d, *J* 2.3 Hz, 1H), 7.53 (d, *J* 0.8 Hz, 1H), 7.39-7.37 (m, 2H), 7.19 (dd, *J* 8.3, 1.3 Hz, 1H), 7.09 (s, 1H), 6.63 (d, *J* 8.6 Hz, 1H), 4.34 (q, *J* 6.8 Hz, 2H), 4.30-4.27 (m, 1H), 3.93-3.89 (m, 1H), 3.82 (d, *J* 11.4 Hz, 1H), 3.78-3.76 (m, 1H), 3.76 (s, 3H), 3.60 (dd, *J* 11.6, 3.4 Hz, 1H), 3.56-3.48 (m, 2H), 3.21 (dd, *J* 14.1, 7.8 Hz, 1H), 3.13 (dd, *J* 14.7, 7.3 Hz, 1H), 2.98 (s, 6H), 1.33 (t, *J* 7.1 Hz, 3H). LCMS (ES^+) 451 ($\text{M}+\text{H}$)⁺.

EXAMPLE 404**3-[(S)-4-(5-Amino-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide**

To a stirred solution of *Example 237* (112 mg, 0.23 mmol) in AcOH (5 mL) was added zinc powder (46 mg, 0.70 mmol). The reaction mixture was heated at 80°C for 1 h, then cooled, quenched with water (50 mL) and saturated sodium carbonate solution (100 mL), and partitioned with EtOAc. The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , 2-30% MeOH/EtOAc), yielding the *title compound* as a white solid (17 mg, 16%). δ_{H} (d_6 -DMSO at 110°C) 7.55 (s, 1H), 7.39 (d, *J* 8.6 Hz, 1H), 7.27 (d, *J* 2.0 Hz, 1H), 7.19 (dd, *J* 8.3, 1.5 Hz, 1H), 7.09 (s, 1H), 6.72 (d, *J* 2.0 Hz, 1H), 4.67 (s, 2H), 4.37-4.34 (m, 1H), 3.91 (s, 3H), 3.91-3.87 (m, 1H), 3.80-3.75 (m, 2H), 3.76 (s, 3H), 3.53 (dd, *J* 11.6, 3.0 Hz, 1H), 3.49-3.42 (m, 2H), 3.25 (dd, *J* 14.1, 8.3 Hz, 1H), 3.07 (dd, *J* 14.1, 6.6 Hz, 1H), 2.98 (s, 6H). LCMS (ES^+) 452 ($\text{M}+\text{H}$)⁺.

EXAMPLE 4053-[(S)-4-(5-Hydroxy-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

To a degassed solution of *Example 402* (150 mg, 0.29 mmol) in 1,4-dioxane (0.5 mL), under nitrogen, were added 2-di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl (3 mg, 0.0058 mmol), potassium hydroxide (49 mg, 0.87 mmol) and Pd₂(dba)₃ (2 mg, 0.0015 mmol). The reaction mixture was heated to reflux for 18 h, then neutralized with HCl, and partitioned between DCM (10 mL) and water (10 mL). The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The residue was purified by preparative HPLC, yielding the *title compound* (75 mg, 57%) as an off-white solid. δ_{H} (d₆-DMSO at 110°C) 9.10 (br s, 1H), 7.54 (s, 1H), 7.46 (d, *J* 2.0 Hz, 1H), 7.38 (d, *J* 8.3 Hz, 1H), 7.19 (dd, *J* 8.6, 1.5 Hz, 1H), 7.09 (s, 1H), 6.86 (d, *J* 2.0 Hz, 1H), 4.36-4.33 (m, 1H), 3.95-3.88 (m, 1H), 3.91 (s, 3H), 3.80 (d, *J* 11.4 Hz, 1H), 3.81-3.76 (m, 1H), 3.76 (s, 3H), 3.56 (dd, *J* 11.4, 3.0 Hz, 1H), 3.51-3.43 (m, 2H), 3.23 (dd, *J* 14.1, 8.1 Hz, 1H), 3.09 (dd, *J* 14.4, 7.1 Hz, 1H), 2.98 (s, 6H). LCMS (ES⁺) 453 (M+H)⁺.

