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(GB). **MACK, Stephen Robert** [GB/GB]; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **PITT, William Ross** [GB/GB]; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **RICHARD, Marianna Dilani** [GB/GB]; UCB Celltech, 208 Bath Road, Slough Berk SL1 3WE (GB). **SHARPE, Andrew** [GB/GB]; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **TAIT, Laura Jane** [GB/GB]; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB).

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(74) Agent: **THOMPSON, John**; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB).

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(71) Applicant (*for all designated States except US*): **UCB PHARMA S.A.** [BE/BE]; 60 Allée de la Recherche, B-1070 Brussels (BE).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **ALEXANDER, Rikki Peter** [GB/GB]; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **BAILEY, Stuart** [GB/GB]; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **BRAND, Stephen** [GB/GB]; Level 1, The James Black Building, Wellcome Foundation, Dundee University, Dundee DD1 5EH (GB). **BROOKINGS, Daniel Christopher** [GB/GB]; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **BROWN, Julien Alistair** [GB/GB]; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **HAUGHAN, Alan Findlay** [GB/GB]; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **KINSELLA, Natasha** [GB/GB]; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **LOWE, Christopher** [GB/GB]; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE

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(54) Title: FUSED THIOPHENE DERIVATIVES AS KINASE INHIBITORS

(57) Abstract: A series of 5,6-dihydro-1-benzothiophen-7(4H)-one derivatives, and analogues thereof, which are substituted in the 2-position by an optionally substituted morpholin-4-yl moiety, 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.

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FUSED THIOPHENE DERIVATIVES AS KINASE INHIBITORS

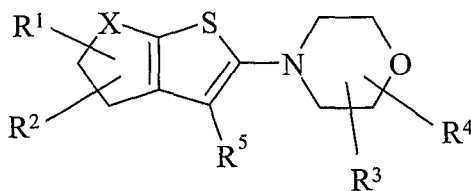
The present invention relates to a class of fused thiophene derivatives, and to their use in therapy. More particularly, the invention provides a family of 5,6-dihydro-1-benzothiophen-7(4*H*)-one derivatives, and analogues thereof, which are substituted in the 2-position by an optionally substituted morpholin-4-yl moiety. 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 of use in 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 of use in 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 use in this invention may be useful as radioligands in assays for detecting compounds capable of binding to human
5 PI3K enzymes.

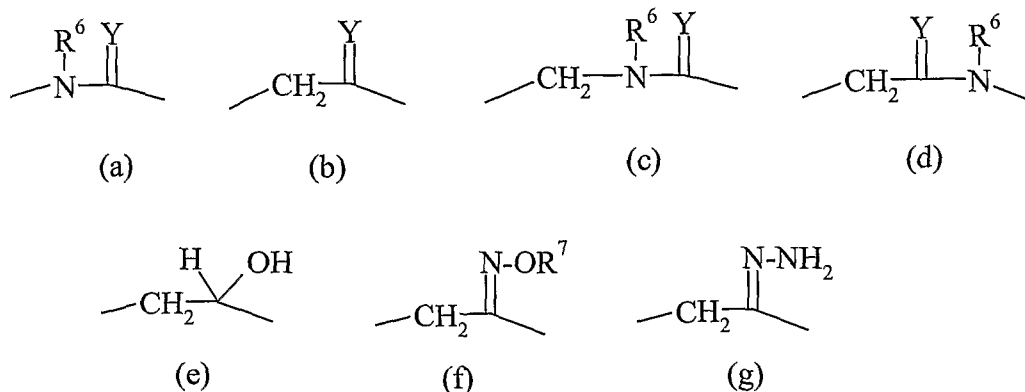
The compounds of use in the present invention are potent and selective PI3K inhibitors having a binding affinity (IC_{50}) for the human PI3K α and/or PI3K β and/or PI3K γ and/or PI3K δ isoform of 50 μ M or less, generally of 20 μ M or less, usually of 5 μ M or less, typically of 1 μ M or less, suitably of 500 nM or less, ideally of 100 nM or less, and
10 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.
15 The present invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof:



(I)

20 wherein

-X- represents a group of formula (a), (b), (c), (d), (e), (f) or (g):



Y represents oxygen or sulphur;

R^1 and R^2 independently represent hydrogen; or C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl-
 5 cycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; or

R^1 and R^2 , when both are attached to the same carbon atom, represent, when taken together with the carbon atom to which they are both attached, C_{3-7} cycloalkyl or C_{3-7}
 10 heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents; or

R^1 and R^2 , when attached to adjacent carbon atoms, represent, when taken together with the carbon atoms to which they are attached, C_{5-7} cycloalkyl, phenyl or heteroaryl, any of which groups may be optionally benzo-fused and/or substituted by one or more
 15 substituents;

R^3 and R^4 independently represent hydrogen; or C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, biaryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkylcarbonyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl-aryl(C_{1-6})alkyl or
 20 aryl-heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; or

R^3 and R^4 , when both are attached to the same carbon atom, represent, when taken together with the carbon atom to which they are both attached, C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be optionally substituted by one or more
 25 substituents; or

R^3 and R^4 , when attached to adjacent carbon atoms, represent, when taken together with the carbon atoms to which they are attached, C_{5-7} cycloalkyl, phenyl or heteroaryl,

any of which groups may be optionally benzo-fused and/or substituted by one or more substituents;

- R^5 represents hydrogen, halogen, cyano, $-SR^a$, $-COR^e$, $-CO_2R^b$ or $-CONR^cR^d$; or R^5 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkenylcarbonyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, C_{3-7} cycloalkyl(C_{2-6})alkenyl, C_{3-7} cycloalkyl(C_{2-6})alkynyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, biaryl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl(C_{2-6})alkenyl, C_{3-7} heterocycloalkyl(C_{2-6})alkynyl, C_{3-7} heterocycloalkylcarbonyl(C_{2-6})alkynyl, C_{5-9} heterobicycloalkyl(C_{2-6})alkynyl, C_{3-7} heterocycloalkyl-aryl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl-aryl, C_{3-7} heterocycloalkyl-biaryl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{1-6})alkylcarbonyl, heteroaryl(C_{2-6})alkenyl, heteroaryl(C_{2-6})alkynyl, heteroaroylcarbonyl, C_{3-7} heterocycloalkyl-heteroaryl, C_{3-7} heterocycloalkyl-heteroaryl(C_{2-6})alkynyl, heteroaryl-aryl, heteroaryl-aryl(C_{1-6})alkyl, aryl-heteroaryl, aryl-heteroaryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl-aryl-heteroaryl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl-aryl-heteroaryl, C_{5-9} heterobicycloalkyl(C_{1-6})alkyl-aryl-heteroaryl, heteroaryl-aryl-heteroaryl, bi(heteroaryl), C_{3-7} heterocycloalkylcarbonyl-bi(heteroaryl), aryloxyaryl, aryl(C_{1-6})alkoxyaryl, heteroaryl(C_{1-6})alkoxyaryl, aryl(C_{1-6})alkylaminoaryl, heteroaryl(C_{1-6})alkylaminoaryl, C_{3-7} cycloalkylcarbonylaminoaryl, arylcarbonylaminoaryl, aryl(C_{1-6})alkylcarbonylaminoaryl, C_{3-7} heterocycloalkylcarbonylaminoaryl, heteroarylcarbonylaminoaryl, aryl-
 20 (C_{3-7})heterocycloalkylcarbonylaminoaryl, arylsulphonylaminoaryl, aryl(C_{1-6})alkylsulphonylaminoaryl, heteroaryl(C_{1-6})alkylsulphonylaminoaryl, C_{3-7} cycloalkylaminocarbonylaminoaryl, arylaminocarbonylaminoaryl, C_{3-7} heterocycloalkylaminocarbonylaminoaryl, C_{3-7} heterocycloalkylaminocarbonylaminoaryl, heteroaryl(C_{1-6})alkylaminocarbonylaminoaryl, C_{3-7} heterocycloalkylcarbonylcarbonylaminoaryl, C_{3-7} heterocycloalkyl(C_{1-6})alkylaminocarbonylcarbonylaminoaryl, arylcarbonylaryl, C_{3-7} heterocycloalkylcarbonylaryl, C_{3-7} heterocycloalkylcarbonyl(C_{1-6})alkylaryl, aryl(C_{1-6})alkylaminocarbonylaryl, C_{3-7} heterocycloalkyl(C_{1-6})alkylaminocarbonylaryl, heteroarylaminocarbonylaryl, heteroaryl(C_{1-6})alkylaminocarbonylaryl, C_{3-7} heterocycloalkylaminocarbonyl(C_{1-6})alkylaryl, C_{3-7} heterocycloalkyl(C_{1-6})alkylaminocarbonyl(C_{1-6})alkylaryl, heteroarylaminocarbonyl(C_{1-6})alkylaryl, heteroaryl(C_{1-6})alkylaminocarbonyl(C_{1-6})alkylaryl, arylaminoheteroaryl, C_{3-7} heterocycloalkylamino-aryl-heteroaryl, C_{3-7} heterocycloalkylcarbonylamino-aryl-heteroaryl, C_{3-7} heterocycloalkylaminocarbonylamino-aryl-heteroaryl, C_{3-7} heterocycloalkylcarbonyl-aryl-heteroaryl, C_{3-7}

heterocycloalkyl(C₁₋₆)alkylcarbonyl-aryl-heteroaryl, C₅₋₉ heterobicycloalkylcarbonyl-aryl-heteroaryl, C₃₋₇ heterocycloalkylcarbonyl(C₁₋₆)alkyl-aryl-heteroaryl, C₃₋₇ heterocycloalkylaminocarbonyl-aryl-heteroaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylaminocarbonyl-aryl-heteroaryl or C₃₋₇ heterocycloalkylaminocarbonyl(C₁₋₆)alkyl-aryl-heteroaryl, any of which groups may be optionally substituted by one or more substituents;

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

R^b represents hydrogen; or optionally substituted C₁₋₆ alkyl;

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

R^d represents hydrogen or C₁₋₆ alkyl;

R^e represents C₁₋₆ alkyl; and

R⁶ and R⁷ independently represent hydrogen or C₁₋₆ alkyl.

The present invention also provides a compound of formula (I) as depicted above, or a pharmaceutically acceptable salt or solvate thereof, wherein

-X-, R¹, R², R³ and R⁴ are as defined above;

R⁵ represents hydrogen, halogen, cyano, -SR^a, -CO₂R^b or -CONR^cR^d; or R⁵ represents C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, C₃₋₇ cycloalkyl(C₂₋₆)alkenyl, C₃₋₇ cycloalkyl(C₂₋₆)alkynyl, aryl, aryl(C₁₋₆)alkyl, aryl-(C₂₋₆)alkenyl, aryl(C₂₋₆)alkynyl, biaryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl-(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl(C₂₋₆)alkenyl, C₃₋₇ heterocycloalkyl(C₂₋₆)alkynyl, C₅₋₉ heterobicycloalkyl(C₂₋₆)alkynyl, C₃₋₇ heterocycloalkyl-aryl, C₃₋₇ heterocycloalkyl-(C₁₋₆)alkyl-aryl, heteroaryl, heteroaryl(C₁₋₆)alkyl, heteroaryl(C₂₋₆)alkenyl, heteroaryl-(C₂₋₆)alkynyl, C₃₋₇ heterocycloalkyl-heteroaryl(C₂₋₆)alkynyl, heteroaryl-aryl, heteroaryl-aryl(C₁₋₆)alkyl, aryl-heteroaryl, aryl-heteroaryl(C₁₋₆)alkyl or bi(heteroaryl), any of which groups may be optionally substituted by one or more substituents; and

R^a, R^b, R^c and R^d are as defined above.

Where R¹ and/or R² and/or R³ and/or R⁴ in the compounds of formula (I) above is other than hydrogen, and/or where R⁵ is other than hydrogen, halogen or cyano, this group may be unsubstituted, or substituted by one or more substituents. Typically, R¹ and/or R² and/or R³ and/or R⁴ and/or R⁵ will be unsubstituted, or substituted by one or two

substitutents. Suitably, R¹ and/or R² and/or R³ and/or R⁴ and/or R⁵ 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 use in the invention include straight-chained and branched C₁₋₆ alkyl groups, for example C₁₋₄ 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 and 2,2-dimethylpropyl. Derived expressions such as "C₁₋₆ alkoxy", "C₁₋₆ alkylthio", "C₁₋₆ alkylsulphonyl" and "C₁₋₆ alkylamino" are to be construed accordingly.

Typical C₂₋₆ alkenyl groups include vinyl and allyl.

Typical C₂₋₆ alkynyl groups include ethynyl, prop-1-yn-1-yl, but-1-yn-1-yl and 3-methylbut-1-yn-1-yl.

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 naphthylmethyl.

Specific aryl(C₂₋₆)alkenyl groups include 2-phenylethenyl and 3-phenylprop-2-en-1-yl.

Specific aryl(C₂₋₆)alkynyl groups include phenylethynyl, 3-phenylprop-1-yn-1-yl and 3-phenylprop-2-yn-1-yl.

Particular biaryl groups include biphenyl and naphthylphenyl.

Suitable heterocycloalkyl groups, which may comprise benzo-fused analogues thereof, include azetidiny, tetrahydrofuranyl, pyrrolidinyl, indolinyl, imidazolidinyl, tetrahydropyranyl, piperidinyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl, piperazinyl, 1,2,3,4-tetrahydroquinoxalinyl, homopiperazinyl, morpholinyl, benzomorpholinyl and thiomorpholinyl.

Typical heterobicycloalkyl groups include quinuclidinyl, 8-azabicyclo[3.2.1]octyl and 3,8-diazabicyclo[3.2.1]octyl.

Suitable heteroaryl groups include furyl, benzofuryl, dibenzofuryl, thienyl, benzothienyl, dibenzothienyl, pyrrolyl, indolyl, pyrrolo[2,3-*b*]pyridinyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, imidazo[1,2-*a*]pyridinyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, benzotriazolyl, tetrazolyl, pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl and pyrazinyl groups.

Typical bi(heteroaryl) groups include benzofuryl-pyridinyl, benzothienyl-pyridinyl, indolyl-pyridinyl, isoxazolyl-pyridinyl, bipyridinyl and isoquinolinyl-pyridinyl.

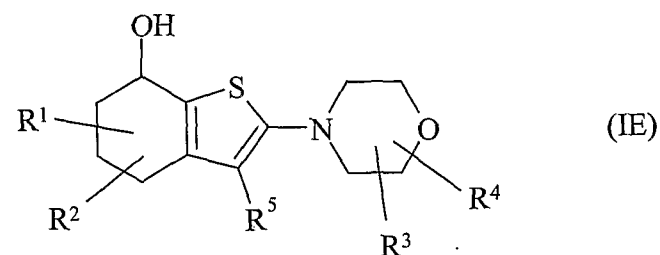
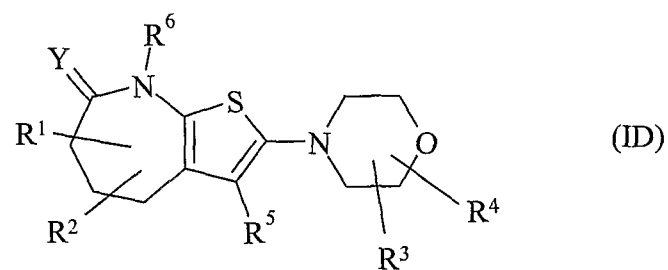
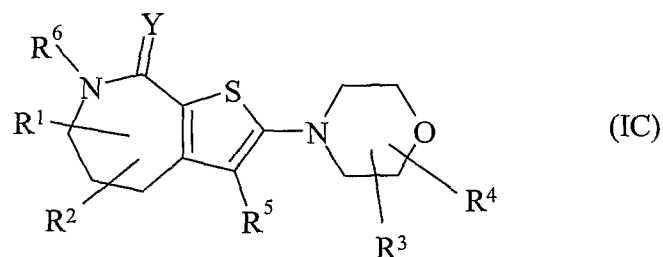
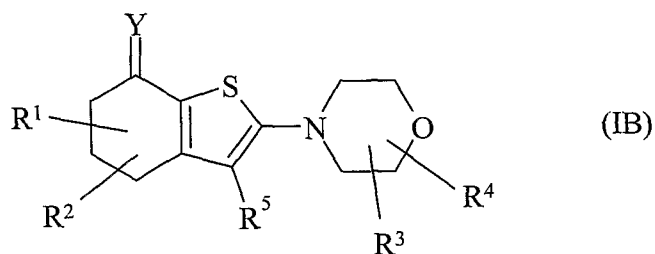
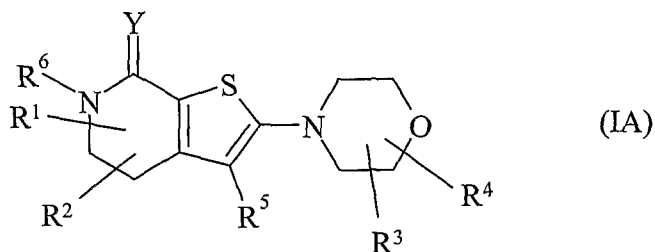
The term "halogen" as used herein is intended to include fluorine, chlorine, bromine and iodine atoms, especially fluoro or chloro.

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 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 exist as tautomers, for example keto (CH₂C=O)-enol (CH=CHOH) tautomers. Formula (I)

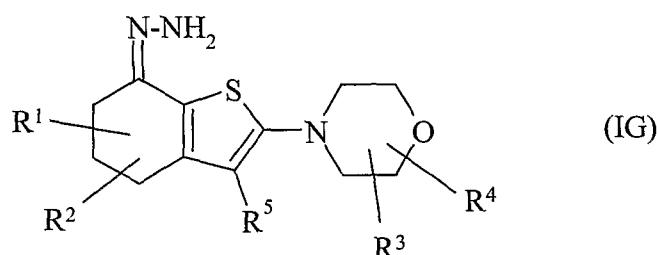
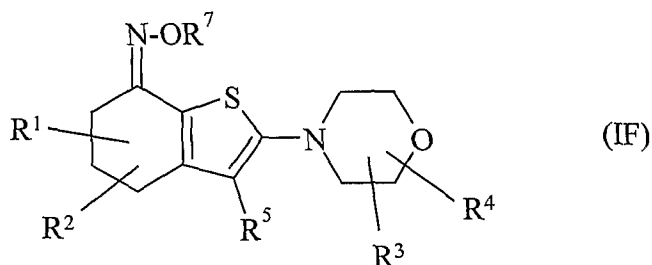
and the formulae depicted hereinafter are intended to represent all individual tautomers and all possible mixtures thereof, unless stated or shown otherwise.

Specific sub-classes of compounds in accordance with the present invention are represented by the compounds of formula (IA), (IB), (IC), (ID), (IE), (IF) and (IG):

5



10



wherein Y, R¹, R², R³, R⁴, R⁵, R⁶ and R⁷ are as defined above.

5 Particular sub-classes of compounds in accordance with the present invention are represented by the compounds of formula (IA), (IB) and (IC) as depicted above.

In the compounds of formula (I), -X- suitably represents a group of formula (a), (b) or (c) as depicted above. In one embodiment, -X- represents a group of formula (a). In another embodiment, -X- represents a group of formula (b). In a further embodiment, -X-
 10 represents a group of formula (c).

In one embodiment, Y is oxygen. In another embodiment, Y is sulphur.

Suitably, R¹ represents hydrogen; or C₁₋₆ alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

Suitably, R² represents hydrogen or optionally substituted C₁₋₆ alkyl.

15 Examples of typical substituents on R¹ and/or R² include halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxy carbonylamino, 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)alkylaminosulphonyl; especially halogen, C₁₋₆ alkoxy or C₁₋₆ alkylthio.

20 Examples of particular substituents on R¹ and/or R² include fluoro, chloro, bromo, cyano, nitro, methyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, phenoxy, methylthio, methylsulphonyl, amino, methylamino, dimethylamino, acetyl, carboxy, methoxycarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy,

methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl; especially chloro, methoxy or methylthio.

Typical values of R^1 include hydrogen, methyl, *n*-propyl, isopropyl, phenyl, chlorophenyl, methoxyphenyl, methylthiophenyl and furyl. In one embodiment, R^1 is hydrogen. A particular value of R^1 is methyl.

Typical values of R^2 include hydrogen and methyl. In one embodiment, R^2 is hydrogen. In another embodiment, R^2 is C_{1-6} alkyl, especially methyl.

Alternatively, R^1 and R^2 , when both are attached to the same carbon atom, may together form an optionally substituted spiro linkage. Thus, R^1 and R^2 , when both are attached to the same carbon atom, may represent, when taken together with the carbon atom to which they are both attached, C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be unsubstituted, or substituted by one or more, typically by one or two, substituents. In this context, R^1 and R^2 , when taken together with the carbon atom to which they are both attached, may suitably represent an optionally substituted cyclopentyl, cyclohexyl, pyrrolidine or piperidine ring, especially cyclopentyl or cyclohexyl.

Alternatively, R^1 and R^2 , when attached to adjacent carbon atoms, may together form an optionally benzo-fused and/or substituted cycloalkyl, phenyl or heteroaryl (e.g. pyridinyl) ring fused to the ring containing the variable X. Thus, R^1 and R^2 , when attached to adjacent carbon atoms, may represent, when taken together with the carbon atoms to which they are attached, C_{5-7} cycloalkyl, phenyl or heteroaryl (e.g. pyridinyl), any of which groups may be benzo-fused and/or unsubstituted, or substituted by one or more, typically by one or two, substituents. In this context, in one embodiment, R^1 and R^2 , when taken together with the adjacent carbon atoms to which they are attached, suitably represent a phenyl ring fused to the ring containing the variable X. Also in this context, in another embodiment, R^1 and R^2 , when taken together with the adjacent carbon atoms to which they are attached, suitably represent a benzo-fused cyclopentyl ring, i.e. an indanyl moiety fused to the ring containing the variable X.

Typically, R^3 represents hydrogen; or C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, aryl- (C_{2-6}) alkynyl, biaryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl-carbonyl, heteroaryl(C_{1-6})alkyl, heteroaryl-aryl(C_{1-6})alkyl or aryl-heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

In a representative embodiment, R³ represents C₁₋₆ alkyl, aryl(C₁₋₆)alkyl, biaryl-(C₁₋₆)alkyl, heteroaryl(C₁₋₆)alkyl or heteroaryl-aryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents. Preferably, R³ represents methyl, arylmethyl, biarylmethyl, heteroarylmethyl or heteroaryl-arylmethyl, any of which groups
 5 may be optionally substituted by one or more substituents.

In a particular embodiment, R³ represents substituted or unsubstituted indolyl-(C₁₋₆)alkyl. Advantageously, R³ represents substituted or unsubstituted indolylmethyl.

Illustratively, R³ represents hydrogen; or methyl, phenyl, benzyl, phenylethyl, naphthylmethyl, phenylpropynyl, biphenylmethyl, naphthylphenylmethyl,
 10 indolylmethyl, 1,2,3,4-tetrahydroquinolylmethyl, 1,2,3,4-tetrahydroisoquinolylmethyl, piperidinylcarbonyl, 1,2,3,4-tetrahydroquinolylcarbonyl, 1,2,3,4-tetrahydroisoquinolylcarbonyl, 1,2,3,4-tetrahydroquinoxalylcarbonyl, benzothienylmethyl, indolylmethyl, pyrrolo[2,3-*b*]pyridylmethyl, benzimidazolylmethyl, benzotriazolylmethyl, pyridylmethyl, quinolylmethyl, isoquinolylmethyl,
 15 benzofurylbenzyl, thienylbenzyl, benzothienylbenzyl, indolylbenzyl, isoxazolylbenzyl, pyrazolylbenzyl, pyridylbenzyl, pyrimidinylbenzyl or phenylpyridylmethyl, any of which groups may be optionally substituted by one or more substituents.

Suitably, R⁴ represents hydrogen or optionally substituted C₁₋₆ alkyl.

Examples of suitable substituents on R³ and/or R⁴ include halogen, cyano, nitro,
 20 C₁₋₆ alkyl, hydroxy(C₁₋₆)alkyl, trifluoromethyl, aryl(C₁₋₆)alkyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, aryl(C₁₋₆)alkoxy, methylenedioxy, C₁₋₆ alkylthio, arylthio, C₁₋₆ alkylsulphonyl, arylsulphonyl, C₁₋₆ alkylsulphonyloxy, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, phenylamino, [(C₁₋₆)alkyl](phenyl)amino, pyridinylamino, pyrrolidinyl, morpholinyl, C₂₋₆ alkylcarbonylamino, benzofurylcarbonylamino, C₂₋₆
 25 alkoxycarbonylamino, C₁₋₆ alkylsulphonylamino, arylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxycarbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, benzothienylmethylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl and di(C₁₋₆)alkylaminosulphonyl.

Examples of representative substituents on R³ and/or R⁴ include fluoro, chloro,
 30 bromo, cyano, nitro, methyl, hydroxymethyl, trifluoromethyl, benzyl, hydroxy, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, phenoxy, benzyloxy, methylenedioxy, methylthio, phenylthio, methylsulphonyl, phenylsulphonyl, methylsulphonyloxy, amino, methylamino, dimethylamino, phenylamino, *N*-methyl-*N*-phenylamino, pyridinylamino,

pyrrolidinyl, morpholinyl, acetylamino, benzofurylcarbonylamino, methoxycarbonylamino, methylsulphonylamino, phenylsulphonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, benzothienylmethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and

5 dimethylaminosulphonyl.

Specific values of R^3 include hydrogen, methyl, phenoxyethyl, phenylthiomethyl, aminomethyl, phenylaminomethyl, *N*-methyl-*N*-phenylaminomethyl, pyridinylaminomethyl, benzofurylcarbonylaminomethyl, phenylsulphonylaminomethyl, benzothienylmethylaminocarbonylmethyl, phenyl, benzyl, chlorobenzyl, bromobenzyl, pyrrolidinyl-

10 benzyl, morpholinyl-benzyl, phenylethyl, naphthylmethyl, phenylpropynyl, biphenylmethyl, fluorobiphenylmethyl, difluorobiphenylmethyl, chlorobiphenylmethyl, dichlorobiphenylmethyl, bromobiphenylmethyl, cyanobiphenylmethyl, methylbiphenylmethyl, (fluoro)(methyl)biphenylmethyl, dimethylbiphenylmethyl, hydroxymethylbiphenylmethyl, trifluoromethylbiphenylmethyl, bis(trifluoromethyl)biphenylmethyl,

15 methoxybiphenylmethyl, dimethoxybiphenylmethyl, ethoxybiphenylmethyl, methylenedioxybiphenylmethyl, trifluoromethoxybiphenylmethyl, phenoxybiphenylmethyl, methylthiobiphenylmethyl, aminobiphenylmethyl, acetylamino-biphenylmethyl, methylsulphonylaminobiphenylmethyl, acetylaminobiphenylmethyl, aminocarbonylbiphenylmethyl, naphthylphenylmethyl, indolylmethyl, 1,2,3,4-

20 tetrahydroquinolylmethyl, 1,2,3,4-tetrahydroisoquinolylmethyl, piperidinylcarbonyl, 1,2,3,4-tetrahydroquinolylcarbonyl, methyl-1,2,3,4-tetrahydroquinolylcarbonyl, methoxy-1,2,3,4-tetrahydroquinolylcarbonyl, 1,2,3,4-tetrahydroisoquinolylcarbonyl, 1,2,3,4-tetrahydroquinoxalylcarbonyl, benzothienylmethyl, indolylmethyl, methylindolylmethyl, hydroxyindolylmethyl, benzyloxyindolylmethyl, acetylindolylmethyl,

25 methylsulphonyloxyindolylmethyl, pyrrolo[2,3-*b*]pyridinylmethyl, benzimidazolylmethyl, benzotriazolylmethyl, bromopyridinylmethyl, quinolylmethyl, isoquinolylmethyl, benzofurylbenzyl, thienylbenzyl, methylthienylbenzyl, acetylthienylbenzyl, benzothienylbenzyl, phenylsulphonylindolylbenzyl, dimethylisoxazolylbenzyl, methylpyrazolylbenzyl, benzylpyrazolylbenzyl, pyridinylbenzyl, fluoropyridinylbenzyl,

30 chloropyridinylbenzyl, methoxypyridinylbenzyl, pyrimidinylbenzyl and phenylpyridinylmethyl.

Typical values of R^4 include hydrogen and methyl. In a preferred embodiment, R^4 is hydrogen. In another embodiment, R^4 is C_{1-6} alkyl, especially methyl.

Alternatively, R^3 and R^4 , when both are attached to the same carbon atom, may together form an optionally substituted spiro linkage. Thus, R^3 and R^4 , when both are attached to the same carbon atom, may represent, when taken together with the carbon atom to which they are both attached, C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be unsubstituted, or substituted by one or more, typically by one or two, substituents. In this context, R^3 and R^4 , when taken together with the carbon atom to which they are both attached, may suitably represent an optionally substituted cyclopentyl, cyclohexyl, pyrrolidine or piperidine ring, especially cyclopentyl or cyclohexyl.

Alternatively, R^3 and R^4 , when attached to adjacent carbon atoms, may together form an optionally benzo-fused and/or substituted cycloalkyl, phenyl or heteroaryl (e.g. pyridinyl) ring fused to the morpholine ring. Thus, R^3 and R^4 , when attached to adjacent carbon atoms, may represent, when taken together with the carbon atoms to which they are attached, C_{5-7} cycloalkyl, phenyl or heteroaryl (e.g. pyridinyl), any of which groups may be benzo-fused and/or unsubstituted, or substituted by one or more, typically by one or two, substituents. In this context, in one embodiment, R^3 and R^4 , when taken together with the adjacent carbon atoms to which they are attached, suitably represent a phenyl ring fused to the morpholine ring. Also in this context, in another embodiment, R^3 and R^4 , when taken together with the adjacent carbon atoms to which they are attached, suitably represent a benzo-fused cyclopentyl ring, i.e. an indanyl moiety fused to the morpholine ring.

Suitably, R^a represents substituted or unsubstituted aryl.

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

Examples of typical substituents on R^a and/or R^b and/or R^c include halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxycarbonylamino, C_{1-6} alkylsulphonylamino, formyl, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, aminocarbonyl, C_{1-6} alkylamino-carbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulphonyl, C_{1-6} alkylaminosulphonyl and di(C_{1-6})alkylaminosulphonyl.

Examples of particular substituents on R^a and/or R^b and/or R^c include fluoro, chloro, bromo, cyano, nitro, methyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy,

trifluoromethoxy, phenoxy, methylthio, methylsulphonyl, amino, methylamino, dimethylamino, acetylamino, methoxycarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and
 5 dimethylaminosulphonyl.

A particular value of R^a is phenyl.

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

Particular values of R^c include hydrogen, phenyl, benzyl, pyridinylmethyl and
 10 (phenyl)(pyridinyl)methyl.

In one embodiment, R^d represents hydrogen. In another embodiment, R^d represents C₁₋₆ alkyl, especially methyl or ethyl, particularly ethyl.

Suitably, R^e represents methyl.

Generally, R^f represents hydrogen, halogen, cyano, -SR^a, -COR^e, -CO₂R^b or
 15 -CONR^cR^d; or R^f represents C₁₋₆ alkyl, C₂₋₆ alkenylcarbonyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl(C₂₋₆)alkynyl, aryl, aryl(C₁₋₆)alkyl, aryl(C₂₋₆)alkenyl, aryl(C₂₋₆)alkynyl, biaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl(C₂₋₆)alkynyl, C₃₋₇ heterocycloalkylcarbonyl(C₂₋₆)alkynyl, C₅₋₉ heterobicycloalkyl(C₂₋₆)alkynyl, C₃₋₇ heterocycloalkyl-aryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl-aryl, C₃₋₇ heterocycloalkyl-biaryl,
 20 heteroaryl, heteroaryl(C₁₋₆)alkyl, heteroaryl(C₁₋₆)alkylcarbonyl, heteroaryl(C₂₋₆)alkenyl, heteroaryl(C₂₋₆)alkynyl, heteroarylcarbonyl, C₃₋₇ heterocycloalkyl-heteroaryl, C₃₋₇ heterocycloalkyl-heteroaryl(C₂₋₆)alkynyl, heteroaryl-aryl, aryl-heteroaryl, C₃₋₇ heterocycloalkyl-aryl-heteroaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl-aryl-heteroaryl, C₅₋₉ heterobicycloalkyl(C₁₋₆)alkyl-aryl-heteroaryl, heteroaryl-aryl-heteroaryl, bi(heteroaryl),
 25 C₃₋₇ heterocycloalkylcarbonyl-bi(heteroaryl), aryloxyaryl, aryl(C₁₋₆)alkoxyaryl, heteroaryl(C₁₋₆)alkoxyaryl, aryl(C₁₋₆)alkylaminoaryl, heteroaryl(C₁₋₆)alkylaminoaryl, C₃₋₇ cycloalkylcarbonylaminoaryl, arylcarbonylaminoaryl, aryl(C₁₋₆)alkylcarbonylaminoaryl, C₃₋₇ heterocycloalkylcarbonylaminoaryl, heteroarylcarbonylaminoaryl, aryl-
 30 (C₃₋₇)heterocycloalkylcarbonylaminoaryl, arylsulphonylaminoaryl, aryl(C₁₋₆)alkylsulphonylaminoaryl, heteroaryl(C₁₋₆)alkylsulphonylaminoaryl, C₃₋₇ cycloalkylamino-
 carbonylaminoaryl, arylaminocarbonylaminoaryl, C₃₋₇ heterocycloalkylaminocarbonylaminoaryl, C₃₋₇ heterocycloalkylaminocarbonylaminoaryl, heteroaryl(C₁₋₆)alkyl-
 aminocarbonylaminoaryl, C₃₋₇ heterocycloalkylcarbonylcarbonylaminoaryl, C₃₋₇

- heterocycloalkyl(C₁₋₆)alkylaminocarbonylcarbonylaminoaryl, arylcarbonylaryl, C₃₋₇ heterocycloalkylcarbonylaryl, C₃₋₇ heterocycloalkylcarbonyl(C₁₋₆)alkylaryl, aryl(C₁₋₆)alkylaminocarbonylaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylaminocarbonylaryl, heteroarylaminocarbonylaryl, heteroaryl(C₁₋₆)alkylaminocarbonylaryl, C₃₋₇ heterocycloalkylamino-
- 5 carbonyl(C₁₋₆)alkylaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylaminocarbonyl(C₁₋₆)alkylaryl, heteroarylaminocarbonyl(C₁₋₆)alkylaryl, heteroaryl(C₁₋₆)alkylaminocarbonyl(C₁₋₆)alkylaryl, arylaminoheteroaryl, C₃₋₇ heterocycloalkylamino-aryl-heteroaryl, C₃₋₇ heterocycloalkylcarbonylamino-aryl-heteroaryl, C₃₋₇ heterocycloalkylaminocarbonylamino-aryl-heteroaryl, C₃₋₇ heterocycloalkylcarbonyl-aryl-heteroaryl, C₃₋₇
- 10 heterocycloalkyl(C₁₋₆)alkylcarbonyl-aryl-heteroaryl, C₅₋₉ heterobicycloalkylcarbonyl-aryl-heteroaryl, C₃₋₇ heterocycloalkylcarbonyl(C₁₋₆)alkyl-aryl-heteroaryl, C₃₋₇ heterocycloalkylaminocarbonyl-aryl-heteroaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylaminocarbonyl-aryl-heteroaryl or C₃₋₇ heterocycloalkylaminocarbonyl(C₁₋₆)alkyl-aryl-heteroaryl, any of which groups may be optionally substituted by one or more substituents.
- 15 Typically, R⁵ represents hydrogen, halogen, cyano, -SR^a, -CO₂R^b or -CONR^cR^d; or R⁵ represents C₁₋₆ alkyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl(C₂₋₆)alkynyl, aryl, aryl(C₁₋₆)alkyl, aryl(C₂₋₆)alkynyl, biaryl, C₃₋₇ heterocycloalkyl(C₂₋₆)alkynyl, C₅₋₉ heterobicycloalkyl(C₂₋₆)alkynyl, C₃₋₇ heterocycloalkyl-aryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl-aryl, heteroaryl, heteroaryl(C₂₋₆)alkynyl, C₃₋₇ heterocycloalkyl-heteroaryl(C₂₋₆)alkynyl, heteroaryl-aryl,
- 20 aryl-heteroaryl or bi(heteroaryl), any of which groups may be optionally substituted by one or more substituents.

In an illustrative embodiment, R⁵ represents hydrogen; or C₂₋₆ alkynyl, C₃₋₇ cycloalkyl(C₂₋₆)alkynyl, aryl, aryl(C₂₋₆)alkynyl, biaryl, C₃₋₇ heterocycloalkyl(C₂₋₆)alkynyl, C₃₋₇ heterocycloalkylcarbonyl(C₂₋₆)alkynyl, C₅₋₉ heterobicycloalkyl(C₂₋₆)alkynyl, C₃₋₇

25 heterocycloalkyl-aryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl-aryl, C₃₋₇ heterocycloalkyl-biaryl, heteroaryl, heteroaryl(C₂₋₆)alkynyl, C₃₋₇ heterocycloalkyl-heteroaryl, C₃₋₇ heterocycloalkyl-heteroaryl(C₂₋₆)alkynyl, heteroaryl-aryl, aryl-heteroaryl, C₃₋₇ heterocycloalkyl-aryl-heteroaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl-aryl-heteroaryl, C₅₋₉ heterobicycloalkyl(C₁₋₆)alkyl-aryl-heteroaryl, heteroaryl-aryl-heteroaryl, bi(heteroaryl),

30 C₃₋₇ heterocycloalkylcarbonyl-bi(heteroaryl), aryloxyaryl, aryl(C₁₋₆)alkoxyaryl, heteroaryl(C₁₋₆)alkoxyaryl, aryl(C₁₋₆)alkylaminoaryl, heteroaryl(C₁₋₆)alkylaminoaryl, C₃₋₇ cycloalkylcarbonylaminoaryl, arylcarbonylaminoaryl, aryl(C₁₋₆)alkylcarbonylaminoaryl, C₃₋₇ heterocycloalkylcarbonylaminoaryl, heteroarylcarbonylaminoaryl, aryl-

(C₃₋₇)heterocycloalkylcarbonylaminoaryl, arylsulphonylaminoaryl, aryl(C₁₋₆)alkylsulphonylaminoaryl, heteroaryl(C₁₋₆)alkylsulphonylaminoaryl, C₃₋₇ cycloalkylamino-carbonylaminoaryl, arylaminocarbonylaminoaryl, C₃₋₇ heterocycloalkylaminocarbonylaminoaryl, C₃₋₇ heterocycloalkylaminocarbonylaminoaryl, heteroaryl(C₁₋₆)alkylaminocarbonylaminoaryl, C₃₋₇ heterocycloalkylcarbonylcarbonylaminoaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylaminocarbonylcarbonylaminoaryl, arylcarbonylaryl, C₃₋₇ heterocycloalkylcarbonylaryl, C₃₋₇ heterocycloalkylcarbonyl(C₁₋₆)alkylaryl, aryl(C₁₋₆)alkylaminocarbonylaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylaminocarbonylaryl, heteroarylaminocarbonylaryl, heteroaryl(C₁₋₆)alkylaminocarbonylaryl, C₃₋₇ heterocycloalkylamino-carbonyl(C₁₋₆)alkylaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylaminocarbonyl(C₁₋₆)alkylaryl, heteroarylaminocarbonyl(C₁₋₆)alkylaryl, heteroaryl(C₁₋₆)alkylaminocarbonyl(C₁₋₆)alkylaryl, arylaminoheteroaryl, C₃₋₇ heterocycloalkylamino-aryl-heteroaryl, C₃₋₇ heterocycloalkylcarbonylamino-aryl-heteroaryl, C₃₋₇ heterocycloalkylaminocarbonylamino-aryl-heteroaryl, C₃₋₇ heterocycloalkylcarbonyl-aryl-heteroaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylcarbonyl-aryl-heteroaryl, C₅₋₉ heterobicycloalkylcarbonyl-aryl-heteroaryl, C₃₋₇ heterocycloalkylcarbonyl(C₁₋₆)alkyl-aryl-heteroaryl, C₃₋₇ heterocycloalkylaminocarbonyl-aryl-heteroaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylaminocarbonyl-aryl-heteroaryl or C₃₋₇ heterocycloalkylaminocarbonyl(C₁₋₆)alkyl-aryl-heteroaryl, any of which groups may be optionally substituted by one or more substituents.

20 In one aspect, R⁵ represents C₂₋₆ alkynyl, C₃₋₇ cycloalkyl(C₂₋₆)alkynyl, aryl(C₂₋₆)alkynyl, C₃₋₇ heterocycloalkyl(C₂₋₆)alkynyl, C₃₋₇ heterocycloalkylcarbonyl(C₂₋₆)alkynyl, C₅₋₉ heterobicycloalkyl(C₂₋₆)alkynyl, heteroaryl(C₂₋₆)alkynyl or C₃₋₇ heterocycloalkyl-heteroaryl(C₂₋₆)alkynyl, any of which groups may be optionally substituted by one or more substituents.

25 In another aspect, R⁵ represents aryl, biaryl, C₃₋₇ heterocycloalkyl-aryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl-aryl, C₃₋₇ heterocycloalkyl-biaryl, heteroaryl, C₃₋₇ heterocycloalkyl-heteroaryl, heteroaryl-aryl, aryl-heteroaryl, C₃₋₇ heterocycloalkyl-aryl-heteroaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl-aryl-heteroaryl, C₅₋₉ heterobicycloalkyl(C₁₋₆)alkyl-aryl-heteroaryl, heteroaryl-aryl-heteroaryl, bi(heteroaryl), C₃₋₇ heterocycloalkylcarbonyl-bi(heteroaryl), aryloxyaryl, aryl(C₁₋₆)alkoxyaryl, heteroaryl(C₁₋₆)alkoxyaryl, aryl(C₁₋₆)alkylaminoaryl, heteroaryl(C₁₋₆)alkylaminoaryl, C₃₋₇ cycloalkylcarbonylaminoaryl, arylcarbonylaminoaryl, aryl(C₁₋₆)alkylcarbonylaminoaryl, C₃₋₇ heterocycloalkylcarbonylaminoaryl, heteroarylcarbonylaminoaryl, aryl-

(C₃₋₇)heterocycloalkylcarbonylaminoaryl, arylsulphonylaminoaryl, aryl(C₁₋₆)alkylsulphonylaminoaryl, heteroaryl(C₁₋₆)alkylsulphonylaminoaryl, C₃₋₇ cycloalkylaminocarbonylaminoaryl, arylaminocarbonylaminoaryl, C₃₋₇ heterocycloalkylaminocarbonylaminoaryl, C₃₋₇ heterocycloalkylaminocarbonylaminoaryl, heteroaryl(C₁₋₆)alkylaminocarbonylaminoaryl, C₃₋₇ heterocycloalkylcarbonylcarbonylaminoaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylaminocarbonylcarbonylaminoaryl, arylcarbonylaryl, C₃₋₇ heterocycloalkylcarbonylaryl, C₃₋₇ heterocycloalkylcarbonyl(C₁₋₆)alkylaryl, aryl(C₁₋₆)alkylaminocarbonylaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylaminocarbonylaryl, heteroarylaminocarbonylaryl, heteroaryl(C₁₋₆)alkylaminocarbonylaryl, C₃₋₇ heterocycloalkylaminocarbonyl(C₁₋₆)alkylaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylaminocarbonyl(C₁₋₆)alkylaryl, heteroarylaminocarbonyl(C₁₋₆)alkylaryl, heteroaryl(C₁₋₆)alkylaminocarbonyl(C₁₋₆)alkylaryl, arylaminoheteroaryl, C₃₋₇ heterocycloalkylamino-aryl-heteroaryl, C₃₋₇ heterocycloalkylcarbonylamino-aryl-heteroaryl, C₃₋₇ heterocycloalkylaminocarbonylamino-aryl-heteroaryl, C₃₋₇ heterocycloalkylcarbonyl-aryl-heteroaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylcarbonyl-aryl-heteroaryl, C₅₋₉ heterobicycloalkylcarbonyl-aryl-heteroaryl, C₃₋₇ heterocycloalkylcarbonyl(C₁₋₆)alkyl-aryl-heteroaryl, C₃₋₇ heterocycloalkylaminocarbonyl-aryl-heteroaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylaminocarbonyl-aryl-heteroaryl or C₃₋₇ heterocycloalkylaminocarbonyl(C₁₋₆)alkyl-aryl-heteroaryl, any of which groups may be optionally substituted by one or more substituents.