EXAMPLE 4063-[(S)-4-(5-Chloro-6-methoxypyridine-3-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid *N*-[2-(dimethylamino)ethyl]-*N*-methylamide

To a stirred solution of *Intermediate 76* (120 mg, 0.2 mmol) in THF (5 mL) and *N,N,N'*-trimethylethylenediamine (52 μ L, 0.4 mmol) was added DIPEA (60 μ L, 0.4 mmol). The reaction mixture was stirred at r.t. for 18 h, then concentrated *in vacuo*. The residue was purified using preparative HPLC, yielding the *title compound* (43 mg, 40%) as a white solid. δ_{H} (d₆-DMSO at 100°C) 7.90 (d, *J* 2.0 Hz, 1H), 7.51 (s, 1H), 7.42-7.37 (m, 2H), 7.17 (dd, *J* 8.6, 1.5 Hz, 1H), 7.09 (s, 1H), 4.34-4.25 (m, 1H), 4.01-3.90 (m, 5H), 3.87-3.74 (m, 6H), 3.64 (dd, *J* 11.4, 3.0 Hz, 1H), 3.52 (d, *J* 8.8 Hz, 2H), 3.46 (t, *J* 6.8 Hz, 2H), 3.18 (d, *J* 7.3 Hz, 2H), 2.97 (s, 3H), 2.16 (s, 6H). LCMS (ES⁺) 528 (M+H)⁺.

EXAMPLE 407

{5-[(S)-3-(5-Dimethylcarbamoyl-1-methyl-1*H*-indol-3-ylmethyl)morpholine-4-carbonyl]-pyridin-3-yl}carbamic acid methyl ester

- 5 To a stirred solution of *Example 193* (140 mg, 0.3 mmol) in DCM (5 mL) and methyl chloroformate (26 μ L, 0.3 mmol) was added TEA (93 μ L, 0.6 mmol). The reaction mixture was stirred at r.t. for 18 h, then partitioned between DCM (20 mL) and saturated brine (20 mL). The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried (phase separator) and concentrated *in vacuo*. The
- 10 residue was purified by column chromatography (SiO₂, 5-20% MeOH/EtOAc) to yield the *title compound* (41 mg, 26%) as a yellow solid. δ_{H} (d₆-DMSO at 100°C) 9.47-9.39 (m, 1H), 8.57 (d, *J* 2.3 Hz, 1H), 7.97 (s, 1H), 7.63 (s, 1H), 7.47 (s, 1H), 7.36 (d, *J* 8.3 Hz, 1H), 7.17 (dd, *J* 8.3, 1.3 Hz, 1H), 7.09 (s, 1H), 4.37-4.20 (s, 1H), 3.99-3.89 (m, 1H), 3.85-3.79 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.60 (dd, *J* 11.6, 3.0 Hz, 1H), 3.55-3.47 (m, 2H),
- 15 3.26-3.18 (m, 1H), 3.17-3.08 (m, 1H), 2.98 (s, 6H). LCMS (ES⁺) 480 (M+H)⁺.

EXAMPLE 408

[(S)-3-{5-[(R)-3-(Aminomethyl)pyrrolidine-1-carbonyl]-1-methyl-1*H*-indol-3-ylmethyl}-morpholin-4-yl]-(2-chloro-5-fluoro-6-methoxypyridin-3-yl)-methanone