In a representative embodiment, R⁵ represents hydrogen; or C₂₋₆ alkynyl, C₃₋₇ cycloalkyl(C₂₋₆)alkynyl, aryl, aryl(C₂₋₆)alkynyl, biaryl, heteroaryl, heteroaryl(C₂₋₆)alkynyl, heteroaryl-aryl, aryl-heteroaryl or bi(heteroaryl), any of which groups may be optionally substituted by one or more substituents.

Suitably, R⁵ represents hydrogen, halogen, cyano, -SR^a, -COR^e, -CO₂R^b or -CONR^cR^d; or R⁵ represents methyl, propyl, ethenylcarbonyl, ethynyl, propynyl, butynyl, 3-methylbutynyl, cyclopropylethynyl, cyclohexylethynyl, phenyl, naphthyl, benzyl, phenylethyl, phenylethenyl, phenylethynyl, phenylpropynyl, biphenyl, piperidinylethyl, pyrrolidinylethynyl, piperidinylethynyl, 1,2,3,4-tetrahydroisoquinolinylpropynyl, piperazinylpropynyl, pyrrolidinylcarbonylethynyl, quinuclidinylethynyl, piperazinylphenyl, morpholinylphenyl, piperidinylmethylphenyl, piperazinyl-biphenyl, benzofuryl, dibenzofuryl, benzothienyl, dibenzothienyl, pyridinyl, isoquinolinyl, imidazolylethyl, imidazolylmethylcarbonyl, imidazolylethenyl, indolylethynyl, pyrazolylethynyl, imidazolylethynyl, pyridinylethynyl, pyrimidinylethynyl, imidazo[1,2-*a*]pyridinylethynyl,

imidazolylcarbonylcarbonyl, benzomorpholinyl-pyridinyl, pyrrolidinylpyridinylethynyl, pyrazolylphenyl, pyridinylphenyl, phenylisoxazolyl, phenylthiazolyl, phenylpyridinyl, phenylpyrimidinyl, azetidinyphenylpyridinyl, pyrrolidinylphenylpyridinyl, piperidinylphenylpyridinyl, piperazinylphenylpyridinyl, morpholinylphenylpyridinyl, 5 piperazinylphenylpyrimidinyl, pyrrolidinylmethylphenylpyridinyl, piperidinylmethylphenylpyridinyl, piperazinylmethylphenylpyridinyl, homopiperazinylmethylphenylpyridinyl, morpholinylmethylphenylpyridinyl, azabicyclo[3.2.1]octylmethylphenylpyridinyl, diazabicyclo[3.2.1]octylmethylphenylpyridinyl, tetrazolylphenylpyridinyl, benzofurylpyridinyl, benzothienylpyridinyl, indolylpyridinyl, isoxazolylpyridinyl, 10 bi(pyridinyl), isoquinolinylpyridinyl, morpholinylcarbonylbi(pyridinyl), phenoxyphenyl, benzyloxyphenyl, pyridinylmethoxyphenyl, benzylaminophenyl, furylmethylaminophenyl, pyridinylmethylaminophenyl, cyclopentylcarbonylaminophenyl, phenylcarbonylamino-phenyl, benzylcarbonylaminophenyl, pyrrolidinylcarbonylaminophenyl, piperidinylcarbonylaminophenyl, piperazinylcarbonylaminophenyl, morpholinylcarbonylamino-15 phenyl, indolylcarbonylaminophenyl, isoxazolylcarbonylaminophenyl, pyridinylcarbonylaminophenyl, phenylpyrrolidinylcarbonylaminophenyl, phenylsulphonylaminophenyl, benzylsulphonylaminophenyl, isoxazolylsulphonylaminophenyl, cyclopentylaminocarbonylaminophenyl, phenylaminocarbonylaminophenyl, azetidylaminocarbonylaminophenyl, morpholinylethylaminocarbonylaminophenyl, imidazolylmethylaminocarbonylaminophenyl, morpholinylcarbonylcarbonylaminophenyl, pyrrolidinylethylaminocarbonylcarbonylaminophenyl, phenylcarbonylphenyl, morpholinylcarbonylphenyl, pyrrolidinylcarbonylmethylphenyl, piperidinylcarbonylmethylphenyl, benzylaminocarbonylphenyl, morpholinylethylaminocarbonylphenyl, imidazolylaminocarbonylphenyl, imidazolylmethylaminocarbonylphenyl, pyridinylmethylaminocarbonylphenyl, azetidylaminocarbonylmethylphenyl, pyrrolidinylmethylaminocarbonylmethylphenyl, pyridinylaminocarbonylmethylphenyl, pyridinylmethylaminocarbonylmethylphenyl, phenylaminopyridinyl, azetidylaminophenylpyridinyl, pyrrolidinylaminophenylpyridinyl, piperazinylcarbonylaminophenylpyridinyl, piperidinylaminocarbonylaminophenylpyridinyl, azetidylcarbonylphenylpyridinyl, pyrrolidinylcarbonylphenylpyridinyl, piperidinylcarbonylphenylpyridinyl, 30 piperazinylcarbonylphenylpyridinyl, morpholinylcarbonylphenylpyridinyl, piperidinylcarbonylphenylpyrimidinyl, morpholinylmethylcarbonylphenylpyridinyl, azabicyclo[3.2.1]octylcarbonylphenylpyridinyl, azetidylcarbonylmethylphenyl-

pyridinyl, pyrrolidinylcarbonylmethylphenylpyridinyl, piperidinylcarbonylmethylphenylpyridinyl, piperazinylcarbonylmethylphenylpyridinyl, azetidinyaminocarbonylphenylpyridinyl, pyrrolidinylaminocarbonylphenylpyridinyl, piperidinylaminocarbonylphenylpyridinyl, piperidinylmethylaminocarbonylphenylpyridinyl or azetidinyaminocarbonylmethylphenylpyridinyl, any of which groups may be optionally substituted by one or more substituents.

Illustratively, R⁵ represents hydrogen, halogen, cyano, -SR^a, -CO₂R^b or -CONR^cR^d; or R⁵ represents methyl, ethynyl, propynyl, butynyl, 3-methylbutynyl, cyclopropylethynyl, cyclohexylethynyl, phenyl, benzyl, phenylethyl, phenylethynyl, biphenyl, 1,2,3,4-tetrahydroisoquinolinylpropynyl, piperazinylpropynyl, quinuclidinylethynyl, piperazinylphenyl, morpholinylphenyl, piperidinylmethylphenyl, dibenzofuryl, pyridinyl, pyrazolylethynyl, imidazolylethynyl, pyridinylethynyl, pyrimidinylethynyl, imidazo[1,2-*a*]pyridinylethynyl, pyrrolidinylpyridinylethynyl, pyrazolylphenyl, phenylisoxazolyl, phenylthiazolyl, phenylpyridinyl, isoxazolylpyridinyl or bi(pyridinyl), any of which groups may be optionally substituted by one or more substituents.

Examples of representative substituents on R⁵ include halogen, cyano, nitro, oxo, C₁₋₆ alkyl, trifluoromethyl, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, dihydroxy(C₁₋₆)alkoxy, aryl(C₁₋₆)alkoxy, methoxyaryl(C₁₋₆)alkoxy, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, amino(C₁₋₆)alkyl, C₁₋₆ alkylamino(C₁₋₆)alkyl, di(C₁₋₆)alkylamino(C₁₋₆)alkyl, di(C₁₋₆)alkylamino(C₁₋₆)alkylamino, methoxyaryl(C₁₋₆)alkylamino, C₁₋₆ alkylcarbonylamino, C₁₋₆ alkoxycarbonyl(C₁₋₆)alkylcarbonylamino, C₁₋₆ alkylcarbonylamino(C₁₋₆)alkyl, C₁₋₆ alkoxycarbonylamino, *N*-(C₁₋₆ alkoxycarbonyl)-*N*-(C₁₋₆ alkyl)amino, C₁₋₆ alkoxy-carbonylamino(C₁₋₆)alkyl, *N*-(C₁₋₆ alkoxycarbonyl)-*N*-(C₁₋₆ alkyl)amino(C₁₋₆)alkyl, C₁₋₆ alkylsulphonylamino, C₁₋₆ alkylsulphonylamino(C₁₋₆)alkyl, C₁₋₆ alkylaminocarbonylamino, di(C₁₋₆)alkylamino(C₁₋₆)alkylaminocarbonylamino, *N*-(C₁₋₆ alkyl)-*N*-[di(C₁₋₆)alkylamino(C₁₋₆)alkyl]aminocarbonylamino, carboxycarbonylamino, C₁₋₆ alkoxycarbonyl-carbonylamino, C₁₋₆ alkylaminocarbonylcarbonylamino, di(C₁₋₆)alkylamino(C₁₋₆)alkylaminocarbonylcarbonylamino, di(C₁₋₆)alkylaminosulphonylamino, formyl, C₁₋₆ alkylcarbonyl, di(C₁₋₆)alkylamino(C₁₋₆)alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkoxycarbonyl(C₁₋₆)alkyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, cyano(C₁₋₆)alkylaminocarbonyl, di(C₁₋₆)alkylamino(C₁₋₆)alkylaminocarbonyl, dihydroxy(C₁₋₆)alkylaminocarbonyl, *N*-(C₁₋₆ alkyl)-*N*-[amino(C₁₋₆)alkyl]aminocarbonyl, *N*-(C₁₋₆ alkyl)-*N*-[di(C₁₋₆)alkylamino(C₁₋₆)alkyl]aminocarbonyl,

di(C₁₋₆)alkylaminocarbonyl(C₁₋₆)alkyl, *N*-(C₁₋₆ alkyl)-*N*-[di(C₁₋₆)alkylamino(C₁₋₆)alkyl]-aminocarbonyl(C₁₋₆)alkyl, aminocarbonyl(C₁₋₆)alkoxy, C₁₋₆ alkoxyaminocarbonyl, *N*-(C₁₋₆ alkoxy)-*N*-(C₁₋₆ alkyl)aminocarbonyl, C₁₋₆ alkylsulphonyl, C₁₋₆ alkylsulphonyloxy(C₁₋₆)-alkyl, trifluoromethylsulphonyloxy and tri(C₁₋₆)alkylsilyl.

- 5 Examples of suitable substituents on R⁵ include halogen, cyano, nitro, C₁₋₆ alkyl, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, aryl(C₁₋₆)alkoxy, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, amino(C₁₋₆)alkyl, C₁₋₆ alkylamino(C₁₋₆)alkyl, di(C₁₋₆)alkylamino-(C₁₋₆)alkyl, di(C₁₋₆)alkylamino(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, C₁₋₆ alkylsulphonylamino, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl and tri(C₁₋₆)alkylsilyl.

- Examples of specific substituents on R⁵ include fluoro, chloro, bromo, cyano, nitro, oxo, methyl, ethyl, isopropyl, trifluoromethyl, hydroxy, hydroxymethyl, methoxy, ethoxy, dihydroxypropoxy, isobutoxy, benzyloxy, methoxybenzyloxy, amino, methylamino, dimethylamino, diethylamino, aminomethyl, methylaminomethyl, dimethylaminomethyl, *N*-isopropyl-*N*-methylaminomethyl, dimethylaminoethylamino, methoxybenzylamino, acetylamino, ethoxycarbonylacetylamino, ethylcarbonylamino, methoxycarbonyl-ethylcarbonylamino, acetylaminomethyl, *tert*-butoxycarbonylamino, *N*-(*tert*-butoxycarbonyl)-*N*-(methyl)amino, *tert*-butoxycarbonylaminoethyl, *N*-(*tert*-butoxycarbonyl)-*N*-(methyl)aminomethyl, methylsulphonylamino, ethylsulphonylamino, methylsulphonyl-aminomethyl, ethylaminocarbonylamino, dimethylaminoethylaminocarbonylamino, *N*-(dimethylaminoethyl)-*N*-(methyl)aminocarbonylamino, carboxycarbonylamino, ethoxycarbonylcarbonylamino, ethylaminocarbonylcarbonylamino, dimethylaminoethylaminocarbonylcarbonylamino, dimethylaminosulphonylamino, formyl, acetyl, dimethyl-aminoacetyl, ethylcarbonyl, carboxy, carboxymethyl, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, methoxycarbonylmethyl, *tert*-butoxycarbonylmethyl, aminocarbonyl, methylaminocarbonyl, cyanomethylaminocarbonyl, ethylaminocarbonyl, dimethylaminoethylaminocarbonyl, dihydroxypropylaminocarbonyl, isopropylaminocarbonyl, dimethylaminocarbonyl, *N*-ethyl-*N*-methylaminocarbonyl, *N*-(aminoethyl)-*N*-(methyl)-aminocarbonyl, *N*-(dimethylaminoethyl)-*N*-(methyl)aminocarbonyl, diethylamino-carbonyl, dimethylaminocarbonylmethyl, *N*-(diethylaminoethyl)-*N*-(methyl)amino-carbonylmethyl, aminocarbonylmethoxy, methoxyaminocarbonyl, *N*-(methoxy)-*N*-

(methyl)aminocarbonyl, methylsulphonyl, methylsulphonyloxymethyl, trifluoromethylsulphonyloxy and tri(C₁₋₆)alkylsilyl.

Examples of typical substituents on R⁵ include fluoro, chloro, bromo, nitro, methyl, hydroxy, hydroxymethyl, methoxy, benzyloxy, amino, dimethylamino, diethylamino, aminomethyl, dimethylaminomethyl, dimethylaminoethylamino, acetylamino, methylsulphonylamino, acetyl, carboxy, carboxymethyl, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, aminocarbonyl, methylaminocarbonyl and triethylsilyl.

Specific values of R⁵ include hydrogen, fluoro, chloro, bromo, iodo, cyano, phenylthio, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, phenylaminocarbonyl, benzylaminocarbonyl, pyridinylmethylaminocarbonyl, (phenyl)(pyridinyl)methylaminocarbonyl, *N*-ethyl-*N*-pyridinylmethylaminocarbonyl, dimethylaminomethyl, dimethylaminosulphonylaminoethyl, dimethylaminoethenylcarbonyl, ethynyl, triethylsilylethynyl, diethylaminopropynyl, methylsulphonylaminoethyl, dimethylaminosulphonylaminoethyl, hydroxybutynyl, 3-hydroxy-3-methylbutynyl, cyclopropylethynyl, hydroxycyclohexylethynyl, aminocyclohexylethynyl, phenyl, bromophenyl, (bromo)(nitro)phenyl, hydroxyphenyl, methoxyphenyl, ethoxyphenyl, isobutoxyphenyl, (benzyloxy)(chloro)phenyl, aminophenyl, (amino)(bromo)phenyl, aminomethylphenyl, acetylaminophenyl, ethoxycarbonylacetylaminophenyl, ethylcarbonylaminophenyl, methoxycarbonyl-ethylcarbonylaminophenyl, methylsulphonylaminoethyl, ethylsulphonylaminoethyl, ethylaminocarbonylaminophenyl, dimethylaminoethylaminocarbonylaminophenyl, *N*-(dimethylaminoethyl)-*N*-(methyl)aminocarbonylaminophenyl, carboxycarbonylaminophenyl, ethoxycarbonylaminocarbonylaminophenyl, ethylaminocarbonylaminocarbonylaminophenyl, dimethylaminoethylaminocarbonylaminocarbonylaminophenyl, acetylphenyl, carboxyphenyl, carboxymethylphenyl, methoxycarbonylphenyl, (chloro)(methoxycarbonyl)phenyl, ethoxycarbonylphenyl, methoxycarbonylmethylphenyl, aminocarbonylphenyl, methylaminocarbonylphenyl, cyanomethylaminocarbonylphenyl, ethylaminocarbonylphenyl, dihydroxypropylaminocarbonylphenyl, isopropylaminocarbonylphenyl, dimethylaminocarbonylphenyl, dimethylaminocarbonylmethylphenyl, *N*-(diethylaminoethyl)-*N*-(methyl)aminocarbonylmethylphenyl, naphthyl, benzyl, phenylethyl, phenylethenyl, phenylethynyl, fluorophenylethynyl, nitrophenylethynyl, hydroxyphenylethynyl, methoxyphenylethynyl, dimethylaminophenylethynyl,

phenylpropynyl, biphenyl, (bromo)(dinitro)biphenyl, methoxybiphenyl, aminobiphenyl, dimethylaminobiphenyl, dimethylaminomethylbiphenyl, (dimethylaminocarbonyl)-(methyl)biphenyl, acetylpiperidinylolethynyl, *tert*-butoxycarbonylpyrrolidinylolethynyl, piperidinylolethynyl, acetylpiperidinylolethynyl, *tert*-butoxycarbonylpiperidinylolethynyl, 5 methylsulphonylpiperidinylolethynyl, 1,2,3,4-tetrahydroisoquinolinylolethynyl, methylpiperazinylolethynyl, pyrrolidinylolethynyl, hydroxyquinuclidinylolethynyl, piperazinylolethynyl, *tert*-butoxycarbonylpiperazinylolethynyl, morpholinylolethynyl, piperidinylolethynyl, piperazinylolethynyl, *tert*-butoxycarbonylpiperazinylolethynyl, benzofuryl, dibenzofuryl, benzothienyl, dibenzothienyl, pyridinylolethynyl, chloropyridinylolethynyl, 10 dichloropyridinylolethynyl, bromopyridinylolethynyl, carboxypyridinylolethynyl, ethoxycarbonylpyridinylolethynyl, isoquinolinylolethynyl, methylimidazolylolethynyl, methylimidazolylolethynyl, methylimidazolylolethynyl, indolylolethynyl, methylindolylolethynyl, pyrazolylolethynyl, methylpyrazolylolethynyl, methylimidazolylolethynyl, dimethylimidazolylolethynyl, pyridinylolethynyl, chloropyridinylolethynyl, aminopyridinylolethynyl, dimethylaminoethylaminopyridinylolethynyl, 15 ethynyl, aminopyrimidinylolethynyl, imidazo[1,2-*a*]pyridinylolethynyl, dimethylamino-methylimidazo[1,2-*a*]pyridinylolethynyl, methylimidazolylolethynyl, methylbenzomorpholinylolethynyl, hydroxymethylpyrrolidinylolethynyl, pyrazolylolethynyl, methylpyrazolylolethynyl, pyridinylolethynyl, (amino)(chloropyridinylolethynyl)phenyl, phenylisoxazolylolethynyl, phenylthiazolylolethynyl, (methyl)(trifluoromethylphenyl)thiazolylolethynyl, phenylpyridinylolethynyl, 20 fluorophenylpyridinylolethynyl, chlorophenylpyridinylolethynyl, cyanophenylpyridinylolethynyl, methylphenylpyridinylolethynyl, (bromo)(methyl)phenylpyridinylolethynyl, ethylphenylpyridinylolethynyl, hydroxyphenylpyridinylolethynyl, hydroxymethylphenylpyridinylolethynyl, methoxyphenylpyridinylolethynyl, aminocarbonylmethoxyphenylpyridinylolethynyl, dihydroxypropoxyphenylpyridinylolethynyl, methoxybenzyloxyphenylpyridinylolethynyl, trifluoromethylsulphonyloxyphenylpyridinylolethynyl, methylsulphonyloxyphenylpyridinylolethynyl, aminophenylpyridinylolethynyl, (amino)(cyano)phenylpyridinylolethynyl, 25 dimethylaminophenylpyridinylolethynyl, aminomethylphenylpyridinylolethynyl, (aminomethyl)(fluoro)phenylpyridinylolethynyl, methylaminomethylphenylpyridinylolethynyl, dimethylaminomethylphenylpyridinylolethynyl, *N*-isopropyl-*N*-methylaminomethylphenylpyridinylolethynyl, methoxybenzylaminophenylpyridinylolethynyl, acetylaminophenylpyridinylolethynyl, acetylaminomethylphenylpyridinylolethynyl, *tert*-butoxycarbonylaminomethylphenylpyridinylolethynyl, *N*-(*tert*-butoxycarbonyl)-*N*-(methyl)-aminomethylphenylpyridinylolethynyl, methylsulphonylaminomethylphenylpyridinylolethynyl, formylphenylpyridinylolethynyl, acetylphenylpyridinylolethynyl, dimethylaminomethylcarbonylphenylpyridinylolethynyl, carboxyphenylpyridinylolethynyl, (amino)(carboxy)phenylpyridinylolethynyl, 30

ethoxycarbonylphenylpyridinyl, *tert*-butoxycarbonylphenylpyridinyl, methoxycarbonylmethylphenylpyridinyl, aminocarbonylphenylpyridinyl, methylaminocarbonylphenylpyridinyl, dimethylaminoethylaminocarbonylphenylpyridinyl, dihydroxypropylaminocarbonylphenylpyridinyl, dimethylaminocarbonylphenylpyridinyl, (dimethylamino-carbonyl)(fluoro)phenylpyridinyl, (dimethylaminocarbonyl)(nitro)phenylpyridinyl, (amino)(dimethylaminocarbonyl)phenylpyridinyl, *N*-ethyl-*N*-methylaminocarbonylphenylpyridinyl, *N*-(aminoethyl)-*N*-(methyl)aminocarbonylphenylpyridinyl, *N*-(dimethylaminoethyl)-*N*-(methyl)aminocarbonylphenylpyridinyl, diethylaminocarbonylphenylpyridinyl, methoxyaminocarbonylphenylpyridinyl, *N*-methoxy-*N*-methylaminocarbonylphenylpyridinyl, dimethylaminocarbonylmethylphenylpyridinyl, *N*-(diethylaminoethyl)-*N*-(methyl)aminocarbonylmethylphenylpyridinyl, methylsulphonylphenylpyridinyl, phenylpyrimidinyl, bromophenylpyrimidinyl, aminoazetidinyphenylpyridinyl, methylaminoazetidinyphenylpyridinyl, aminopyrrolidinylphenylpyridinyl, aminopiperidinylphenylpyridinyl, methylaminopiperidinylphenylpyridinyl, piperazinylphenylpyridinyl, *tert*-butoxycarbonylpiperazinylphenylpyridinyl, *tert*-butoxycarbonylmethylpiperazinylphenylpyridinyl, morpholinylphenylpyridinyl, piperazinylphenylpyrimidinyl, pyrrolidinylmethylphenylpyridinyl, hydroxypyrrolidinylmethylphenylpyridinyl, dioxopyrrolidinylmethylphenylpyridinyl, aminopyrrolidinylmethylphenylpyridinyl, carboxypyrrolidinylmethylphenylpyridinyl, *tert*-butoxycarbonylpyrrolidinylmethylphenylpyridinyl, aminopiperidinylmethylphenylpyridinyl, methylaminopiperidinylmethylphenylpyridinyl, piperazinylmethylphenylpyridinyl, methylpiperazinylmethylphenylpyridinyl, oxopiperazinylmethylphenylpyridinyl, homopiperazinylmethylphenylpyridinyl, morpholinylmethylphenylpyridinyl, dimethylmorpholinylmethylphenylpyridinyl, aminoazabicyclo[3.2.1]octylmethylphenylpyridinyl, diazabicyclo[3.2.1]octylmethylphenylpyridinyl, tetrazolylphenylpyridinyl, benzofurylpyridinyl, benzothienylpyridinyl, indolylpyridinyl, dimethylisoxazolylpyridinyl, bi(pyridinyl), chlorobi(pyridinyl), carboxybi(pyridinyl), methoxycarbonylbi(pyridinyl), isoquinolinylpyridinyl, morpholinylcarbonylbi(pyridinyl), phenoxyphenyl, benzyloxyphenyl, methoxybenzyloxyphenyl, pyridinylmethoxyphenyl, *N*-(benzyl)-*N*-(ethylcarbonyl)aminophenyl, methylfurylmethylaminophenyl, pyridinylmethylaminophenyl, cyclopentylcarbonylaminophenyl, phenylcarbonylaminophenyl, benzylcarbonylaminophenyl, hydroxypyrrolidinylcarbonylaminophenyl, aminopyrrolidinylcarbonylaminophenyl, *tert*-butoxycarbonylaminopyrrolidinylcarbonylaminophenyl, (isopropyl)-

(oxo)pyrrolidinylcarbonylaminophenyl, *tert*-butoxycarbonylpiperidinylcarbonylaminophenyl, piperazinylcarbonylaminophenyl, methylpiperazinylcarbonylaminophenyl, *tert*-butoxycarbonylpiperazinylcarbonylaminophenyl, morpholinylcarbonylaminophenyl, indolylcarbonylaminophenyl, methylisoxazolylcarbonylaminophenyl, pyridinylcarbonylaminophenyl, hydroxypyridinylcarbonylaminophenyl, (oxo)(phenyl)pyrrolidinylcarbonylaminophenyl, phenylsulphonylaminophenyl, benzylsulphonylaminophenyl, dimethylisoxazolylsulphonylaminophenyl, cyclopentylaminocarbonylaminophenyl, phenylaminocarbonylaminophenyl, methylazetidinyllaminocarbonylaminophenyl, morpholinylethylaminocarbonylaminophenyl, methylimidazolylmethylaminocarbonylaminophenyl, morpholinylcarbonylcarbonylaminophenyl, pyrrolidinylethylaminocarbonylcarbonylaminophenyl, phenylcarbonylphenyl, morpholinylcarbonylphenyl, aminopyrrolidinylcarbonylmethylphenyl, *tert*-butoxycarbonylaminopyrrolidinylcarbonylmethylphenyl, aminopiperidinylcarbonylmethylphenyl, methylaminopiperidinylcarbonylmethylphenyl, *tert*-butoxycarbonylaminopiperidinylcarbonylmethylphenyl, *N*-(*tert*-butoxycarbonyl)-*N*-(methyl)aminopiperidinylcarbonylmethylphenyl, benzylaminocarbonylphenyl, morpholinylethylaminocarbonylphenyl, imidazolylaminocarbonylphenyl, methylimidazolylmethylaminocarbonylphenyl, pyridinylmethylaminocarbonylphenyl, azetidinyllaminocarbonylmethylphenyl, *tert*-butoxycarbonylazetidinyllaminocarbonylmethylphenyl, pyrrolidinylmethylaminocarbonylmethylphenyl, *tert*-butoxycarbonylpyrrolidinylmethylaminocarbonylmethylphenyl, pyridinylaminocarbonylmethylphenyl, pyridinylmethylaminocarbonylmethylphenyl, phenylaminopyridinyl, *N*-methyl-*N*-phenylaminopyridinyl, azetidinyllaminophenylpyridinyl, pyrrolidinylaminophenylpyridinyl, *tert*-butoxycarbonylpyrrolidinylaminophenylpyridinyl, piperazinylcarbonylaminophenylpyridinyl, piperidinylaminocarbonylaminophenylpyridinyl, aminoazetidinyllaminocarbonylphenylpyridinyl, methylaminoazetidinyllaminocarbonylphenylpyridinyl, *tert*-butoxycarbonylaminoazetidinyllaminocarbonylphenylpyridinyl, *N*-(*tert*-butoxycarbonyl)-*N*-(methyl)aminoazetidinyllaminocarbonylphenylpyridinyl, pyrrolidinylcarbonylphenylpyridinyl, hydroxypyrrolidinylcarbonylphenylpyridinyl, aminopyrrolidinylcarbonylphenylpyridinyl, aminopyrrolidinylcarbonylphenyl(amino)pyridinyl, methylaminopyrrolidinylcarbonylphenylpyridinyl, *tert*-butoxycarbonylaminopyrrolidinylcarbonylphenylpyridinyl, *tert*-butoxycarbonylaminopyrrolidinylcarbonylphenyl(methoxybenzylamino)pyridinyl, piperidinylcarbonylphenylpyridinyl, aminopiperidinylcarbonylphenylpyridinyl, methylaminopiperidinylcarbonylphenylpyridinyl, *tert*-butoxycarbonylaminopiperidinylcarbonyl-

phenylpyridinyl, dimethylaminopiperidinylcarbonylphenylpyridinyl, *N*-(*tert*-butoxycarbonyl)-*N*-(methyl)aminopiperidinylcarbonylphenylpyridinyl, piperazinylcarbonylphenylpyridinyl, methylpiperazinylcarbonylphenylpyridinyl, *tert*-butoxycarbonylpiperazinylcarbonylphenylpyridinyl, morpholinylcarbonylphenylpyridinyl, methylaminopiperidinylcarbonylphenylpyrimidinyl, dimethylaminopiperidinylcarbonylphenylpyrimidinyl, morpholinylmethylcarbonylphenylpyridinyl, aminoazabicyclo[3.2.1]octylcarbonylphenylpyridinyl, aminoazetidiny carbonylmethylphenylpyridinyl, *tert*-butoxycarbonylaminoazetidiny carbonylmethylphenylpyridinyl, pyrrolidinylcarbonylmethylphenylpyridinyl, aminopyrrolidinylcarbonylmethylphenylpyridinyl, *tert*-butoxycarbonylaminopyrrolidinylcarbonylmethylphenylpyridinyl, methylaminopiperidinylcarbonylmethylphenylpyridinyl, *N*-(*tert*-butoxycarbonyl)-*N*-(methyl)aminopiperidinylcarbonylmethylphenylpyridinyl, methylpiperazinylcarbonylmethylphenylpyridinyl, azetidiny aminocarbonylphenylpyridinyl, *tert*-butoxycarbonylazetidiny aminocarbonylphenylpyridinyl, *N*-(*tert*-butoxycarbonylazetidiny)-*N*-(ethyl)aminocarbonylphenylpyridinyl, *tert*-butoxycarbonylpyrrolidinylaminocarbonylphenylpyridinyl, *N*-(methylpyrrolidinyl)-*N*-(methyl)aminocarbonylphenylpyridinyl, *N*-(methylpiperidinyl)-*N*-(methyl)aminocarbonylphenylpyridinyl, piperidinylmethylaminocarbonylphenylpyridinyl, *tert*-butoxycarbonylpiperidinylmethylaminocarbonylphenylpyridinyl, azetidiny aminocarbonylmethylphenylpyridinyl and *tert*-butoxycarbonylazetidiny aminocarbonylmethylphenylpyridinyl.

Typical values of R⁵ include hydrogen, fluoro, chloro, bromo, iodo, cyano, phenylthio, carboxy, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, phenylaminocarbonyl, benzylaminocarbonyl, pyridinylmethylaminocarbonyl, (phenyl)(pyridinyl)methylaminocarbonyl, *N*-ethyl-*N*-pyridinylmethylaminocarbonyl, dimethylaminomethyl, ethynyl, triethylsilylethynyl, diethylaminopropynyl, methylsulphonylaminopropynyl, hydroxybutynyl, 3-hydroxy-3-methylbutynyl, cyclopropylethynyl, hydroxycyclohexylethynyl, aminocyclohexylethynyl, phenyl, (bromo)(nitro)phenyl, hydroxyphenyl, (benzyloxy)(chloro)phenyl, aminophenyl, aminomethyl-phenyl, acetylaminophenyl, acetylphenyl, carboxymethyl-phenyl, methoxycarbonylphenyl, (chloro)(methoxycarbonyl)phenyl, ethoxycarbonylphenyl, aminocarbonylphenyl, methylaminocarbonyl-phenyl, benzyl, phenylethyl, phenylethynyl, fluorophenylethynyl, nitrophenylethynyl, hydroxyphenylethynyl, methoxyphenylethynyl, dimethylaminophenylethynyl, biphenyl, (bromo)(dinitro)biphenyl, dimethylaminomethylbiphenyl, 1,2,3,4-tetrahydroisoquinolinylpropynyl, methylpiperazinyl-propynyl,

hydroxyquinuclidinyl-ethynyl, piperazinyl-phenyl, *tert*-butoxycarbonylpiperazinyl-phenyl, morpholinylphenyl, piperidinylmethylphenyl, dibenzofuryl, pyridinyl, chloropyridinyl, bromopyridinyl, carboxypyridinyl, ethoxycarbonylpyridinyl, pyrazolylethynyl, methylimidazolylethynyl, pyridinylethynyl, chloropyridinylethynyl, dimethylamino-ethylaminopyridinylethynyl, aminopyrimidinylethynyl, imidazo[1,2-*a*]pyridinylethynyl, dimethylaminomethyl-imidazo[1,2-*a*]pyridinylethynyl, hydroxymethylpyrrolidinyl-pyridinylethynyl, pyrazolylphenyl, methylpyrazolylphenyl, phenylisoxazolyl, phenylthiazolyl, phenylpyridinyl, hydroxyphenyl-pyridinyl, acetaminophenyl-pyridinyl, dimethylaminomethyl-phenylpyridinyl, dimethylisoxazolyl-pyridinyl and bi(pyridinyl).

10 Suitably, when R^3 and R^4 are both hydrogen, then R^5 is other than hydrogen.

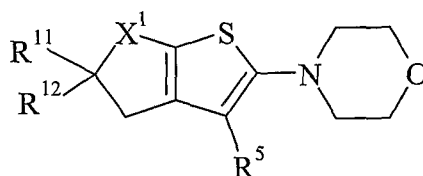
Suitably, when R^5 is hydrogen, then R^3 and/or R^4 is other than hydrogen.

In one embodiment, R^6 represents hydrogen. In another embodiment, R^6 represents C_{1-6} alkyl, especially methyl.

In one embodiment, R^7 represents hydrogen. In another embodiment, R^7

15 represents C_{1-6} alkyl, especially methyl.

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



(IIA)

20

wherein

- X^1 - represents a group of formula (a), (b) or (c) as defined above;

R^5 is as defined above;

R^{11} represents hydrogen or optionally substituted C_{1-6} alkyl; and

25 R^{12} represents hydrogen; or C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; or

R^{11} and R^{12} , when taken together with the carbon atom to which they are both attached, represent C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents.

In one embodiment, $-X^1$ represents a group of formula (a). In another embodiment, $-X^1$ represents a group of formula (b). In a further embodiment, $-X^1$ represents a group of formula (c).

Suitably, R^5 in the compounds of formula (IIA) is other than hydrogen.

Where R^{11} and/or R^{12} in the compounds of formula (IIA) above is stated to be optionally substituted, this group may be unsubstituted, or substituted by one or more substituents. Typically, R^{11} and/or R^{12} will be unsubstituted, or substituted by one or two substituents. Suitably, R^{11} and/or R^{12} will be unsubstituted or monosubstituted.

Suitably, R^{11} represents hydrogen or unsubstituted C_{1-6} alkyl.

Suitably, R^{12} represents hydrogen; or C_{1-6} alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents. Particular values of R^{12} include hydrogen and unsubstituted C_{1-6} alkyl.

Examples of typical substituents on R^{11} and/or R^{12} include halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxycarbonylamino, C_{1-6} alkylsulphonylamino, formyl, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, aminocarbonyl, C_{1-6} alkylamino-carbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulphonyl, C_{1-6} alkylaminosulphonyl and di(C_{1-6})alkylaminosulphonyl; especially halogen, C_{1-6} alkoxy or C_{1-6} alkylthio.

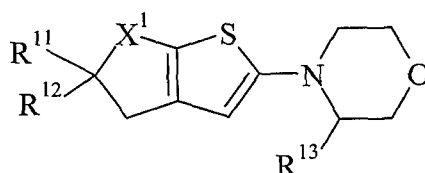
Examples of particular substituents on R^{11} and/or R^{12} include fluoro, chloro, bromo, cyano, nitro, methyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, phenoxy, methylthio, methylsulphonyl, amino, methylamino, dimethylamino, acetilamino, methoxycarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl; especially chloro, methoxy or methylthio.

Typical values of R^{11} include hydrogen and methyl. In one embodiment, R^{11} is hydrogen. In another embodiment, R^{11} is methyl.

Typical values of R^{12} include hydrogen, methyl, *n*-propyl, isopropyl, phenyl, chlorophenyl, methoxyphenyl, methylthiophenyl and furyl, especially hydrogen or methyl. In one embodiment, R^{12} is hydrogen. In another embodiment, R^{12} is methyl.

Alternatively, R^{11} and R^{12} may together form an optionally substituted spiro linkage. Thus, R^{11} and R^{12} , when taken together with the carbon atom to which they are both attached, may represent C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be unsubstituted, or substituted by one or more, typically by one or two, substituents. In this context, R^{11} and R^{12} , when taken together with the carbon atom to which they are both attached, may suitably represent an optionally substituted cyclopentyl, cyclohexyl, pyrrolidine or piperidine ring, especially cyclopentyl or cyclohexyl.

Another sub-class of compounds according to the invention is represented by the compounds of formula (IIB), and pharmaceutically acceptable salts and solvates thereof:



(IIB)

15

wherein

$-X^1-$, R^{11} and R^{12} are as defined above; and

R^{13} represents hydrogen; or C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, biaryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkylcarbonyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl-aryl(C_{1-6})alkyl or aryl-heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Typically, R^{13} represents hydrogen; or C_{1-6} alkyl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkynyl, biaryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkylcarbonyl, heteroaryl(C_{1-6})alkyl, heteroaryl-aryl(C_{1-6})alkyl or aryl-heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Suitably, R^{13} is other than hydrogen.

In a representative embodiment, R^{13} represents C_{1-6} alkyl, aryl(C_{1-6})alkyl, biaryl-
(C_{1-6})alkyl, heteroaryl(C_{1-6})alkyl or heteroaryl-aryl(C_{1-6})alkyl, any of which groups may be

optionally substituted by one or more substituents. Preferably, R¹³ represents methyl, arylmethyl, biarylmethyl, heteroarylmethyl or heteroaryl-arylmethyl, any of which groups may be optionally substituted by one or more substituents.

In a particular embodiment, R¹³ represents substituted or unsubstituted indolyl-
5 (C₁₋₆)alkyl. Advantageously, R¹³ represents substituted or unsubstituted indolylmethyl.

Illustratively, R¹³ represents hydrogen; or methyl, benzyl, phenylethyl,
naphthylmethyl, phenylpropynyl, biphenylmethyl, naphthylphenylmethyl,
indolylmethyl, 1,2,3,4-tetrahydroquinolylmethyl, 1,2,3,4-tetrahydroisoquinolyl-
methyl, piperidinylcarbonyl, 1,2,3,4-tetrahydroquinolylcarbonyl, 1,2,3,4-
10 tetrahydroisoquinolylcarbonyl, 1,2,3,4-tetrahydroquinoxalylcarbonyl,
benzothienylmethyl, indolylmethyl, pyrrolo[2,3-*b*]pyridylmethyl, benzimidazolylmethyl,
benzotriazolylmethyl, pyridylmethyl, quinolylmethyl, isoquinolylmethyl,
benzofurylbenzyl, thienylbenzyl, benzothienylbenzyl, indolylbenzyl, isoxazolylbenzyl,
pyrazolylbenzyl, pyridylbenzyl, pyrimidinylbenzyl or phenylpyridylmethyl, any of
15 which groups may be optionally substituted by one or more substituents.

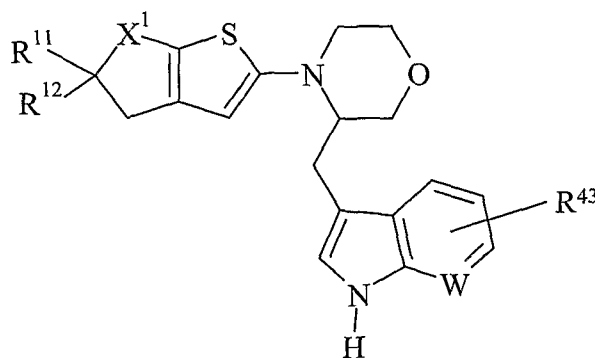
Examples of suitable substituents on R¹³ include halogen, cyano, nitro, C₁₋₆ alkyl,
hydroxy(C₁₋₆)alkyl, trifluoromethyl, aryl(C₁₋₆)alkyl, hydroxy, C₁₋₆ alkoxy,
difluoromethoxy, trifluoromethoxy, aryloxy, aryl(C₁₋₆)alkoxy, methylenedioxy, C₁₋₆
alkylthio, arylthio, C₁₋₆ alkylsulphonyl, arylsulphonyl, C₁₋₆ alkylsulphonyloxy, amino, C₁₋₆
20 alkylamino, di(C₁₋₆)alkylamino, phenylamino, [(C₁₋₆)alkyl](phenyl)amino, pyridinylamino,
pyrrolidinyl, morpholinyl, C₂₋₆ alkylcarbonylamino, benzofurylcarbonylamino, C₂₋₆
alkoxycarbonylamino, C₁₋₆ alkylsulphonylamino, arylsulphonylamino, formyl, C₂₋₆
alkylcarbonyl, carboxy, C₂₋₆ alkoxycarbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl,
di(C₁₋₆)alkylaminocarbonyl, benzothienylmethylaminocarbonyl, aminosulphonyl, C₁₋₆
25 alkylaminosulphonyl and di(C₁₋₆)alkylaminosulphonyl.

Examples of representative substituents on R¹³ include fluoro, chloro, bromo,
cyano, nitro, methyl, hydroxymethyl, trifluoromethyl, benzyl, hydroxy, methoxy, ethoxy,
difluoromethoxy, trifluoromethoxy, phenoxy, benzyloxy, methylenedioxy, methylthio,
phenylthio, methylsulphonyl, phenylsulphonyl, methylsulphonyloxy, amino, methylamino,
30 dimethylamino, phenylamino, *N*-methyl-*N*-phenylamino, pyridinylamino, pyrrolidinyl,
morpholinyl, acetylamino, benzofurylcarbonylamino, methoxycarbonylamino,
methylsulphonylamino, phenylsulphonylamino, formyl, acetyl, carboxy, methoxycarbonyl,

aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, benzothienylmethyl-aminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl.

Specific values of R¹³ include hydrogen, phenoxymethyl, phenylthiomethyl, aminomethyl, phenylaminomethyl, *N*-methyl-*N*-phenylaminomethyl, pyridinylamino-
 5 methyl, benzofurylcarbonylaminomethyl, phenylsulphonylaminomethyl, benzothienyl-methylaminocarbonylmethyl, benzyl, chlorobenzyl, bromobenzyl, pyrrolidinylbenzyl, morpholinyl-benzyl, phenylethyl, naphthylmethyl, phenylpropynyl, biphenylmethyl, fluorobiphenylmethyl, difluorobiphenylmethyl, chlorobiphenylmethyl, dichlorobiphenylmethyl, bromobiphenylmethyl, cyanobiphenylmethyl, methylbiphenyl-
 10 methyl, (fluoro)(methyl)biphenylmethyl, dimethylbiphenylmethyl, hydroxymethyl-biphenylmethyl, trifluoromethylbiphenylmethyl, bis(trifluoromethyl)biphenylmethyl, methoxybiphenylmethyl, dimethoxybiphenylmethyl, ethoxybiphenylmethyl, methylenedioxybiphenylmethyl, trifluoromethoxybiphenylmethyl, phenoxy-biphenylmethyl, methylthiobiphenylmethyl, aminobiphenylmethyl, acetylamino-
 15 biphenylmethyl, methylsulphonylaminobiphenylmethyl, acetyl biphenylmethyl, aminocarbonylbiphenylmethyl, naphthylphenylmethyl, indolylmethyl, 1,2,3,4-tetrahydroquinolylmethyl, 1,2,3,4-tetrahydroisoquinolylmethyl, piperidinylcarbonyl, 1,2,3,4-tetrahydroquinolylcarbonyl, methyl-1,2,3,4-tetrahydroquinolylcarbonyl, methoxy-1,2,3,4-tetrahydroquinolylcarbonyl, 1,2,3,4-tetrahydroisoquinolylcarbonyl, 1,2,3,4-tetrahydroquinoxalylcarbonyl, benzothienylmethyl, indolylmethyl, methyl-
 20 indolylmethyl, hydroxyindolylmethyl, benzyloxyindolylmethyl, acetylindolylmethyl, methylsulphonyloxyindolylmethyl, pyrrolo[2,3-*b*]pyridinylmethyl, benzimidazolylmethyl, benzotriazolylmethyl, bromopyridinylmethyl, quinolylmethyl, isoquinolylmethyl, benzofurylbenzyl, thienylbenzyl, methylthienylbenzyl, acetylthienylbenzyl, benzothienylbenzyl, phenylsulphonylindolylbenzyl, dimethylisoxazolylbenzyl, methylpyrazolylbenzyl, benzylpyrazolylbenzyl, pyridinylbenzyl, fluoropyridinylbenzyl, chloropyridinylbenzyl, methoxypyridinylbenzyl, pyrimidinylbenzyl and phenylpyridinylmethyl.