20

- To a stirred solution of *Intermediate 79* (108 mg, 0.23 mmol), (*R*)-pyrrolidin-3-yl-methylcarbamic acid *tert*-butyl ester (46 mg, 0.23 mmol), EDC (45 mg, 0.35 mmol) and HOBT (31 mg, 0.23 mmol) in DMF (5 mL) was added TEA (0.10 mL, 0.71 mmol). The reaction mixture was stirred at r.t. for 18 h, then partitioned between ethyl acetate (10
- 25 mL) and water (10 mL). The organic layer was washed with water (3 x 10 mL), dried (phase separator), concentrated *in vacuo* and chromatographed (SiO₂, 20-60% EtOAc/hexanes), yielding an off-white solid. This material was dissolved in DCM (5 mL) and trifluoroacetic acid (3 mL) was added. The reaction mixture was stirred at r.t. for 2 h, quenched by the addition of sodium carbonate solution (20 mL) and extracted with DCM
- 30 (20 mL). The combined organic layers were dried (sodium sulphate), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-10% MeOH/EtOAc), yielding the *title compound* (63 mg, 50%) as a white solid. δ_{H} (d₆-DMSO at 100°C) 7.78-7.60 (m, 2H), 7.40-7.38 (m, 1H), 7.33-7.31 (m, 1H), 7.15 (s, 1H),

4.23 (br s, 1H), 3.98 (s, 3H), 3.95-3.92 (m, 2H), 3.86-3.83 (m, 1H), 3.78 (s, 3H), 3.63 (dd, J 11.6, 7.6 Hz, 2H), 3.57-3.47 (m, 4H), 3.30-3.11 (m, 3H), 2.64 (dd, J 6.6, 4.3 Hz, 2H), 2.24-2.20 (m, 1H), 2.00-1.96 (m, 2H), 1.94-1.87 (m, 1H), 1.70-1.57 (m, 1H). LCMS (ES^+) 544 ($\text{M}+\text{H}$)⁺.

5

EXAMPLE 409

{(S)-3-[5-(3-Aminoazetidine-1-carbonyl)-1-methyl-1H-indol-3-ylmethyl]morpholin-4-yl}-(2-chloro-5-fluoro-6-methoxypyridin-3-yl)-methanone

10 To a stirred solution of *Intermediate 79* (108 mg, 0.23 mmol), azetidin-3-yl-carbamic acid *tert*-butyl ester (46 mg, 0.23 mmol), EDC (45 mg, 0.35 mmol) and HOBt (31 mg, 0.23 mmol) in DMF (5 mL) was added TEA (0.10 mL, 0.71 mmol). The reaction mixture was stirred at r.t. for 18 h, then partitioned between ethyl acetate (10 mL) and water (10 mL). The organic layer was washed with water (3 x 10 mL), dried (phase
15 separator), concentrated *in vacuo* and chromatographed (SiO_2 , 20-60% EtOAc/hexanes), yielding an off-white solid. This material was dissolved in DCM (5 mL) and trifluoroacetic acid (3 mL) was added. The reaction mixture was stirred at r.t. for 2 h, quenched by the addition of sodium carbonate solution (20 mL) and extracted with DCM (20 mL). The combined organic layers were dried (sodium sulphate), filtered and
20 concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , 0-10% MeOH/EtOAc), yielding the *title compound* (63 mg, 50%) as a white solid. δ_{H} (d_6 -DMSO at 100°C) 7.92-7.71 (m, 2H), 7.46-7.44 (m, 1H), 7.41-7.38 (m, 1H), 7.17 (br s, 1H), 4.38-4.26 (m, 3H), 4.01-3.89 (m, 4H), 3.85 (d, J 11.6 Hz, 1H), 3.82-3.74 (m, 6H), 3.70-3.60 (m, 2H), 3.56-3.47 (m, 2H), 3.29-3.12 (m, 2H), 1.97-1.86 (m, 2H). LCMS
25 (ES^+) 516 ($\text{M}+\text{H}$)⁺.

EXAMPLE 410

(3-Aminoazetidin-1-yl)-{3-[(S)-4-(3-hydroxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1H-indol-5-yl}-methanone

30

To a stirred solution of *Intermediate 59* (210 mg, 0.38 mmol) in DCM (5 mL) at 0°C was added trifluoroacetic acid (3 mL). The reaction mixture was stirred at r.t. for 2 h, quenched by the addition of sodium carbonate (20 mL) and extracted with DCM (20 mL).