One particular sub-group of the compounds of formula (IIB) is represented by the
 30 compounds of formula (IIC), and pharmaceutically acceptable salts and solvates thereof:



(IIC)

wherein

$-X^1$, R^{11} and R^{12} are as defined above;

5 W represents CH or N; and

R^{43} represents hydrogen, halogen, cyano, C_{1-6} alkyl, hydroxy(C_{1-6})alkyl, trifluoromethyl, aryl(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy, trifluoromethoxy, aryloxy, aryl(C_{1-6})alkoxy, C_{1-6} alkylthio, arylsulphonyl, C_{1-6} alkylsulphonyloxy, amino, C_{2-6} alkylcarbonylamino, C_{1-6} alkylsulphonylamino, C_{2-6} alkylcarbonyl or aminocarbonyl.

10 In a preferred embodiment, W is CH. In another embodiment, W is N.

Suitable values of R^{43} include hydrogen, C_{1-6} alkyl, hydroxy, aryl(C_{1-6})alkoxy and C_{1-6} alkylsulphonyloxy.

Specific values of R^{43} include hydrogen, fluoro, chloro, bromo, cyano, methyl, hydroxymethyl, trifluoromethyl, benzyl, hydroxy, methoxy, ethoxy, trifluoromethoxy, phenoxy, benzyloxy, methylthio, phenylsulphonyl, methylsulphonyloxy, amino, acetylamino, methylsulphonylamino, acetyl and aminocarbonyl; especially hydrogen, methyl, hydroxy, benzyloxy or methylsulphonyloxy.

A particular value of R^{43} is hydrogen.

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 novel 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.

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 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 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 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 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 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
5 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
10 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
15 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.

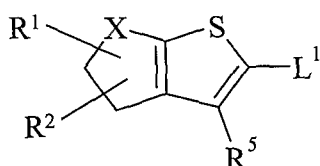
For ophthalmic administration the compounds according to the present invention
20 may be conveniently formulated as microionized suspensions in isotonic, pH-adjusted sterile saline, either with or without a preservative such as a bactericidal or fungicidal agent, for example phenylmercuric nitrate, benzylalkonium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

25 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.

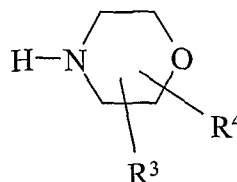
30 The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen and the condition of the patient to be treated. In general, however, daily dosages may range from around 10 ng/kg to 1000 mg/kg, typically from 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.

- 5 The compounds of formula (I) above may be prepared by a process which comprises reacting a compound of formula (III) with a compound of formula (IV):



(III)



(IV)

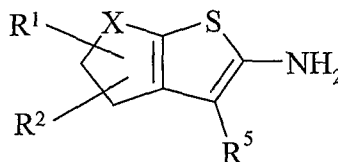
- 10 wherein R^1 , R^2 , R^3 , R^4 , R^5 and X are as defined above, and L^1 represents a suitable leaving group.

The leaving group L^1 is typically a halogen atom, e.g. bromo.

- 15 The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. acetonitrile, dimethylsulphoxide, a lower alkanol such as isopropanol or a cyclic ether such as tetrahydrofuran, typically under basic conditions, e.g. in the presence of an organic base such as *N,N*-diisopropylethylamine.

Alternatively, the reaction may be effected at an elevated temperature in a solvent such as 2-ethoxyethanol in the presence of a catalytic quantity of a mineral acid, e.g. concentrated hydrochloric acid.

- 20 The intermediates of formula (III) above wherein L^1 is bromo may be prepared from a compound of formula (V):

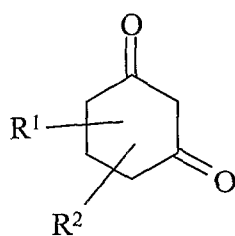


(V)

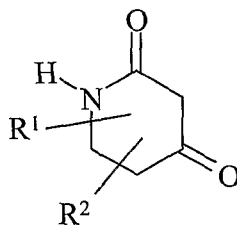
- 25 wherein R^1 , R^2 , R^5 and X are as defined above; by diazotization/bromination.

The reaction is conveniently effected by stirring compound (V) with *tert*-butyl nitrite and copper(II) bromide in a suitable solvent, e.g. acetonitrile.

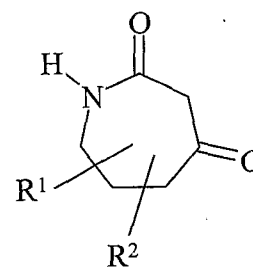
- The intermediates of formula (V) above wherein -X- represents a group of formula (a), (b) or (c) in which Y is oxygen, and R⁵ represents cyano or -CO₂R^b, may be prepared by reacting a compound of formula R^{5a}-CH₂-CN with the appropriate compound of formula (VIA), (VIB) or (VIC):



(VIA)



(VIB)



(VIC)

- wherein R¹ and R² are as defined above, and R^{5a} represents cyano or -CO₂R^b in which R^b is as defined above; in the presence of sulphur.

The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. a lower alkanol such as ethanol, typically under basic conditions, e.g. in the presence of morpholine.

- Where they are not commercially available, the starting materials of formula (IV) and (VIA)/(VIB)/(VIC) may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

- 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 (IA), (IB), (IC) or (ID) wherein Y is oxygen may be converted into the corresponding compound wherein Y is sulphur by treatment with Lawesson's Reagent (i.e. 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide). A compound of formula (IB) wherein Y is oxygen may be converted into the corresponding compound of formula (ID) by treatment with hydroxylamine-*O*-sulfonic acid, typically in the presence of formic acid at an elevated temperature. A compound of formula (IB) wherein Y is oxygen may be converted into the corresponding compound of formula (IE) by treatment with a reducing agent such as lithium aluminium hydride. A compound of

formula (IB) wherein Y is oxygen may be converted into the corresponding compound of formula (IF) by treatment with a hydroxylamine derivative of formula H_2N-OR^7 . A compound of formula (IB) wherein Y is oxygen may be converted into the corresponding compound of formula (IG) by treatment with hydrazine hydrate. A compound of formula (IF) may be converted into the corresponding compound of formula (IC) by treatment with *p*-toluenesulphonyl chloride, typically in the presence of pyridine at an elevated temperature. A compound of formula (IB) wherein Y is oxygen and R^1 is hydrogen may be converted into the corresponding compound wherein R^1 is methyl by treatment with a methyl halide, e.g. iodomethane, in the presence of a strong base, e.g. lithium diisopropylamide.

A compound of formula (I) wherein R^3 represents aryl(C_{1-6})alkyl, substituted on the aryl moiety by a halogen atom such as bromo, may be converted into the corresponding compound wherein R^3 represents biaryl(C_{1-6})alkyl or heteroaryl-aryl(C_{1-6})alkyl by treatment with, respectively, an aryl or heteroaryl boronic acid, in the presence of a catalyst. Similarly, a compound of formula (I) wherein R^3 represents heteroaryl(C_{1-6})alkyl, substituted on the heteroaryl moiety by a halogen atom such as bromo, may be converted into the corresponding compound wherein R^3 represents aryl-heteroaryl(C_{1-6})alkyl by treatment with an aryl boronic acid, in the presence of a catalyst. The catalyst may typically be a transition metal catalyst. A suitable catalyst is tetrakis(triphenylphosphine)palladium(0), in which case the transformation may conveniently be effected at an elevated temperature in the presence of a base such as sodium carbonate or potassium carbonate, in an inert solvent such as 1,2-dimethoxyethane or 1,4-dioxane. Alternatively, the catalyst may be palladium(II) acetate, in which case the transformation may conveniently be effected at an elevated temperature in the presence of 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl and potassium phosphate.

A compound of formula (I) wherein R^3 represents hydroxymethyl may be converted into the corresponding compound wherein R^3 represents a substituted aminomethyl moiety, e.g. phenylaminomethyl, *N*-methyl-*N*-phenylaminomethyl, pyridin-3-ylaminomethyl, indolin-1-ylmethyl, 1,2,3,4-tetrahydroquinolin-1-ylmethyl or 1,2,3,4-tetrahydroisoquinolin-2-ylmethyl, by a two-stage procedure which comprises (i) Swern oxidation of the hydroxymethyl derivative by treatment with oxalyl chloride and dimethyl sulphoxide in the presence of triethylamine; and (ii) reductive amination of the formyl derivative thereby obtained by treatment with the appropriate amine, e.g. aniline, *N*-

methylaniline, 3-aminopyridine, indoline, 1,2,3,4-tetrahydroquinoline or 1,2,3,4-tetrahydroisoquinoline, in the presence of a reducing agent such as sodium cyanoborohydride.

A compound of formula (I) wherein R³ represents hydroxymethyl may be converted into the corresponding compound wherein R³ represents an optionally substituted C₃₋₇ heterocycloalkylcarbonyl moiety, e.g. piperidin-1-ylcarbonyl, 1,2,3,4-tetrahydroquinolin-1-ylcarbonyl, 6-methyl-1,2,3,4-tetrahydroquinolin-1-ylcarbonyl, 6-methoxy-1,2,3,4-tetrahydroquinolin-1-ylcarbonyl, 1,2,3,4-tetrahydroisoquinolin-2-ylcarbonyl or 1,2,3,4-tetrahydroquinoxalin-1-ylcarbonyl, by a two-stage procedure which comprises (i) oxidation of the hydroxymethyl moiety by treatment with potassium permanganate; and (ii) reaction of the carboxy derivative thereby obtained with the appropriate amine, e.g. piperidine, 1,2,3,4-tetrahydroquinoline, 6-methyl-1,2,3,4-tetrahydroquinoline, 6-methoxy-1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline or 1,2,3,4-tetrahydroquinoxaline, in the presence of a condensing agent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), or *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU).

A compound of formula (I) wherein R³ contains a phenyl moiety substituted by chloro may be converted into the corresponding compound wherein the phenyl ring is substituted by morpholin-4-yl by treatment with morpholine in the presence of tris(dibenzylideneacetone)dipalladium(0), 2-(di-*tert*-butylphosphino)biphenyl and sodium *tert*-butoxide. A compound of formula (I) wherein R³ contains a phenyl moiety substituted by bromo may be converted into the corresponding compound wherein the phenyl ring is substituted by pyrrolidin-1-yl by treatment with pyrrolidine in the presence of tris(dibenzylideneacetone)dipalladium(0), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl and a base such as potassium carbonate. A compound of formula (I) wherein R³ contains an indole moiety may be methylated on the indole ring by treatment with a methyl halide, e.g. iodomethane, in the presence of a strong base such as sodium hydride. A compound of formula (I) wherein R³ contains an indole moiety may be acetylated on the indole ring by treatment with acetic anhydride and 4-dimethylaminopyridine, typically in the presence of an organic base such as triethylamine. A compound of formula (I) wherein R³ contains an indoline moiety may be converted into the corresponding compound wherein R³ contains an indole moiety by treatment with an oxidising agent such as manganese dioxide. A compound of formula (I) wherein R³

contains a hydroxy substituent may be converted into the corresponding compound wherein R^3 contains a C_{1-6} alkylsulphonyloxy substituent, e.g. methylsulphonyloxy, by treatment with a C_{1-6} alkylsulphonyl halide, e.g. methanesulphonyl chloride. A compound of formula (I) wherein R^3 contains an amino ($-NH_2$) or carboxy ($-CO_2H$) moiety may be converted into the corresponding compound wherein R^3 contains an amido moiety ($-NHCO-$ or $-CONH-$ respectively) by treatment with, respectively, a compound containing a carboxy or amino group, in the presence of *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), typically in a dipolar aprotic solvent such as *N,N*-dimethylformamide. A compound of formula (I) wherein R^3 contains an amino substituent may be converted into the corresponding compound wherein R^3 contains an arylsulphonylamino substituent, e.g. phenylsulphonylamino, by treatment with an arylsulphonyl halide, e.g. benzenesulphonyl chloride.

A compound of formula (I) wherein R^5 represents $-CO_2R^b$ in which R^b is other than hydrogen may be saponified and then decarboxylated to give the corresponding compounds in which R^5 represents $-CO_2H$ and hydrogen respectively by treatment with a base such as lithium hydroxide. In general, any compound of formula (I) wherein R^5 contains a lower alkyl ester moiety may be converted into the corresponding compound wherein R^5 contains a carboxy ($-CO_2H$) group by treatment with a base such as lithium hydroxide or sodium hydroxide. A compound of formula (I) wherein R^5 represents $-CO_2H$ may be converted into the corresponding compound wherein R^5 represents $-CONR^cR^d$ by treatment with an amine of formula $H-NR^cR^d$ and a condensing agent such as EDC, typically in the presence of an organic base such as triethylamine. In general, any compound of formula (I) wherein R^5 contains a carboxy moiety may be converted into the corresponding compound wherein R^5 contains an amide moiety by treatment with the appropriate amine and a condensing agent such as EDC, typically in the presence of 1-hydroxybenzotriazole (HOBT); alternative condensing agents include isobutyl chloroformate/triethylamine and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate. Likewise, any compound of formula (I) wherein R^5 contains an amino moiety may be converted into the corresponding compound wherein R^5 contains an amide moiety by treatment with the appropriate carboxylic acid under analogous conditions. A compound of formula (I) wherein R^5 represents cyano may be converted into the corresponding compound wherein R^5 represents $-CONH_2$ by heating under acidic conditions, e.g. in a mixture of acetic acid and sulphuric acid; prolonged treatment leads to

conversion to the corresponding carboxylic acid followed by decarboxylation, i.e. conversion into the corresponding compound wherein R^5 represents hydrogen.

A compound of formula (I) wherein R^5 contains a carboxy moiety may be converted into the corresponding compound containing an arylcarbonyl moiety (e.g. benzoyl) by a two-stage procedure which comprises (i) treatment with *N,O*-dimethylhydroxylamine hydrochloride and a condensing agent such as EDC, typically in the presence of HBTU; and (ii) reaction of the compound thereby obtained with the appropriate aryl lithium derivative, e.g. phenyllithium.

A compound of formula (I) wherein R^5 represents hydrogen may be converted into the corresponding compound wherein R^5 represents fluoro by treatment with SelectfluorTM [i.e. 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)]. A compound of formula (I) wherein R^5 represents hydrogen may be converted into the corresponding compound wherein R^5 represents chloro, bromo or iodo by treatment with *N*-chlorosuccinimide, *N*-bromosuccinimide or *N*-iodosuccinimide respectively. Indeed, the latter procedure is generally applicable for converting any compound of formula (I) wherein R^5 contains an aryl or heteroaryl moiety into the corresponding compound wherein the aryl or heteroaryl moiety is substituted by chloro, bromo or iodo respectively. Alternatively, a compound of formula (I) wherein R^5 represents hydrogen may be converted into the corresponding compound wherein R^5 represents bromo or iodo by treatment with elemental bromine or iodine respectively. A compound of formula (I) wherein R^5 represents hydrogen may be converted into the corresponding compound wherein R^5 represents $-SR^a$ by reaction with a compound of formula R^aS-Cl . A compound of formula (I) wherein R^5 represents hydrogen may be converted into the corresponding compound wherein R^5 represents dimethylaminomethyl by treatment with Eschenmoser's salt (i.e. *N,N*-dimethylmethyleammonium iodide).

A compound of formula (I) wherein R^5 represents a halogen atom, e.g. iodo or chloro, may be converted into the corresponding compound wherein R^5 represents $-CO_2R^b$ by treatment with carbon monoxide and an alcohol of formula R^b-OH , in the presence of a catalyst. Indeed, this procedure is generally applicable for converting any compound of formula (I) wherein R^5 contains a halogen atom into the corresponding compound containing a lower alkyl ester functionality. The catalyst may typically be a transition metal catalyst. A suitable catalyst is [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)-dichloromethane complex, in which case the transformation may

conveniently be effected at an elevated temperature and pressure in the presence of an organic base such as triethylamine.

A compound of formula (I) wherein R^5 represents a halogen atom, e.g. bromo or iodo, may be converted into the corresponding compound wherein R^5 represents aryl, biaryl, C_{3-7} heterocycloalkyl-aryl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl-aryl, heteroaryl or heteroaryl-aryl by treatment with, respectively, an aryl, biaryl, C_{3-7} heterocycloalkyl-aryl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl-aryl, heteroaryl or heteroaryl-aryl boronic acid or a cyclic ester thereof formed with an organic diol, e.g. pinacol, in the presence of a catalyst.

Similarly, a compound of formula (I) wherein R^5 represents aryl, substituted on the aryl moiety by a halogen atom such as bromo, may be converted into the corresponding compound wherein R^5 represents biaryl or heteroaryl-aryl by treatment with, respectively, an aryl or heteroaryl boronic acid or a cyclic ester thereof formed with an organic diol, e.g. pinacol, in the presence of a catalyst. Likewise, a compound of formula (I) wherein R^5 represents heteroaryl, substituted on the heteroaryl moiety by a halogen atom such as

chloro or bromo, may be converted into the corresponding compound wherein R^5 represents aryl-heteroaryl or bi(heteroaryl) by treatment with, respectively, an aryl or heteroaryl boronic acid or a cyclic ester thereof formed with an organic diol, e.g. pinacol or *N*-phenyldiethanolamine, in the presence of a catalyst. The catalyst may typically be a transition metal catalyst. A suitable catalyst is tetrakis(triphenylphosphine)palladium(0), in which case the transformation may conveniently be effected at an elevated temperature in the presence of a base such as sodium carbonate, potassium carbonate, potassium hydroxide or potassium phosphate, in an inert solvent such as 1,2-dimethoxyethane, tetrahydrofuran or 1,4-dioxane. Alternatively, the catalyst may be palladium(II) acetate, in which case the transformation may conveniently be effected at an elevated temperature in the presence of 1,3-bis(diphenylphosphino)propane and potassium phosphate, or in the presence of $PdCl_2.dppf$ and potassium phosphate. In general, any compound of formula (I) wherein R^5 represents or contains a halogen atom, e.g. bromo or iodo, may be converted by means of the foregoing procedure into the corresponding compound wherein the halogen atom is replaced by a substituted or unsubstituted aryl, heteroaryl or alkenyl group.

A compound of formula (I) wherein R^5 represents a halogen atom, e.g. iodo, may be converted into the corresponding compound wherein R^5 represents aryl(C_{1-6})alkyl, e.g. benzyl, by treatment with a suitable organozinc reagent, in the presence of a catalyst. The

organozinc reagent may conveniently be prepared by reacting the appropriate aryl(C₁₋₆)-alkyl halide, e.g. benzyl bromide, with zinc dust. The catalyst may typically be a transition metal catalyst. A suitable catalyst is dichlorobis(triphenylphosphine)-palladium(II), in which case the transformation may conveniently be effected at an elevated temperature in the presence of an inert solvent such as tetrahydrofuran.

A compound of formula (I) wherein R⁵ contains a halogen atom, e.g. chloro, may be converted into the corresponding compound wherein the halogen atom is replaced by an arylamino or heteroaryl amino moiety, e.g. phenylamino, by treatment with the appropriate amine, e.g. aniline, and a transition metal catalyst, e.g. palladium acetate, typically in the presence of tributylphosphine tetrafluoroborate and a base such as sodium *tert*-butoxide.

A compound of formula (I) wherein R⁵ represents a halogen atom, e.g. iodo, may be converted into the corresponding compound wherein R⁵ represents C₂₋₆ alkynyl, C₃₋₇ cycloalkyl(C₂₋₆)alkynyl, aryl(C₂₋₆)alkynyl, C₃₋₇ heterocycloalkyl(C₂₋₆)alkynyl, C₅₋₉ heterobicycloalkyl(C₂₋₆)alkynyl or heteroaryl(C₂₋₆)alkynyl by treatment with, respectively, a suitable C₂₋₆ alkyne, C₃₋₇ cycloalkyl(C₂₋₆)alkyne, aryl(C₂₋₆)alkyne, C₃₋₇ heterocycloalkyl(C₂₋₆)alkyne, C₅₋₉ heterobicycloalkyl(C₂₋₆)alkyne or heteroaryl(C₂₋₆)alkyne, in the presence of a catalyst. Similarly, a compound of formula (I) wherein R⁵ represents C₂₋₆ alkynyl, e.g. ethynyl, may be converted into the corresponding compound wherein R⁵ represents aryl(C₂₋₆)alkynyl, heteroaryl(C₂₋₆)alkynyl or C₃₋₇ cycloalkyl-heteroaryl(C₂₋₆)alkynyl by treatment with, respectively, a suitable aryl, heteroaryl or C₃₋₇ cycloalkyl-heteroaryl iodide, in the presence of a catalyst. The catalyst may typically be a transition metal catalyst. A suitable catalyst is dichlorobis(triphenylphosphine)palladium(II), in which case the transformation may conveniently be effected at an elevated temperature in the presence of copper(I) iodide and an organic base such as diisopropylamine.

A compound of formula (I) wherein R⁵ represents arylethynyl, e.g. phenylethynyl, may be converted into the corresponding compound wherein R⁵ represents arylethyl, e.g. 2-phenylethyl, by catalytic hydrogenation. Indeed, this procedure is generally applicable for converting any compound of formula (I) wherein R⁵ contains a -C≡C- moiety into the corresponding compound containing a -CH₂CH₂- moiety. A suitable hydrogenation catalyst is palladium on carbon, in which case the conversion can conveniently be accomplished at an elevated temperature in a suitable solvent, e.g. a lower alkanol such as ethanol, in the presence of a hydrogen donor such as ammonium formate. Under appropriate, generally less forcing, hydrogenation conditions, it is also possible to convert

a compound of formula (I) wherein R⁵ contains a -C≡C- moiety into the corresponding compound containing a -CH=CH- moiety.

A compound of formula (I) wherein R⁵ contains a -C≡C- moiety may be converted into the corresponding compound containing a -COCH₂- moiety by treatment with a pH 2 buffer solution. Moreover, a compound of formula (I) wherein R⁵ contains a -C≡C- moiety may be converted into the corresponding compound containing a -COCO- moiety by treatment with a mineral acid such as hydrochloric acid.

A compound of formula (I) wherein R⁵ represents nitro may be converted into the corresponding compound wherein R⁵ represents amino by catalytic hydrogenation, which typically comprises reacting the nitro compound with hydrogen in the presence of a catalyst such as palladium on charcoal.

A compound of formula (I) wherein R⁵ contains a hydroxy moiety may be converted into the corresponding compound containing a -OCH₂- moiety by treatment with the appropriate alkyl halide, typically in the presence of a base such as potassium carbonate. A compound of formula (I) wherein R⁵ contains a hydroxy moiety may be converted into the corresponding compound containing a -OSO₂- moiety by treatment with the appropriate sulphonyl halide, typically in the presence of a base such as triethylamine. A compound of formula (I) wherein R⁵ contains a hydroxy moiety may be converted into the corresponding compound containing a trifluoromethylsulphonyloxy moiety by treatment with *N*-phenyltrifluoromethanesulphonimide, typically in the presence of a base such as triethylamine.

A compound of formula (I) wherein R⁵ contains a methylsulphonyloxymethyl moiety may be converted into the corresponding compound containing an aminomethyl moiety by treatment with the appropriate amine derivative, typically in the presence of a base such as triethylamine. Similarly, a compound of formula (I) wherein R⁵ contains a halomethyl (e.g. chloromethyl) moiety may be converted into the corresponding compound containing an aminomethyl moiety by treatment with the appropriate amine derivative (including cyclic amines), typically in the presence of a base such as potassium carbonate. Furthermore, a compound of formula (I) wherein R⁵ contains a hydroxymethyl moiety may be converted into the corresponding compound containing an aminomethyl moiety by treatment with the appropriate amine derivative (including cyclic amines), generally in the presence of triphenylphosphine and diethyl azodicarboxylate.

A compound of formula (I) wherein R⁵ contains a trifluoromethylsulphonyloxy moiety may be converted into the corresponding compound wherein the trifluoromethylsulphonyloxy moiety is replaced by an amino functionality by treatment with the appropriate amine derivative (including cyclic amines) and a transition metal catalyst, e.g. acetato(2'-di-*tert*-butylphosphino-1,1'-biphenyl-2-yl)palladium(II), typically at an elevated temperature in the presence of a base such as potassium *tert*-butoxide.

A compound of formula (I) wherein R⁵ contains an amino moiety may be alkylated by treatment with the appropriate alkyl halide (e.g. methyl iodide, ethyl bromide, benzyl bromide or *tert*-butyl bromoacetate), typically in the presence of a base such as sodium

hydride or triethylamine. A compound of formula (I) wherein R⁵ contains an amino moiety may be converted into the corresponding compound containing a -NCH₂- motif by a reductive amination procedure which comprises treatment with the appropriate aldehyde derivative in the presence of a base such as sodium triacetoxyborohydride. A compound of formula (I) wherein R⁵ contains an amino moiety may be converted into the

corresponding compound containing a carbonylamino moiety by treatment with the appropriate carbonyl halide, typically in the presence of a base such as triethylamine. A compound of formula (I) wherein R⁵ contains an amino moiety may be converted into the corresponding compound containing a urea functionality by treatment with the appropriate isocyanate derivative. Alternatively, a compound of formula (I) wherein R⁵ contains an

amino moiety may be converted into the corresponding compound containing a urea functionality by a two-stage procedure which comprises (i) treatment with triphosgene, typically in the presence of a base such as triethylamine; and (ii) reaction of the compound thereby obtained with the appropriate amine derivative (including cyclic amines). A compound of formula (I) wherein R⁵ contains an amino moiety may be converted into the corresponding compound containing a sulphonylamino moiety by treatment with the appropriate sulphonyl halide, typically in the presence of a base such as triethylamine.

A compound of formula (I) wherein R⁵ represents a halogen atom, e.g. iodo, may be converted into the corresponding compound wherein R⁵ represents acetyl by a two-stage procedure which comprises (i) reaction with butyl vinyl ether and a transition metal catalyst such as tris(dibenzylideneacetone)dipalladium(0), typically in the presence of 1,3-bis(diphenylphosphino)propane and a base such as potassium carbonate; and (ii) hydrolysis of the resulting compound by treatment with a mineral acid, e.g. hydrochloric acid. A compound of formula (I) wherein R⁵ represents acetyl may be converted into the

corresponding compound wherein R⁵ represents 3-(dimethylamino)-1-oxoprop-2-en-1-yl by treatment with *N,N*-dimethylformamide dimethyl acetal, typically at an elevated temperature. A compound of formula (I) wherein R⁵ represents 3-(dimethylamino)-1-oxoprop-2-en-1-yl may be converted into the corresponding compound wherein R⁵ represents a substituted or unsubstituted pyrimidinyl moiety by treatment with the appropriate amidine derivative, typically at an elevated temperature in the presence of a base such as sodium ethoxide.

A compound of formula (I) wherein R⁶ represents hydrogen may be converted into the corresponding compound wherein R⁶ represents C₁₋₆ alkyl, e.g. methyl, by treatment with the appropriate alkyl halide, e.g. methyl iodide, typically in the presence of a base such as sodium hydride.

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

	DME: ethylene glycol dimethyl ether	DMSO: dimethylsulphoxide
	ⁱ Pr: isopropyl	Et ₂ O: diethyl ether
	THF: tetrahydrofuran	r.t.: room temperature
	sat.: saturated	DMAP: 4-(dimethylamino)pyridine
5	EtOAc: ethyl acetate	MeOH: methanol
	AcOH: acetic acid	EtOH: ethanol
	IPA: isopropyl alcohol	RT: retention time
	Me: methyl	h: hour
	MeCN: acetonitrile	SiO ₂ : silica
10	br.: broad	wt: weight
	brine: saturated aqueous sodium chloride solution	
	HPLC: High Performance Liquid Chromatography	
	LCMS: Liquid Chromatography Mass Spectrometry	
	DIPEA: <i>N,N</i> -diisopropylethylamine	TFA: trifluoroacetic acid
15	ES+: Electrospray Positive Ionisation	ES-: Electrospray Negative Ionisation
	M: mass	
	EDC: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride	
	Eschenmoser's salt: <i>N,N</i> -dimethylmethyleammonium iodide	
	NIS: <i>N</i> -iodosuccinimide	NCS: <i>N</i> -chlorosuccinimide
20	NBS: <i>N</i> -bromosuccinimide	dppf 1,1'-bis(diphenylphosphino)ferrocene

Hydrogenation procedure

Hydrogenations were performed using either a balloon filled with hydrogen and with 10% wt palladium on carbon, or a Thales H-cube™ hydrogenation kit, software
25 24/33 using a continuous flow and 10%Pd/C CatCart™.

Analytical Conditions

All NMRs were obtained either at 300 MHz or 400 MHz.
Compounds were named with the aid of ACD Labs Name (v. 7.0 or 9.0) supplied
30 by Advanced Chemical Development, Toronto, Canada.
All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen atmosphere using dried solvents and glassware.

Procedure used for preparative HPLC:

Column: Luna C18 250 mm x 21.2 mm, 5 µm particle size ex. Phenomenex

Mobile Phase for pH 2.5:

Mobile Phase A: 0.08% formic acid in water

5 Mobile Phase B: 0.08% formic acid in MeCN

Mobile Phase for pH 5.8:

Mobile Phase A: 10 mM ammonium acetate in water

Mobile Phase B: 10 mM ammonium acetate in MeCN

Injection: 1 mL in DMSO

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INTERMEDIATE 1 (METHOD A)**Ethyl 2-bromo-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate**

To a stirred solution of CuBr₂ (5.0 g, 22.5 mmol) in MeCN (60 mL) at 0°C was
15 slowly added *tert*-butyl nitrite (2.4 mL, 18.5 mmol). The reaction mixture was then
stirred for 15 minutes before 2-amino-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-
carboxylic acid ethyl ester (3.9 g, 16.1 mmol) was added portionwise. The reaction
mixture was then allowed to warm, with stirring, to r.t. and, after stirring for 4 h, it was
partitioned between 2M HCl (200 mL) and EtOAc (3 x 200 mL). The combined organics
20 were dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by column
chromatography (SiO₂, 1:6 EtOAc/hexanes) gave the *title compound* as a pale brown
solid (3.5 g, 71%). δ_H (DMSO-d₆) 4.33 (2H, q, *J* 7.1 Hz), 3.00 (2H, t, *J* 6.0 Hz), 2.58-
2.51 (2H, m), 2.12-2.04 (2H, m), 1.33 (3H, t, *J* 7.1 Hz).

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INTERMEDIATE 2**3-Iodo-2-morpholino-5,6-dihydro-1-benzothiophen-7(4*H*)-one**

To a stirred solution of *Example 2* (0.62 g, 2.61 mmol) in THF (20 mL) at 0°C
was added I₂ (0.67 g, 2.61 mmol) and the reaction mixture was stirred for 10 minutes
30 before being poured into brine (200 mL). The mixture was then extracted with EtOAc (3
x 150 mL) and the combined organics were washed with brine (200 mL), dried (MgSO₄),
filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 0-30%
EtOAc in hexanes) gave the *title compound* as an off-white solid (0.54 g, 56%). δ_H

(CDCl₃) 3.84-3.81 (4H, m), 3.22-3.19 (4H, m), 2.73 (2H, t, *J* 6.0 Hz), 2.57-2.53 (2H, m), 2.17-2.09 (2H, m). LCMS (ES+) 364.0 (M+H)⁺.

INTERMEDIATE 3

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2-Bromo-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid

To a stirred solution of *Intermediate 1* (1.0 g, 3.3 mmol) in THF (10 mL) was added LiOH (0.2 g, 5.0 mmol) in water (5 mL) and the reaction mixture was heated to 70°C for 18 h. The volatiles were then removed *in vacuo* and the crude residue was dissolved in hot water (10 mL). The solution was allowed to cool and was then acidified to pH 1 by the addition of aqueous 2M HCl dropwise. The resultant precipitate was collected via filtration and dried in a vacuum oven to give the *title compound* as an off-white solid (0.8 g, 92%). δ_H (DMSO-d₆) 13.52 (1H, br. s), 3.00 (2H, t, *J* 6.0 Hz), 2.57-2.49 (2H, m), 2.09-2.04 (2H, m). LCMS (ES+) 275.0 and 277.0 (M+H)⁺.

15

INTERMEDIATE 4

2-Bromo-7-oxo-N-phenyl-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide

To a stirred solution of *Intermediate 3* (0.20 g, 0.73 mmol) in DCM (5 mL) was added EDC (0.20 g, 1.00 mmol) and, after stirring for 15 minutes, aniline (0.10 g, 1.00 mmol) was added. The reaction mixture was then stirred at r.t. for 18 h before being diluted with DCM (100 mL) and washed with brine (2 x 100 mL). The organic phase was dried over MgSO₄, filtered and the solvent removed *in vacuo*. Purification by column chromatography (SiO₂, 1:6 EtOAc/hexanes) gave the *title compound* as an off-white solid (0.72 g, 28%). δ_H (DMSO-d₆) 7.64-7.60 (3H, m), 7.42-7.37 (2H, m), 7.23-7.19 (1H, m), 3.04 (2H, t, *J* 6.0 Hz), 2.64-2.60 (2H, m), 2.23-2.16 (2H, m). LCMS (ES+) 350.0 and 352.0 (M+H)⁺.

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INTERMEDIATE 5

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Ethyl 2-[3(S)-3-(1*H*-indol-3-ylmethyl)morpholin-4-yl]-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate

To a stirred solution of *Intermediate 1* (0.47 g, 1.60 mmol) in MeCN (5 mL) was added DIPEA (0.34 mL, 1.90 mmol) and *Intermediate 9* (0.42 g, 1.90 mmol). The reaction mixture was then heated to 180°C in a sealed tube, under microwave irradiation, for 1 h. After cooling, the solution was partitioned between DCM (100 mL) and brine (200 mL) and the aqueous phase was further extracted with DCM (2 x 100 mL). The combined organic phases were then dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 10-50% EtOAc in hexanes) gave the *title compound* as an off-white solid (0.23 g, 33%). δ_{H} (CDCl₃) 7.99 (1H, br. s), 7.51 (1H, d, *J* 9.8 Hz), 7.33 (1H, d, *J* 8.0 Hz), 7.21-7.03 (3H, m), 4.29 (2H, q, *J* 7.2 Hz), 4.15-4.02 (2H, m), 3.82-3.72 (4H, m), 3.36 (1H, m), 3.19-3.16 (1H, m), 3.06-2.87 (3H, m), 2.57-2.51 (2H, m), 2.15-2.06 (2H, m), 1.36 (3H, t, *J* 7.2 Hz). LCMS (ES⁺) 439.0 (M+H)⁺.

INTERMEDIATE 6

(2S)-2-Amino-3-(1H-indol-3-yl)propan-1-ol

To a stirred solution of (*S*)-tryptophan (4.0 g, 20.0 mmol) in THF (100 mL) at 0°C was slowly added BH₃.Me₂S complex (5.9 mL, 10M solution in THF, 59.0 mmol). The reaction mixture was heated to 70°C for 16 h and, after cooling, the excess borane was quenched by the addition of MeOH (10 mL) at 0°C. The reaction mixture was then concentrated *in vacuo* and the resultant white solid was dissolved in EtOAc (100 mL) and washed with aqueous 20% NaOH solution (2 x 70 mL). The organic layer was then extracted into aqueous 2M HCl (2 x 100 mL). The combined acidic aqueous layers were then basified to pH 14 (addition of solid NaOH) and were re-extracted with EtOAc (2 x 150 mL). The combined organic fractions were washed with brine (70 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to give the *title compound* (3.5 g, 92%) as a white solid that required no further purification. δ_{H} (CD₃OD) 7.46 (1H, d, *J* 7.9 Hz), 7.21 (1H, d, *J* 8.0 Hz), 6.96 (3H, m), 3.79 (1H, dd, *J* 11.3 and 3.6 Hz), 3.54 (1H, dd, *J* 11.2 and 6.2 Hz), 3.05 (1H, m), 2.80 (1H, m), 2.61 (1H, m). Exchangeable protons were not observed.

INTERMEDIATE 7

2-Chloro-N-[(1S)-2-hydroxy-1-(1H-indol-3-ylmethyl)ethyl]acetamide

To a stirred solution of *Intermediate 6* (2.0 g, 10.0 mmol) and NEt₃ (1.3 g, 1.8 mL, 13.0 mmol) in THF (120 mL) at 0°C was added chloroacetyl chloride (1.3 g, 1.0 mL, 12.0 mmol) dropwise. The reaction mixture was stirred at r.t. for 1.5 h and was then quenched
5 by the addition of water (5 mL). The reaction mixture was diluted with EtOAc (120 mL) and partitioned with water (100 mL). The organic fraction was washed with brine (100 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to give the *title compound* (2.4 g, 90%) as a beige solid that was used without further purification. δ_{H} (CDCl₃) 8.15 (1H, br. s), 7.59 (1H, d, *J* 7.9 Hz), 7.28 (1H, d, *J* 8.0 Hz), 7.11 (3H, m), 6.97 (1H, d, *J* 2.3 Hz),
10 4.19 (1H, m), 3.92 (2H, d, *J* 2.9 Hz), 3.59 (2H, m), 2.98 (2H, d, *J* 6.0 Hz), 2.52 (1H, br. s).

INTERMEDIATE 8(5S)-5-(1H-Indol-3-ylmethyl)morpholin-3-one

To a stirred solution of *Intermediate 7* (2.4 g, 9.5 mmol) in THF (100 mL) at 0°C was added NaH (0.8 g, 60% dispersion in oil, 19.0 mmol) portionwise. The reaction mixture was stirred at r.t. for 1.5 h and then quenched at 0°C by the addition of ice. The solution was then partitioned between EtOAc (100 mL) and water (100 mL) and the
20 organic fraction was dried over MgSO₄, filtered and concentrated *in vacuo* to give the *title compound* (1.8 g, 82%) as a yellow solid that was used without further purification. δ_{H} (CD₃OD) 7.46 (1H, d, *J* 7.8 Hz), 7.25 (1H, d, *J* 7.8 Hz), 6.95 (3H, m), 3.99 (2H, s), 3.65 (2H, m), 3.52 (1H, m), 2.91 (2H, d, *J* 6.3 Hz). Exchangeable protons were not observed. LCMS (ES⁺) 231.0 (M+H)⁺.

25

INTERMEDIATE 93-[(3S)-Morpholin-3-ylmethyl]-1H-indole

To a stirred solution of *Intermediate 8* (1.8 g, 7.8 mmol) in THF (100 mL) was
30 slowly added, at 0°C, LiAlH₄ (1.0 g, 27.0 mmol). After stirring for 16 h at r.t. the reaction mixture was quenched by the dropwise addition of aqueous sat. NaHCO₃ solution (20 mL). The resulting mixture was filtered through Celite[®] and the filtrate was concentrated *in vacuo*. The resulting solid was dissolved in toluene and the solvent

removed by evaporation *in vacuo*. Purification by column chromatography (SiO₂, EtOAc) yielded the *title compound* (1.5 g, 89%) as a cream solid. δ_{H} (CDCl₃) 8.11 (1H, br. s), 7.55 (1H, d, *J* 7.8 Hz), 7.28 (1H, d, *J* 8.0 Hz), 7.11 (3H, m), 3.83 (1H, dd, *J* 10.9 and 2.8 Hz), 3.71 (1H, dt, *J* 11.3 and 2.2 Hz), 3.47 (1H, m), 3.24 (1H, t, *J* 9.8 Hz), 3.06 (1H, m), 2.78 (3H, m), 2.56 (1H, m), 1.92 (1H, br. s). LCMS (ES⁺) 217.0 (M+H)⁺.

INTERMEDIATE 10

(3,3-Dimethyl-5-oxocyclohexylidene)malonitrile

To a stirred solution of dimedone (98.0 g, 700.0 mmol) and malonitrile (46.2 g, 700.0 mmol) in EtOH (400 mL) at r.t. was added piperidine (8.5 g, 9.9 mL, 100.0 mmol) dropwise over 15 minutes. The reaction mixture was then heated to reflux for 3 days before cooling. The solvent was removed *in vacuo* and the residue was re-dissolved in EtOAc (500 mL) and dried (MgSO₄). Filtration and concentration *in vacuo* gave a black oil that was purified by column chromatography (SiO₂, 1:6 MeOH/DCM) to give the *title compound* as a yellow solid (108.0 g, 82%). δ_{H} (DMSO-d₆) 8.31 (2H, br. s), 2.51 (2H, t, *J* 1.8 Hz), 2.30 (2H, s), 1.04 (6H, s). LCMS (ES⁻) 187.3 (M-H)⁻.

INTERMEDIATE 11

2-Amino-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile

To a stirred solution of *Intermediate 10* (50.8 g, 270.0 mmol) and sulphur (10.3 g, 320.0 mmol), in EtOH (600 mL), was slowly added morpholine (46.0 g, 46.0 mL, 530.0 mmol) at r.t. The reaction mixture was stirred at 80°C for 24 h and then cooled. The solids formed were isolated by filtration and washed with cold Et₂O to give the *title compound* as a buff solid (41.2 g, 53%). δ_{H} (DMSO-d₆) 8.31 (2H, br. s), 2.51 (2H, t, *J* 1.8 Hz), 2.30 (2H, s), 1.04 (6H, s). LCMS (ES⁻) 219.2 (M-H)⁻.

INTERMEDIATE 12

2-Bromo-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile

The *title compound* was prepared from *Intermediate 11* according to *Method A* and was isolated as a pale tan solid (40%) after purification by column chromatography

(SiO₂, 1:3 DCM/hexanes). δ_{H} (DMSO-d₆) 2.84 (2H, s), 2.51 (2H, s), 1.07 (6H, s). LCMS (ES+) 285.9 (M+H)⁺.

INTERMEDIATE 13

5

3-[(Dimethylamino)methyl]-6-iodoimidazo[1,2-a]pyridine

A stirred solution of 6-iodoimidazo[1,2-a]pyridine (2.0 g, 8.2 mmol) and Eschenmoser's salt (5.0 g, 2.7 mmol) in THF (50 mL) was heated to reflux for 24 h. The reaction mixture was then diluted with EtOAc (50 mL), washed with water (3 x 20 mL),
10 dried (MgSO₄), filtered and concentrated *in vacuo*. The residual solid was triturated from Et₂O, collected by filtration and dried to give the *title compound* (1.1 g, 45%) as a brown powder. δ_{H} (DMSO-d₆) 8.67 (1H, m), 7.45 (1H, s), 7.43-7.41 (2H, m), 3.72 (2H, s), 2.14 (6H, s). LCMS (ES+) 302.2 (M+H)⁺.

15

INTERMEDIATE 14

N,N-Dimethyl-N'-(5-iodopyridin-2-yl)ethane-1,2-diamine

A stirred solution of 2-chloro-5-iodopyridine (0.50 g, 2.18 mmol) and N,N-dimethylethylenediamine (0.81 g, 1.00 mL, 9.20 mmol) in 2-ethoxyethanol (5 mL) was
20 heated in a sealed tube under microwave irradiation at 125°C for 1 h. The reaction mixture was then diluted with EtOAc (50 mL), washed with water (3 x 20 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The residual oil was purified by column chromatography (SiO₂, 3:1 EtOAc/MeOH) to give the *title compound* (0.22 g, 36%) as a viscous oil which solidified on standing. δ_{H} (CDCl₃) 8.19 (1H, br. s), 7.53 (1H, m), 6.23
25 (1H, m), 3.29 (2H, m), 2.52 (2H, m), 2.24 (6H, s). Exchangeable proton not observed. LCMS (ES+) 292.0 (M+H)⁺.