The combined organic layers were dried (sodium sulphate), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-10% MeOH/EtOAc), yielding the *title compound* (18 mg, 10%) as a white solid. δ_{H} (d₆-DMSO at 100°C) 8.19 (s, 1H), 7.80 (s, 1H), 7.45-7.43 (m, 1H), 7.39-7.37 (m, 1H), 7.16-7.07 (m, 2H), 6.81-6.78 (m, 1H), 6.66-6.64 (m, 1H), 6.59 (d, *J* 7.6 Hz, 1H), 4.38-4.27 (m, 3H), 3.91 (d, *J* 7.6 Hz, 1H), 3.82-3.69 (m, 8H), 3.52 (dd, *J* 11.6, 3.3 Hz, 1H), 3.46-3.41 (m, 2H), 3.32-2.96 (m, 4H). LCMS (ES⁺) 449 (M+H)⁺.

EXAMPLE 411

1-{3-[(*S*)-4-(4-Chloro-3-hydroxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carbonyl}azetidine-3-carboxylic acid amide

To a stirred solution of *Example 248* (0.32 mg, 0.65 mmol) in EtOH (5 mL) was added sodium hydroxide (5.0 mL, 1M solution) and the reaction mixture was cooled to 0°C. Hydrogen peroxide (1.0 mL, 35% solution) was added and the reaction mixture was stirred at r.t. for 18 h. The reaction mixture was diluted with water (10 mL) and neutralised with Dowex, filtered and the resin washed with MeOH. The filtrate was concentrated *in vacuo* and the residue was purified using preparative HPLC, yielding the *title compound* (5 mg, 1%) as a white solid. δ_{H} (d₆-DMSO at 110°C) 8.22 (s, 1H), 7.84 (d, *J* 0.5 Hz, 1H), 7.49 (dd, *J* 8.6, 1.3 Hz, 1H), 7.40-7.38 (m, 1H), 7.21 (d, *J* 8.1 Hz, 1H), 7.13 (s, 1H), 6.99 (d, *J* 1.8 Hz, 2H), 6.58 (dd, *J* 8.1, 1.8 Hz, 1H), 4.37-4.19 (m, 6H), 3.92-3.90 (m, 1H), 3.85-3.76 (m, 5H), 3.56 (dd, *J* 11.4, 3.0 Hz, 1H), 3.51-3.42 (m, 3H), 3.31-3.28 (m, 2H). LCMS (ES⁺) 510 (M-H)⁺.

EXAMPLE 412

1-{3-[(*S*)-4-(3-Fluoro-5-hydroxybenzoyl)morpholin-3-ylmethyl]-1-methyl-1*H*-indole-5-carbonyl}azetidine-3-carboxylic acid

To a stirred solution of *Example 128* (0.40 mg, 0.84 mmol) in EtOH (5 mL) was added sodium hydroxide (5.0 mL, 1M solution) and the reaction mixture was cooled to 0°C. Hydrogen peroxide (1.0 mL, 35% solution) was added and the reaction mixture was stirred at r.t. for 18 h. The reaction mixture was diluted with water (10 mL) and neutralised with Dowex, filtered and the resin washed with MeOH. The filtrate was

concentrated *in vacuo* and the residue was purified using preparative HPLC, yielding the *title compound* (19 mg, 4%) as a white solid. δ_{H} (d_6 -DMSO at 110°C) 8.22 (s, 1H), 7.75 (s, 1H), 7.46-7.35 (m, 2H), 7.11 (s, 1H), 6.54 (dt, J 10.9, 2.0 Hz, 1H), 6.46 (s, 1H), 6.25 (d, J 8.6 Hz, 1H), 4.35-4.18 (m, 5H), 3.92-3.89 (m, 1H), 3.82-3.68 (m, 5H), 3.56 (dd, J 11.6, 3.0 Hz, 2H), 3.49-3.43 (m, 2H), 3.37-3.32 (m, 1H), 3.24 (dd, J 14.4, 8.1 Hz, 2H). LCMS (ES^+) 496 ($\text{M}+\text{H}$)⁺.

EXAMPLE 413

10 {{(S)-[5-(3-Aminoazetidine-1-carbonyl)-1-methyl-1*H*-indol-3-ylmethyl]morpholin-4-yl}-(5-chloro-6-methoxypyridin-3-yl)-methanone

To a stirred solution of *Intermediate 62* (140 mg, 0.23 mmol), azetidin-3-yl-carbamic acid *tert*-butyl ester (48 mg, 0.23 mmol), EDC (68 mg, 0.35 mmol) and HOBT (32 mg, 0.23 mmol) in DMF (5 mL) was added TEA (0.07 mL, 0.71 mmol). The reaction mixture was stirred at r.t. for 18 h, then partitioned between ethyl acetate (10 mL) and water (10 mL). The organic layer was washed with water (3 x 10 mL), dried (phase separator), concentrated *in vacuo* and chromatographed (SiO_2 , 20-60% EtOAc/hexanes), yielding an off-white solid. This material was dissolved in DCM (5 mL) and trifluoroacetic acid (3 mL) was added. The reaction mixture was stirred at r.t. for 2 h, quenched by the addition of sodium carbonate solution (20 mL) and extracted with DCM (20 mL). The combined organic layers were dried (sodium sulphate), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , 0-10% MeOH/EtOAc), yielding the *title compound* (64 mg, 38%) as a white solid. δ_{H} (d_6 -DMSO at 100°C) 7.90 (d, J 2.0 Hz, 1H), 7.82 (s, 1H), 7.48-7.41 (m, 2H), 7.39 (d, J 0.5 Hz, 1H), 7.15 (s, 1H), 4.47-4.45 (m, 2H), 4.38-4.32 (m, 1H), 4.21-4.18 (m, 2H), 4.14-4.07 (m, 1H), 3.98 (s, 3H), 3.94 (d, J 8.6 Hz, 1H), 3.85-3.83 (m, 1H), 3.78 (s, 4H), 3.65 (dd, J 11.6, 3.0 Hz, 1H), 3.57-3.49 (m, 2H), 3.19-3.15 (m, 4H). LCMS (ES^+) 498 ($\text{M}+\text{H}$)⁺.

EXAMPLE 414

3-[(S)-4-[5-Chloro-6-(methylamino)pyridine-3-carbonyl]morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

- 5 The *title compound* was prepared from *Intermediate 80* and methylamine according to *Method B* and was isolated as a white solid (53 mg, 47%). δ_{H} (d_6 -DMSO at 110°C) 7.87 (d, J 2.0 Hz, 1H), 7.55 (d, J 0.5 Hz, 1H), 7.38 (d, J 8.6 Hz, 1H), 7.19-7.16 (m, 2H), 7.09 (s, 1H), 6.32 (s, 1H), 4.35-4.30 (m, 1H), 3.93-3.91 (m, 1H), 3.84-3.81 (m, 2H), 3.77 (s, 3H), 3.61 (dd, J 11.6, 3.3 Hz, 1H), 3.54-3.48 (m, 2H), 3.16 (t, J 6.8 Hz, 2H),
10 2.98 (s, 6H), 2.92 (d, J 4.8 Hz, 3H). LCMS (ES^+) 469 ($\text{M}+\text{H}$)⁺.