INTERMEDIATE 15

[2(S)-1-(5-Iodopyridin-2-yl)pyrrolidin-2-yl]methanol

A stirred solution of 2-chloro-5-iodopyridine (0.50 g, 2.18 mmol) and 2(S)-2-hydroxymethylpyrrolidine (1.00 g, 10.00 mmol) in 2-ethoxyethanol (5 mL) was heated in a sealed tube under microwave irradiation at 125°C for 30 minutes. The reaction mixture

was then diluted with EtOAc (50 mL), washed with water (3 x 20 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The residual oil was purified by column chromatography (SiO₂, 3:1 EtOAc/MeOH) to give the *title compound* (0.42 g, 63%) as a viscous oil which solidified on standing. δ_{H} (DMSO-d₆) 8.19 (1H, d, *J* 2.3 Hz), 7.70 (1H, dd, *J* 8.9 and 2.3 Hz), 6.41 (1H, d, *J* 8.9 Hz), 4.77 (1H, t, *J* 5.8 Hz), 3.95 (1H, m), 3.55-3.21 (4H, m), 2.05-1.81 (4H, m). LCMS (ES⁺) 305.1 (M+H)⁺.

INTERMEDIATE 16

10 Ethyl 2-amino-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate

To a stirred solution of sulphur (1.0 g, 31.0 mmol), 6,6-dimethylpiperidine-2,4-dione (4.0 g, 28.0 mmol) and ethyl cyanoacetate (3.7 g, 3.5 mL, 29.0 mmol) in EtOH (20 mL) at 45°C was added morpholine (2.9 g, 2.9 mL, 33.0 mmol) dropwise over 15 minutes. The reaction mixture was stirred at this temperature for 15 minutes and then at 15 65°C for 48 h before it was cooled and concentrated *in vacuo*. To the residue was added water and the resulting solid was filtered and washed with water to give the *title compound* as a pale brown solid (4.1 g, 54%). δ_{H} (DMSO-d₆) 7.86 (2H, s), 7.28 (1H, s), 4.21 (2H, q, *J* 7.0 Hz), 2.88 (2H, s), 1.27 (3H, t, *J* 7.1 Hz), 1.23 (6H, s). LCMS (ES⁺) 269.1 (M+H)⁺.

20

INTERMEDIATE 17 (METHOD E)

Ethyl 2-bromo-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate

To a stirred suspension of *Intermediate 16* (0.20 g, 0.75 mmol) in MeCN (5 mL) 25 at 0-5°C was added CuBr₂ (0.20 g, 0.90 mmol) followed by *tert*-butyl nitrite (0.10 g, 0.10 mL, 0.80 mmol) dropwise. The reaction mixture was stirred at this temperature for 10 minutes before it was partitioned between EtOAc (50 mL) and water (50 mL). The organics were separated, washed with water (3 x 20 mL) and brine (20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude residue was washed with Et₂O to 30 give the *title compound* as a pale brown solid (0.15 g, 61%). δ_{H} (DMSO-d₆) 8.53 (1H, s), 4.32 (2H, q, *J* 7.0 Hz), 3.10 (2H, s), 1.33 (3H, t, *J* 7.1 Hz), 1.26 (6H, s). LCMS (ES⁺) 332.0 and 334.0 (M+H)⁺.

INTERMEDIATE 18 (METHOD F)

Ethyl 5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate

5 To a stirred solution of *Intermediate 17* (1.4 g, 4.1 mmol) in IPA (25 mL) at r.t. was added morpholine (1.0 g, 1.0 mL, 11.5 mmol) and the reaction mixture was heated at 60°C for 48 h. After cooling, the mixture was partitioned between EtOAc (100 mL) and water (50 mL). The organics were separated, washed with water (2 x 20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was then purified by column
10 chromatography (SiO₂, EtOAc) to give the *title compound* as an off-white solid (1.0 g, 76%). δ_H (DMSO-*d*₆) 7.56 (1H, s), 4.23 (2H, q, *J* 7.0 Hz), 3.74 (4H, br. m), 3.17 (4H, br. m), 2.90 (2H, s), 1.28 (3H, t, *J* 7.1 Hz), 1.23 (6H, s). LCMS (ES⁺) 339.0 (M+H)⁺.

INTERMEDIATE 19 (METHOD H)

15

5,5-Dimethyl-3-iodo-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one

To a stirred solution of *Example 49* (0.45 g, 1.67 mmol) in THF (20 mL) at r.t. was added NIS (0.39 g, 1.76 mmol). After stirring for 2 h, Na₂CO₃ (2.00 g, 18.87 mmol) was added and the reaction mixture was stirred for a further minute, prior to the addition
20 of sat. aqueous Na₂CO₃ (10 mL). The resulting solid was filtered and washed with water and Et₂O to give the *title compound* as a white solid (0.35 g, 53%). δ_H (DMSO-*d*₆) 7.63 (1H, s), 3.76 (4H, br. m), 3.07 (4H, m), 2.64 (2H, s), 1.25 (6H, s). LCMS (ES⁺) 393.0 (M+H)⁺.

25

INTERMEDIATE 20

Ethyl 2-amino-5,5-dimethyl-8-oxo-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*c*]azepine-3-carboxylate

To a stirred solution of 6,6-dimethylazepane-2,4-dione (0.50 g, 3.20 mmol),
30 sulphur (0.12 g, 3.75 mmol) and ethyl cyanoacetate (0.39 g, 3.48 mmol) in EtOH (2.5 mL) at 45°C was added morpholine (0.30 g, 0.30 mL, 3.48 mmol) over a period of 20 minutes. The reaction mixture was then heated to 50°C for 3 h before it was stirred for 12 h at 40°C. The solution was cooled to r.t. and the resulting solid was

filtered, washed (3:1 water/EtOH) and dried to give the *title compound* as an off-white powder (0.45 g, 50%). δ_{H} (DMSO- d_6) 7.73 (2H, t, J 5.1 Hz), 7.69 (1H, s), 4.22 (2H, q, J 7.1 Hz), 2.82 (2H, s), 2.79 (2H, d, J 5.2 Hz), 1.28 (3H, t, J 7.1 Hz), 0.95 (6H, s). LCMS (ES+) 283.0 (M+H)⁺.

5

INTERMEDIATE 21

Ethyl 2-bromo-5,5-dimethyl-8-oxo-5,6,7,8-tetrahydro-4H-thieno[2,3-*c*]azepine-3-carboxylate

10 The *title compound* was prepared from *Intermediate 20* according to *Method E* and was isolated as a brown solid (74%). δ_{H} (CDCl₃) 6.20 (1H, br. s), 4.41 (2H, q, J 7.0 Hz), 2.99 (2H, d, J 5.5 Hz), 2.90 (2H, s), 1.44 (3H, t, J 7.1 Hz), 1.08 (6H, s). LCMS (ES+) 346.0 and 348.0 (M+H)⁺.

15

INTERMEDIATE 22

Ethyl 5,5-dimethyl-2-(morpholin-4-yl)-8-oxo-5,6,7,8-tetrahydro-4H-thieno[2,3-*c*]azepine-3-carboxylate

20 To a stirred solution of *Intermediate 21* (0.31 g, 0.90 mmol) in DMSO (4 mL) at r.t. was added morpholine (0.10 g, 0.10 mL, 1.10 mmol) and the reaction mixture was heated to 90°C for 12 h. The reaction mixture was then partitioned between EtOAc (50 mL) and water (20 mL) and the organics were separated, washed with water (3 x 15 mL) and brine (15 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give the *title compound* as a white powder (0.28 g, 90%). δ_{H} (DMSO- d_6) 7.94 (1H, t, J 5.0 Hz) 4.24
25 (2H, q, J 7.1 Hz), 3.73 (4H, m), 3.08 (4H, m), 2.80 (2H, d, J 4.2 Hz), 2.64 (2H, s), 1.28 (3H, t, J 7.1 Hz), 0.94 (6H, s). LCMS (ES+) 353.0 (M+H)⁺.

INTERMEDIATE 23 (METHOD N)

30 2-Ethynyl-1-methyl-1H-imidazole

To a stirred solution of 1-methyl-2-imidazolecarboxaldehyde (0.25 g, 2.27 mmol) and K₂CO₃ (0.63 g, 4.54 mmol) in MeOH (5 mL) was added dimethyl-1-diazo-2-oxypropylphosphate (0.44 g, 2.27 mmol) in MeOH (5 mL) dropwise at r.t. The reaction

mixture was stirred for 3 h and concentrated *in vacuo* to give a green oil. The residue was dissolved in Et₂O (15 mL) and aqueous sat. NaHCO₃ (10 mL) was added. The layers were separated and the aqueous layer was extracted with Et₂O (2 x 10 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated *in vacuo*.

- 5 Purification by column chromatography (SiO₂, EtOAc) gave the *title compound* (0.14 g, 58%) as a pale brown oil. δ_{H} (CDCl₃) 7.06 (1H, s), 6.92 (1H, s), 3.76 (3H, s), 3.34 (1H, s). MS (ES⁺) 107.1 (M+H)⁺.

INTERMEDIATE 24

10

tert-Butyl 4-ethynylpiperidine-1-carboxylate

The *title compound* was prepared from 4-formylpiperidine-1-carboxylic acid *tert*-butyl ester according to *Method N* and was isolated as an off-white solid (48%) after purification by column chromatography (SiO₂, EtOAc). δ_{H} (CDCl₃) 3.82-3.63 (2H, m),
15 3.21 (2H, ddd, *J* 13.4, 8.3 and 3.3 Hz), 2.67-2.52 (1H, m), 2.12 (1H, d, *J* 2.3 Hz), 1.90-1.73 (2H, m), 1.69-1.54 (2H, m), 1.48 (9H, s). MS (ES⁺) 154.0 (M-^tBu+H)⁺.

INTERMEDIATE 25 (METHOD P)

20 4-Ethynylpiperidine trifluoroacetate

To a stirred solution of *Intermediate 24* (0.12 g, 0.57 mmol) in DCM (5 mL) was added TFA (0.5 mL). The reaction mixture was stirred at r.t. for 16 h and concentrated *in vacuo* to give the *title compound* (0.19 g, quantitative) as a brown oil that was used without further purification. δ_{H} (CDCl₃) 8.85 (2H, br. s), 3.54-3.30 (2H, m), 3.29-3.13
25 (2H, m), 2.97-2.80 (1H, m), 2.25 (1H, d, *J* 2.5 Hz), 2.18-2.06 (2H, m), 2.03-1.87 (2H, m). MS (ES⁺) 110.0 (M+H)⁺.

INTERMEDIATE 26 (METHOD O)

30 (2*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carbaldehyde

To a stirred solution of *tert*-butyloxycarbonyl-L-prolinol (3.50 g, 17.41 mmol) in DCM (25 mL) at 0°C was added triethylamine (9.7 mL, 60.93 mmol), followed by sulfur trioxide-pyridine complex (8.30 g, 6.96 mmol) in DMSO (10 mL). The reaction mixture

was stirred at 0°C for 1 h. Hexanes (20 mL), Et₂O (10 mL) and aqueous sat. NaHCO₃ (30 mL) were added and the layers separated. The aqueous layer was extracted with a mixture of hexanes (20 mL) and Et₂O (10 mL) twice. The combined organic layers were washed with 1M aqueous NaH₂PO₄ (30 mL), then brine (30 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 20% EtOAc/hexanes) gave the *title compound* (2.70 g, 77%) as a colourless oil. δ_{H} (DMSO-d₆), mixture of rotamers: 9.49-9.36 (1H, m), 4.14-4.02 (1H, m), 3.45-3.26 (2H, m), 2.14-2.00 (1H, m), 1.96-1.69 (3H, m), 1.42 and 1.34 (9H, s, rotameric).

INTERMEDIATE 27

(2S)-1-(tert-Butoxycarbonyl)-2-ethynylpyrrolidine

The *title compound* was prepared from *Intermediate 26* according to *Method N* and was isolated as an off-white solid (80%) that was used without further purification.

δ_{H} (DMSO-d₆) 4.37 (1H, br. s), 3.34-3.26 (1H, m), 3.27-3.09 (2H, m), 2.16-1.98 (1H, m), 1.88 (3H, s), 1.40 (9H, s). MS (ES⁺) 140.1 (M-^tBu+H)⁺.

INTERMEDIATE 28 (METHOD Z)

tert-Butyl 2-(hydroxymethyl)piperidine-1-carboxylate

To a stirred solution of 2-piperidinemethanol (3.0 g, 25.60 mmol) in DCM (100 mL) was added triethylamine (14.5 mL, 91.08 mmol) and then di-*tert*-butyl dicarbonate (7.2 g, 31.0 mmol) portionwise. The reaction mixture was stirred at r.t. for 16 h. Water (70 mL) was added and the layers were separated. The organic layer was washed with water (2 x 50 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give the *title compound* (6.0 g, quantitative) as a pale brown oil that was used without further purification. δ_{H} (CDCl₃) 4.42-4.22 (1H, m), 4.05-3.91 (1H, m), 3.89-3.77 (1H, m), 3.71-3.53 (1H, m), 2.97-2.81 (1H, m), 2.32-2.08 (1H, m), 1.90 (1H, s), 1.77-1.57 (3H, m), 1.54 (1H, s), 1.52-1.38 (10H, m).

INTERMEDIATE 29

tert-Butyl 2-formylpiperidine-1-carboxylate

The *title compound* was prepared from *Intermediate 28* according to *Method O* and was isolated as a pale yellow oil (75%) after purification by column chromatography (SiO₂, 20% EtOAc/hexanes). δ_{H} (DMSO-d₆) 9.52 (1H, s), 4.50 (1H, s), 3.91-3.61 (1H, m), 3.03-2.60 (1H, m), 2.24-2.04 (1H, m), 1.74-1.48 (3H, m), 1.49-1.24 (10H, m), 1.24-1.02 (1H, m).

INTERMEDIATE 30

tert-Butyl 2-ethynylpiperidine-1-carboxylate

The *title compound* was prepared from *Intermediate 29* according to *Method N* (90%) and was used without further purification. δ_{H} (DMSO-d₆) 4.95 (1H, s), 3.80 (1H, dd, *J* 13.1 and 3.0 Hz), 3.28 (1H, d, *J* 2.3 Hz), 2.88 (1H, s), 1.77-1.50 (5H, m), 1.40 (9H, s), 1.37-1.17 (1H, m).

INTERMEDIATE 31

tert-Butyl 3-(hydroxymethyl)piperidine-1-carboxylate

The *title compound* was prepared from 3-piperidinemethanol according to *Method Z* and was isolated as a yellow oil (quantitative) that was used without further purification. δ_{H} (CDCl₃) 3.94-3.63 (1H, m), 3.62-3.40 (2H, m), 3.25-2.73 (2H, m), 2.09 (1H, s), 1.89-1.58 (3H, m), 1.54 (1H, s), 1.47 (10H, s), 1.37-1.18 (1H, m).

INTERMEDIATE 32

tert-Butyl 3-formylpiperidine-1-carboxylate

The *title compound* was prepared from *Intermediate 31* according to *Method O* and was isolated as a colourless oil (63%) after purification by column chromatography (SiO₂, 20% EtOAc/hexanes). δ_{H} (DMSO-d₆) 9.60 (1H, s), 3.83-3.58 (1H, m), 3.54-3.22 (1H, m), 3.16-2.98 (1H, m), 2.54-2.36 (1H, m), 1.99-1.78 (1H, m), 1.73-1.47 (2H, m), 1.39 (11H, s).

INTERMEDIATE 33

tert-Butyl 3-ethynylpiperidine-1-carboxylate

The *title compound* was prepared from *Intermediate 32* according to *Method N* (96%) and was used without further purification. δ_{H} (DMSO- d_6) 3.75-3.30 (2H, m), 3.18-2.93 (2H, m), 2.89 (1H, d, J 2.3 Hz), 2.42-2.29 (1H, m), 1.87-1.71 (1H, m), 1.63-1.51 (1H, m), 1.51-1.39 (1H, m), 1.34 (9H, s), 1.31-1.21 (1H, m).

INTERMEDIATE 342-Ethynylpiperidine trifluoroacetate

The *title compound* was prepared from *Intermediate 30* according to *Method P* (quantitative) and was used without further purification.

INTERMEDIATE 35 (METHOD V)3-Ethynylpiperidine hydrochloride

To *Intermediate 33* (1.50 g, 7.18 mmol) was added HCl (4N in dioxane, 50 mL). The reaction mixture was stirred at r.t. for 16 h and concentrated *in vacuo*. Trituration with Et₂O gave the *title compound* (0.91 g, 86%). δ_{H} (DMSO- d_6) 9.02 (2H, br. s), 3.38-3.24 (1H, m), 3.21-3.08 (2H, m), 2.94-2.76 (3H, m), 2.00-1.87 (1H, m), 1.83-1.73 (1H, m), 1.73-1.60 (1H, m), 1.60-1.48 (1H, m).

INTERMEDIATE 36 (METHOD Y)5-[(Triethylsilyl)ethynyl]-1H-indole

To a stirred solution of 5-iodoindole (0.50 g, 2.0 mmol) and (triethylsilyl)-acetylene (0.58 g, 4.0 mmol) in diisopropylamine (15 mL) was added Pd(PPh₃)₂Cl₂ (0.07 g, 0.10 mmol) and CuI (0.04 g, 0.20 mmol) and the reaction mixture was stirred at r.t. for 16 h. The solvent was then removed *in vacuo*. EtOAc (15 mL) and water (15 mL) were added and the layers separated. The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with water (2 x 20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 10% EtOAc/hexanes) gave the *title compound* (0.52 g, quantitative). δ_{H} (DMSO- d_6) 11.30 (1H, br. s), 7.69 (1H, s), 7.45-7.41 (1H, m), 7.37 (1H, d, J 8.4 Hz), 7.15 (1H, dd, J 8.4 and

1.5 Hz), 6.48-6.40 (1H, m), 1.02 (9H, t, J 7.8 Hz), 0.65 (6H, q, J 7.9 Hz). MS (ES-) 254.0 (M-H)⁻.

INTERMEDIATE 37

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5-Ethynyl-1H-indole

To a stirred solution of *Intermediate 36* (0.52 g, 0.02 mmol) in MeOH (15 mL) was added K₂CO₃ (0.28 g, 0.02 mmol). The reaction mixture was stirred at 45°C for 2 h and concentrated *in vacuo*. EtOAc (15 mL) and water (15 mL) were added and the layers
10 separated. The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with water (2 x 20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 15% EtOAc/hexanes) gave the *title compound* (0.11 g, 39%) as a pale yellow oil that solidified on
standing. δ_{H} (DMSO-d₆) 11.29 (1H, br. s), 7.70 (1H, s), 7.46-7.39 (2H, m), 7.16 (1H, dd,
15 J 8.4 and 1.1 Hz), 6.45 (1H, s), 3.89 (1H, s). MS (ES-) 140.0 (M-H)⁻.

INTERMEDIATE 38

1,2-Dimethyl-4-iodo-1H-imidazole

To a stirred solution of 2-methyl-4(5)-iodo-1H-imidazole (5.0 g, 24.0 mmol) in THF (50 mL) at 0°C was added sodium hydride (60% dispersion in mineral oil, 1.15 g, 28.80 mmol). The reaction mixture was stirred at this temperature for 30 minutes, then methyl iodide (1.65 mL, 26.40 mmol) was added dropwise. The reaction mixture was stirred for 2 h. EtOAc (50 mL) and water (50 mL) were added and the layers separated.
25 The organic layer was dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 1% EtOAc/hexanes) gave the *title compound* (1.01 g, 19%) as a yellow oil that solidified on standing. δ_{H} (DMSO-d₆) 7.19 (1H, s), 3.52 (3H, s), 2.24 (3H, s). MS (ES+) 223.0 (M+H)⁺.

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INTERMEDIATE 39 (METHOD R)

1,2-Dimethyl-4-[(triethylsilyl)ethynyl]-1H-imidazole

To a stirred solution of *Intermediate 38* (1.01 g, 4.50 mmol) in diisopropylamine (5 mL) and THF (5 mL) were added (triethylsilyl)acetylene (1.28 g, 9.0 mmol), CuI (0.086 g, 0.50 mmol) and Pd(PPh₃)₂Cl₂ (0.159 g, 0.20 mmol). The reaction mixture was stirred at 50°C for 16 h, then cooled to r.t. The salts formed were filtered and the solvent removed *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-20% EtOAc/hexanes) to give the *title compound* (0.94 g, 90%) as a yellow solid. δ_{H} (DMSO-d₆) 7.37 (1H, s), 3.51 (3H, s), 2.23 (3H, s), 0.98 (9H, t, *J* 7.9 Hz), 0.60 (6H, q, *J* 7.9 Hz). MS (ES⁺) 235.0 (M+H)⁺.

INTERMEDIATE 40

1,2-Dimethyl-4-ethynyl-1H-imidazole

To a stirred solution of *Intermediate 39* (0.84 g, 3.50 mmol) in MeOH (25 mL) was added 2M aqueous NaOH (1 mL). The reaction mixture was stirred at 45°C for 6 h then cooled to r.t. The pH was adjusted to 7 by slow addition of 2M aqueous HCl. The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO₂, 0-100% EtOAc/hexanes) to give the *title compound* (0.29 g, 69%) as a white solid. δ_{H} (DMSO-d₆) 7.34 (1H, s), 3.87 (1H, s), 3.52 (3H, s), 2.24 (3H, s). MS (ES⁺) 121.0 (M+H)⁺.

INTERMEDIATE 41

1-Methyl-4-[(triethylsilyl)ethynyl]-1H-indole

The *title compound* was prepared from 4-bromo-1-methyl-1H-indole according to *Method R* and was isolated as a brown solid (92%) after aqueous work-up (EtOAc/water) and purification by column chromatography (SiO₂, 0-15% EtOAc/hexanes). δ_{H} (DMSO-d₆) 7.30 (1H, d, *J* 7.9 Hz), 7.22 (1H, d, *J* 3.0 Hz), 7.03-6.87 (2H, m), 6.22 (1H, dd, *J* 3.0 and 0.6 Hz), 3.60 (3H, s), 0.84 (9H, t, *J* 7.9 Hz), 0.49 (6H, q, *J* 7.9 Hz).