EXAMPLE 415

3-[(S)-4-[5-Chloro-6-(methanesulfonylamino)pyridine-3-carbonyl]morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

- 15 To a stirred solution of *Intermediate 80* (200 mg, 0.42 mmol) in 1,4-dioxane (4 mL) were added methanesulfonamide (48 mg, 0.51 mmol), cesium carbonate (192 mg, 0.59 mmol), Xantphos (8 mg, 0.013 mmol) and $\text{Pd}_2(\text{dba})_3$ (3.9 mg, 0.004 mmol). The reaction mixture was heated to 100°C for 1 h, then partitioned between EtOAc (10 mL)
20 and brine (10 mL). The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The residue was purified by preparative HPLC, yielding the *title compound* (2 mg, 1%) as a white solid. δ_{H} (d_6 -DMSO at 110°C) 7.89 (d, J 2.3 Hz, 1H), 7.61 (s, 1H), 7.39 (d, J 8.3 Hz, 1H), 7.27 (d, J 2.0 Hz, 1H), 7.20 (dd, J 8.6, 1.5 Hz, 1H), 7.10 (s, 1H), 4.37-4.30 (m, 1H), 3.92 (d, J 8.1 Hz, 1H), 3.82-3.80 (m, 2H), 3.77 (s, 4H),
25 3.60 (dd, J 11.6, 3.3 Hz, 1H), 3.54-3.51 (m, 2H), 3.24-3.11 (m, 2H), 3.09 (s, 3H), 2.99 (s, 6H). LCMS (ES^+) 534($\text{M}+\text{H}$)⁺.

EXAMPLE 416

- 30 3-[(S)-4-(5-Methoxypyrazine-2-carbonyl)morpholin-3-ylmethyl]-1-methyl-1H-indole-5-carboxylic acid dimethylamide

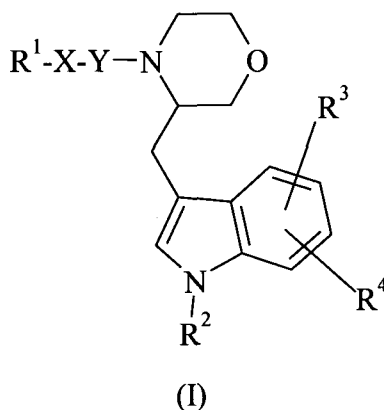
 To a stirred solution of *Example 250* (47 mg, 0.10 mmol) in methanol (1 mL) was added sodium methoxide (6 mg, 0.11 mmol) and the reaction mixture was heated to 50°C

for 2 h, then partitioned between EtOAc (10 mL) and brine (10 mL). The organic layer was separated, dried (magnesium sulphate) and concentrated *in vacuo*. The residue was purified by preparative HPLC, yielding the *title compound* (19 mg, 44%) as a white solid.

5 δ_{H} (d_6 -DMSO at 110°C) 8.08 (s, 1H), 8.02 (s, 1H), 7.51 (s, 1H), 7.34 (d, J 8.4 Hz, 1H), 7.17 (d, J 8.4 Hz, 1H), 7.06 (s, 1H), 4.56-4.54 (m, 1H), 4.03-4.00 (m, 1H), 3.97 (d, J 7.6 Hz, 1H), 3.94 (s, 3H), 3.83 (d, J 11.5 Hz, 1H), 3.75 (s, 3H), 3.60 (dd, J 11.5, 3.1 Hz, 1H), 3.55-3.48 (m, 2H), 3.23-3.15 (m, 2H), 2.99 (s, 6H). LCMS (ES^+) 438($\text{M}+\text{H}$) $^+$.

Claims:

1. A compound of formula (I) or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof:



wherein

X represents oxygen, N-R⁵ or a covalent bond;

Y represents C=O or S(O)₂;

R¹ represents C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents;

R² represents hydrogen; or optionally substituted C₁₋₆ alkyl;

R³ and R⁴ independently represent hydrogen, halogen, cyano, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, -OR^a, -SR^a, -SOR^a, -SO₂R^a, -NR^bR^c, -CH₂NR^bR^c, -NR^cCOR^d, -CH₂NR^cCOR^d, -NR^cCO₂R^d, -NHCONR^bR^c, -NR^cSO₂R^e, -N(SO₂R^e)₂, -NH₂SO₂NR^bR^c, -COR^d, -CO₂R^d, -CONR^bR^c, -CON(OR^a)R^b or -SO₂NR^bR^c; or C₁₋₆ alkyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents;

R⁵ represents hydrogen or C₁₋₆ alkyl;

R^a represents C₁₋₆ alkyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents;

R^b and R^c independently represent hydrogen or trifluoromethyl; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇

heterocycloalkyl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents; or

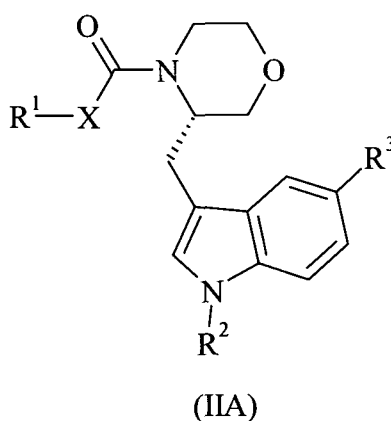
R^b and R^c, when taken together with the nitrogen atom to which they are both attached, represent azetidin-1-yl, pyrrolidin-1-yl, oxazolidin-3-yl, isoxazolidin-2-yl, thiazolidin-3-yl, isothiazolidin-2-yl, piperidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperazin-1-yl, homopiperidin-1-yl, homomorpholin-4-yl or homopiperazin-1-yl, any of which groups may be optionally substituted by one or more substituents;

R^d represents hydrogen; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, C₃₋₇ heterocycloalkyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents; and

R^e represents C₁₋₆ alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

2. A compound as claimed in claim 1 wherein the substituent at the 3-position of the morpholine ring is in the (*S*) configuration.

3. A compound as claimed in claim 1 represented by formula (IIA) or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof:

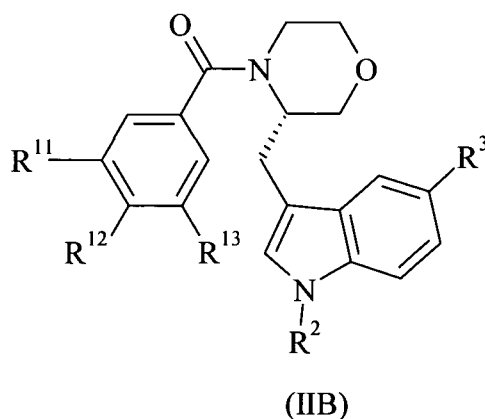


wherein X, R¹, R² and R³ are as defined in claim 1.

4. A compound as claimed in any one of the preceding claims wherein X represents oxygen or a covalent bond.

5. A compound as claimed in any one of the preceding claims wherein R¹ represents methyl, ethyl, propyl, *tert*-butyl, cyclopropyl, cyclohexylmethyl, phenyl, naphthyl, benzyl, tetrahydrofuryl, oxetanylmethyl, pyrrolidinylethyl, furyl, thienyl, thieno[2,3-*b*]pyridinyl, indolyl, pyrrolo[2,3-*b*]pyridinyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, benzimidazolyl, imidazo[1,2-*a*]pyridinyl, oxadiazolyl, triazolyl, pyridinyl, quinolinyl, 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl, pyrimidinyl, pyrazinyl, furylmethyl, indolylmethyl, thiazolylmethyl, imidazolylmethyl, imidazo[1,2-*a*]pyridinylmethyl, triazolylmethyl, benzotriazolylmethyl, tetrazolylmethyl or pyridinylmethyl, any of which groups may be optionally substituted by one or more substituents independently selected from halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl, aryl(C₁₋₆)alkyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, aryloxy, hydroxybenzoyloxy, (hydroxy)(methyl)benzoyloxy, C₁₋₄ alkylenedioxy, C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, oxo, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxycarbonylamino, aryl(C₁₋₆)alkoxycarbonylamino, C₁₋₆ alkylaminocarbonylamino, arylaminocarbonylamino, C₁₋₆ alkylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxycarbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl and di(C₁₋₆)alkylaminosulphonyl.

6. A compound as claimed in claim 3 represented by formula (IIB) or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof:



wherein

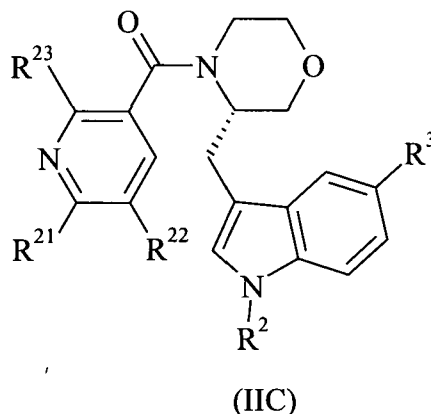
R² and R³ are as defined in claim 1;

R^{11} represents hydrogen, halogen, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, trifluoromethoxy or C_{1-6} alkylaminosulphonyl;

R^{12} represents hydrogen, halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, trifluoromethoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, amino or
5 di(C_{1-6})alkylamino; and

R^{13} represents hydrogen, halogen, trifluoromethyl or C_{1-6} alkoxy.

7. A compound as claimed in claim 3 represented by formula (IIC) or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof:



wherein

R^2 and R^3 are as defined in claim 1;

15 R^{21} represents hydrogen, halogen, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, trifluoroethoxy, C_{1-6} alkylthio, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxy carbonylamino, aryl(C_{1-6})alkoxy carbonylamino, C_{1-6} alkylaminocarbonylamino, arylaminocarbonylamino or C_{1-6} alkylsulphonylamino;

R^{22} represents hydrogen, halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, amino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxy carbonylamino or C_{1-6} alkylsulphonylamino; and

R^{23} represents hydrogen, halogen, cyano, C_{1-6} alkyl, C_{1-6} alkoxy or amino.

8. A compound as claimed in any one of the preceding claims wherein R^2
25 represents hydrogen or methyl.

9. A compound as claimed in any one of the preceding claims wherein R³ represents hydrogen, halogen, cyano, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, -OR^a, -SO₂R^a, -NR^bR^c, -CH₂NR^bR^c, -NR^cCOR^d, -CH₂NR^cCOR^d, -NR^cCO₂R^d, -NHCONR^bR^c, -NR^cSO₂R^e, -N(SO₂R^e)₂, -NHSO₂NR^bR^c, -COR^d, -CO₂R^d, -CONR^bR^c, -CON(OR^a)R^b or -SO₂NR^bR^c, wherein R^a, R^b, R^c, R^d and R^e are as defined in claim 1; or C₁₋₆ alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents independently selected from halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy and C₁₋₄ alkylenedioxy.

10. A compound as claimed in any one of the preceding claims wherein R⁴ represents hydrogen, halogen, -COR^d, -CO₂R^d or -CONR^bR^c, wherein R^b, R^c and R^d are as defined in claim 1.

11. A compound as herein specifically disclosed in any one of the Examples.

12. A compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

13. A compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment and/or prevention of a disorder for which the administration of a selective PI3K inhibitor is indicated.

14. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, in association with a pharmaceutically acceptable carrier.

15. The use of a compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prevention of a disorder for which the administration of a selective PI3K inhibitor is indicated.

16. A method for the treatment and/or prevention of a disorder for which the administration of a selective PI3K inhibitor is indicated which comprises administering to a patient in need of such treatment an effective amount of a compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/001171

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D413/06 C07D413/14 A61K31/5355 A61P35/00 A61P29/00
A61P9/00 A61P25/00

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/047109 A1 (UCB PHARMA SA [BE]; ALEXANDER RIKKI PETER [GB]; BROWN JULIEN ALISTAIR) 24 April 2008 (2008-04-24) pages 1,61; example 1 -----	1-16

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

13 September 2010

Date of mailing of the international search report

17/09/2010

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Authorized officer

Bourghida, E

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2010/001171

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008047109 A1	24-04-2008	EP 2084155 A1	05-08-2009