INTERMEDIATE 42

4-Ethynyl-1-methyl-1H-indole

To a stirred solution of *Intermediate 41* (2.0 g, 7.40 mmol) in MeOH (15 mL) was added K₂CO₃ (1.03 g, 7.40 mmol). The reaction mixture was stirred at 45°C for 2 h. 2M aqueous NaOH (2 mL) was added and the reaction mixture stirred at 45°C for a further 2 h then cooled to r.t. The pH was adjusted to 7 by slow addition of 2M aqueous HCl. The organic solvent was removed *in vacuo*. EtOAc (15 mL) and water (10 mL) were added and the layers separated. The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with water (2 x 20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, hexanes) gave the *title compound* (0.35 g, 31%) as a yellow oil. δ_{H} (DMSO-d₆) 7.27 (1H, d, *J* 8.0 Hz), 7.18 (1H, d, *J* 3.0 Hz), 7.02-6.78 (2H, m), 6.22 (1H, d, *J* 3.0 Hz), 4.04 (1H, s), 3.57 (3H, s). MS (ES⁺) 156.0 (M+H)⁺.

INTERMEDIATE 43

N-(Prop-2-yn-1-yl)methanesulfonamide

To a stirred solution of propargylamine (1.25 mL, 18.20 mmol) in pyridine (20 mL) at 0°C was added methanesulfonyl chloride (1.5 mL, 20.0 mmol) dropwise. The reaction mixture was allowed to warm to r.t., then evaporated *in vacuo*. EtOAc (50 mL) and aqueous sat. NaHCO₃ (50 mL) were added and the layers separated. The organic layer was dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 50% EtOAc/hexanes) gave the *title compound* (2.40 g, quantitative) as a white solid. δ_{H} (DMSO-d₆) 7.59 (1H, s), 3.87 (2H, d, *J* 2.5 Hz), 3.41-3.36 (4H, m). MS (ES⁺) 134.1 (M+H)⁺.

INTERMEDIATE 44

N,N-Dimethyl-*N'*-(prop-2-yn-1-yl)sulfamide

To a stirred solution of propargylamine (1.25 mL, 18.0 mmol) and triethylamine (5.00 mL, 36.0 mmol) in DCM (15 mL) at 0°C was added *N,N*-dimethylsulfamoyl chloride (2.14 mL, 20.0 mmol) dropwise. The reaction mixture was allowed to warm to r.t. and stirred for 16 h. EtOAc (100 mL) and water (50 mL) were added and the layers separated. The organic layer was washed with water (3 x 30 mL), then brine (30 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column

chromatography (SiO₂, 50% EtOAc/hexanes) gave the *title compound* (2.10 g, 72%) as a white solid. δ_{H} (DMSO-d₆) 4.61 (1H, s), 3.87 (2H, dd, *J* 6.1 and 2.5 Hz), 2.87 (6H, s), 2.35 (1H, t, *J* 2.5 Hz). MS (ES⁺) 163.1 (M+H)⁺.

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INTERMEDIATE 45

1-Benzoyl-4-iodo-1*H*-pyrazole

To a stirred solution of 4-iodopyrazole (10.30 g, 53.1 mmol) in toluene (50 mL) at r.t. was added triethylamine (8.10 mL, 58.1 mmol), followed by benzoyl chloride (8.20 g, 58.3 mmol). The reaction mixture was then heated to 100°C and stirred for 4 h. The solid was filtered and washed with toluene (50 mL). The organic filtrate was diluted with EtOAc (100 mL), washed with water (3 x 50 mL), then brine (50 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Recrystallisation from hexanes gave the *title compound* (13.80 g, 87%) as a white solid. δ_{H} (DMSO-d₆) 8.77 (1H, s), 8.05 (1H, s), 8.02-7.95 (2H, m), 7.74-7.67 (1H, m), 7.61-7.53 (2H, m).

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INTERMEDIATE 46

1-Benzoyl-4-[(triethylsilyl)ethynyl]-1*H*-pyrazole

The *title compound* was prepared from *Intermediate 45* according to *Method Y* and was isolated as a brown oil (quantitative) after purification by column chromatography (SiO₂, 50% EtOAc/hexanes). MS (ES⁺) 311.0 (M+H)⁺.

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INTERMEDIATE 47

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4-Ethynyl-1*H*-pyrazole

To a stirred solution of *Intermediate 46* (7.50 g, 24.0 mmol) in MeOH (80 mL) was added 2M aqueous NaOH (30 mL) and the reaction mixture was stirred at r.t. for 48 h. The pH was adjusted to 5-6 by slow addition of concentrated HCl and the reaction mixture was concentrated *in vacuo*. EtOAc (50 mL) and water (50 mL) were added and the layers separated. The aqueous layer was extracted with Et₂O (2 x 50 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 50-100% Et₂O/hexanes) gave the *title*

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compound (2.10 g, 95%) as a white solid. δ_{H} (DMSO- d_6) 13.09 (1H, br. s), 8.04 (1H, br. s), 7.66 (1H, br. s), 3.95 (1H, s).

INTERMEDIATE 48

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4-Ethynyl-1-methyl-1H-pyrazole

To a stirred solution of *Intermediate 47* (0.50 g, 5.40 mmol) in DMF (5 mL) at 0°C was added sodium hydride (60% dispersion in mineral oil, 0.26 g, 6.50 mmol). The reaction mixture was stirred at this temperature for 1 h, then methyl iodide (0.35 mL, 5.40 mmol) was added. The reaction mixture was stirred at 0°C for another hour then allowed to warm to r.t. Et₂O (50 mL) and water (25 mL) were added and the layers separated. The organic layer was washed with water (4 x 20 mL), then brine (20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 20% Et₂O/hexanes) gave the *title compound* (0.52 g, 91%) as a clear oil. δ_{H} (CDCl₃) 7.61 (1H, s), 7.54 (1H, s), 3.91 (3H, s), 3.01 (1H, s). MS (ES⁺) 107.1 (M+H)⁺.

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INTERMEDIATE 49

4-Ethynylpiperidine hydrochloride

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The *title compound* was prepared from *Intermediate 24* according to *Method V* and was isolated as a pale brown solid (97%). δ_{H} (DMSO- d_6) 8.80 (2H, br.s), 3.20-3.10 (2H, m), 3.09 (1H, d, *J* 2.5 Hz), 3.02-2.85 (2H, m), 2.79-2.65 (1H, m), 2.07-1.87 (2H, m), 1.78-1.59 (2H, m).

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INTERMEDIATE 50 (METHOD W)

1-Acetyl-3-ethynylpiperidine

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To a stirred solution of *Intermediate 35* (0.20 g, 1.36 mmol), triethylamine (0.42 mL, 2.99 mmol), and 4-(dimethylamino)pyridine (catalytic) in DCM (10 mL) was added acetic anhydride (0.15 mL, 1.63 mmol) dropwise. The reaction mixture was stirred at r.t. for 4 h then poured onto aqueous sat. NH₄Cl (10 mL). DCM (10 mL) was added and the layers were separated. The organic layer was washed with 1M aqueous HCl (2 x 10 mL), then aqueous sat. NaHCO₃ (2 x 10 mL), dried (Na₂SO₄), filtered and concentrated *in*

vacuo to give the *title compound* (0.18 g, 88%) as a pale yellow oil. δ_{H} (CDCl_3), mixture of rotamers: 4.40-1.19 (9H, m), 2.06 and 2.02 (3H, s, rotameric), 2.05 and 2.00 (1H, d, J 2.3 Hz, rotameric).

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INTERMEDIATE 51

1-Acetyl-4-ethynylpiperidine

The *title compound* was prepared from *Intermediate 49* according to *Method W* and was isolated as a brown oil (71%) that was used without further purification. δ_{H} (CDCl_3) 3.88-3.71 (1H, m), 3.66-3.50 (1H, m), 3.45-3.30 (1H, m), 3.31-3.14 (1H, m), 2.72-2.52 (1H, m), 2.16 (1H, s), 2.06 (1H, d, J 2.5 Hz), 2.02 (3H, s), 1.83-1.68 (2H, m), 1.64-1.55 (1H, m).

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INTERMEDIATE 52 (METHOD X)

3-Ethynyl-1-(methylsulfonyl)piperidine

To a stirred solution of *Intermediate 35* (0.20g, 1.36 mmol) and triethylamine (0.42 mL, 2.99 mmol) in DCM (10 mL) at 0°C was added methanesulphonyl chloride (0.13 mL, 1.63 mmol) dropwise. The reaction mixture was stirred at this temperature for 4 h then poured into EtOAc (50 mL). Water (25 mL) was added and the layers were separated. The organic layer was washed with water (2 x 25 mL), then brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2 , 30% EtOAc/hexanes) gave the *title compound* (0.21 g, 86%) as a white solid. MS (ES^+) 188.1 ($\text{M}+\text{H}^+$).

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INTERMEDIATE 53

4-Ethynyl-1-(methylsulfonyl)piperidine

The *title compound* was prepared from *Intermediate 49* according to *Method X* and was isolated as a white solid (58%) after purification by column chromatography (SiO_2 , 30% EtOAc/hexanes).

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INTERMEDIATE 54

1-Propioloylpyrrolidine

To a stirred solution of pyrrolidine (4.2 mL, 50.0 mmol) in water (25 mL) and MeOH (35 mL) at -50°C was added methylpropiolate (4.5 mL, 50.0 mmol) dropwise.

- 5 The reaction mixture was stirred at this temperature for 5 h then diluted with DCM (200 mL). 2M aqueous HCl (200 mL) was added and the layers were separated. The aqueous layer was extracted with DCM (2 x 100 mL). The combined organic layers were washed with aqueous sat. NaHCO₃ (200 mL), water (200 mL), then brine (200 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give the *title compound* (6.0 g, 98%) as a
- 10 white solid that was used without further purification. δ_{H} (CDCl₃) 3.68 (2H, t, *J* 6.8 Hz), 3.50 (2H, t, *J* 6.3 Hz), 3.04 (1H, s), 2.01-1.90 (4H, m).

INTERMEDIATE 55

- 15 3-[(2*E*)-3-(Dimethylamino)prop-2-enoyl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one

- The *title compound* was prepared from *Example 289* according to *Method AX* and was isolated as a yellow solid (70%). δ_{H} (CDCl₃) 7.79-7.55 (1H, br m), 5.81-5.61 (1H, br m), 5.20 (1H, s), 3.87-3.76 (4H, m), 3.26-3.19 (4H, m), 3.17-3.08 (2H, br s), 3.05-2.84
- 20 (6H, br s), 1.33 (6H, s). LCMS (ES⁺) 364.1 (M+H)⁺.

INTERMEDIATE 56

- 25 3-{2-[3-(Chloroacetyl)phenyl]pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one

- Benzyltrimethylammonium dichloriodate (128 mg, 0.37 mmol) was added to a solution of *Example 334* (85 mg, 0.18 mmol) in DCE (4.5 mL) and MeOH (2.0 mL) and the reaction mixture was heated at reflux for 4 h. The solvent was removed *in vacuo* and the residue was partitioned between DCM (30 mL) and 3% aqueous sodium metabisulfite
- 30 solution (30 mL). The aqueous phase was extracted with further DCM (30 mL) and the combined organic phases were dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was triturated with Et₂O to give the *title compound* (71 mg, 78%) as a yellow solid. δ_{H} (DMSO-*d*₆) 8.81-8.75 (1H, m), 8.69 (1H, s), 8.48-8.42 (1H, m), 8.23-

8.18 (1H, m), 8.09-8.02 (1H, m), 7.71 (1H, t, *J* 7.9 Hz), 7.58 (1H, s), 7.55-7.48 (1H, m), 3.67-3.56 (4H, m), 3.31 (2H, s), 2.96-2.86 (4H, m), 2.73 (2H, s), 1.20 (6H, s).

INTERMEDIATE 57 (METHOD BN)

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3-(1-Butoxyvinyl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

A mixture of *Example 17* (500 mg, 1.28 mmol), butyl vinyl ether (641 mg, 6.40 mmol), potassium carbonate (212 mg, 1.54 mmol), tris(dibenzylideneacetone)-
10 dipalladium(0) (101 mg, 0.11 mmol) and 1,3-bis(diphenylphosphino)propane (103 mg, 0.25 mmol) in DMF (3.0 mL) was heated in a sealed tube at 120°C, under microwave irradiation, for 2 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane) to give the *title compound* (365 mg, 63%) as a beige solid. δ_{H} (CDCl₃) 4.41 (1H, d, *J* 2.0 Hz), 4.20 (1H, d, *J* 2.0 Hz),
15 3.82-3.72 (6H, m), 3.33-3.27 (4H, m), 2.54 (2H, s), 2.38 (2H, s), 1.77-1.67 (2H, m), 1.52-1.39 (2H, m), 1.09 (6H, s), 0.96 (3H, t, *J* 7.3 Hz). LCMS (ES⁺) 364.2 (M+H)⁺.

INTERMEDIATE 58

20 3-(1-Butoxyvinyl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4H)-one

The *title compound* was prepared from *Intermediate 19* according to *Method BN* and was isolated as a pale orange solid (41%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane) and trituration with Et₂O. δ_{H} (DMSO-
25 d₆) 7.37 (1H, s), 4.46 (1H, d, *J* 1.8 Hz), 4.20 (1H, d, *J* 1.8 Hz), 3.78-3.65 (6H, m), 3.14-3.06 (4H, m), 2.59 (2H, s), 1.69-1.58 (2H, m), 1.46-1.33 (2H, m), 1.20 (6H, s), 0.91 (3H, t, *J* 7.2 Hz). LCMS (ES⁺) 365.2 (M+H)⁺.

INTERMEDIATE 59 (METHOD BO)

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3-((3*S*)-3-[(*tert*-Butoxycarbonyl)amino]pyrrolidin-1-yl)carbonyl)phenylboronic acid

A mixture of (3*S*)-(-)-3-(*tert*-butoxycarbonylamino)pyrrolidine (106 mg, 0.57 mmol), (3-chlorocarbonylphenyl)boronic anhydride (100 mg, 0.29 mmol) and

triethylamine (119 μ L, 0.86 mmol) in DCM (5.0 mL) was stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2 , 0-100% EtOAc/heptane) to give the *title compound* (58 mg, 30%) as a white solid. LCMS (ES+) 335 (M+H)⁺.

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INTERMEDIATE 60

3-((3R)-3-((tert-butoxycarbonyl)amino)pyrrolidin-1-yl)carbonylphenylboronic acid

The title compound was prepared from (3R)-(+)-3-(tert-butoxycarbonylamino)-pyrrolidine according to *Method BO* and was obtained as an off-white solid (30%).
LCMS (ES+) 335 (M+H)⁺.

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INTERMEDIATE 61

3-Benzyl 8-tert-butyl 3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate

A mixture of 8-tert-butoxycarbonyl-3,8-diazabicyclo[3.2.1]octane (238 mg, 1.12 mmol), benzyl chloroformate (160 μ L, 1.12 mmol) and triethylamine (280 μ L, 2.0 mmol) in DCM (20 mL) was stirred at room temperature for 22 h. The reaction mixture was diluted with DCM (20 mL) and washed with water (25 mL). The organic phase was dried (magnesium sulfate) and the solvent was removed *in vacuo* to give the *title compound* (336 mg, 87%) as a clear oil. δ_{H} (DMSO- d_6) 7.45-7.28 (5H, m), 5.17-5.03 (2H, m), 4.18-4.06 (2H, m), 3.79-3.69 (2H, m), 3.10-2.90 (2H, m), 1.85-1.72 (2H, m), 1.60-1.49 (2H, m), 1.41 (9H, s).

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INTERMEDIATE 62

Benzyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate

A solution of *Intermediate 61* (336 mg, 0.97 mmol) in trifluoroacetic acid (2.0 mL) and DCM (20 mL) was stirred at room temperature for 17.5 h. The solvent was removed *in vacuo* and the residue was partitioned between DCM (30 mL) and aqueous sodium hydroxide solution (2N, 20 mL). The organic phase was dried (magnesium sulfate) and the solvent was removed *in vacuo* to give the *title compound* (328 mg; containing some impurity) as a clear gum. δ_{H} (DMSO- d_6) 7.47-7.26 (5H, m), 5.11 (2H,

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s), 4.11-3.94 (2H, m), 3.92-3.79 (2H, m), 3.47-3.08 (2H, m), 2.00-1.80 (2H, m), 1.77-1.66 (2H, m). LCMS (ES+) 247.1 (M+H)⁺.

INTERMEDIATE 63

2-[(3-endo)-8-Azabicyclo[3.2.1]oct-3-yl]-1H-isoindole-1,3(2H)-dione, hydrochloride salt

To a suspension of 2-[(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-1H-isoindole-1,3(2H)-dione (52.4 g, 194 mmol) in toluene (500 mL) was added α -chloroethyl chloroformate (30.6 g, 214 mmol) in a dropwise manner and the mixture was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was taken up in MeOH (500 mL) and refluxed gently at 70°C for 1.5 h until gas evolution ceased, then allowed to stir at room temperature for 18 h. The reaction mixture was filtered and the solid washed with MeOH and then dried *in vacuo*. The filtrate was evaporated *in vacuo* and slurried with hot MeOH, refiltered and the solid washed with further MeOH. This procedure was repeated once more and the combined solids were dried *in vacuo* to give the *title compound* (45.5 g, 80%) as a white solid. δ_{H} (CD₃OD) 7.93-7.78 (4H, m), 4.76-4.60 (1H, m), 4.24-4.12 (2H, m), 2.83-2.70 (2H, m), 2.30-2.11 (4H, m), 2.06-1.86 (2H, m). LCMS (ES+) 257.2 (M+H)⁺.

EXAMPLE 1

Ethyl 2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate

The *title compound* was prepared from *Intermediate 1* according to *Method F* and was isolated as a beige solid (94%). δ_{H} (CDCl₃) 4.25 (2H, q, *J* 7.1 Hz), 3.78 (4H, m), 3.22 (4H, m), 2.92 (2H, t, *J* 6.1 Hz), 2.47 (2H, t, *J* 6.1 Hz), 2.06 (2H, m), 1.31 (3H, t, *J* 7.1 Hz). $\delta^{13}\text{C}$ (CDCl₃) 191.3, 171.8, 163.9, 155.2, 124.4, 113.9, 66.5 (2 x CH₂), 61.0, 53.7 (2 x CH₂), 37.8, 27.4, 24.3, 14.8. LCMS (ES+) 310.0 (M+H)⁺.

EXAMPLE 2

2-(Morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

To a stirred suspension of *Example 1* (0.92 g, 2.98 mmol) in THF (10 mL) and water (10 mL) was added LiOH (0.25 g, 6.00 mmol) and the reaction mixture was stirred at r.t. for 24 h. The volatiles were then removed *in vacuo* and the residue was re-dissolved in water (10 mL). To this was added aqueous 2M HCl (10 mL) and the reaction mixture was stirred for 3 h. The mixture was then extracted with EtOAc (3 x 100 mL), the combined organics dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 0-40% EtOAc in hexanes) gave the *title compound* as an off-white solid (0.70 g, 99%). δ_{H} (CDCl₃) 5.85 (1H, m), 3.77-3.74 (4H, m), 3.22-3.19 (4H, m), 2.65 (2H, t, *J* 6.1 Hz), 2.47 (2H, t, *J* 6.1 Hz), 2.08-2.00 (2H, m). δ_{C} (CDCl₃) 190.4, 167.2, 156.5, 121.6, 104.7, 66.3 (2 x CH₂), 49.9 (2 x CH₂), 37.5, 26.7, 24.5. LCMS (ES+) 238.0 (M+H)⁺.

EXAMPLE 3

3-Bromo-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

To a stirred solution of *Example 2* (0.83 g, 3.50 mmol) in THF (50 mL) at 0°C was added, dropwise, Br₂ (0.56 g, 3.50 mmol) and the reaction mixture was stirred for 20 minutes. The reaction mixture was then poured into brine (200 mL) and extracted with EtOAc (3 x 100 mL). The combined organics were dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 1:5 EtOAc/hexanes) gave the *title compound* as a pale brown solid (0.79 g, 72%). δ_{H} (DMSO-d₆) 3.77-3.74 (4H, m), 3.22-3.18 (4H, m), 2.70-2.67 (2H, m), 2.52-2.47 (2H, m), 2.10-2.04 (2H, m). δ_{C} (DMSO-d₆) 189.7, 160.2, 152.7, 124.6, 97.4, 65.9 (2 x CH₂), 51.9 (2 x CH₂), 37.3, 25.9, 23.4. LCMS (ES+) 315.0 and 317.0 (M+H)⁺.

EXAMPLE 4

2-(Morpholin-4-yl)-3-phenyl-5,6-dihydro-1-benzothiophen-7(4H)-one

To a stirred solution of *Example 3* (0.16 g, 0.50 mmol) and Pd(PPh₃)₄ (0.06 g, 0.05 mmol) in DME (5 mL) was added phenylboronic acid (0.07 g, 0.60 mmol) and aqueous 2M Na₂CO₃ solution (0.50 mL). The reaction mixture was then heated to 85°C for 18 h before it was poured into brine (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organics were dried over MgSO₄, filtered and concentrated *in vacuo*.

Purification by column chromatography (SiO₂, 1:9 Et₂O/DCM) gave the *title compound* as a white solid (0.03 g, 19%). δ_{H} (DMSO-d₆) 7.49-7.32 (5H, m), 3.57-3.54 (4H, m), 2.92-2.89 (4H, m), 2.56-2.44 (4H, m), 2.02-1.94 (2H, m). $\delta^{13}\text{C}$ (DMSO-d₆) 189.9, 162.8, 153.9, 135.2, 129.6 (2 x CH), 129.1 (2 x CH), 127.8, 124.0, 123.3, 65.7 (2 x CH₂), 51.6 (2 x CH₂), 37.8, 25.8, 24.3. LCMS (ES⁺) 314.0 (M+H)⁺.

EXAMPLE 5

3-Benzyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

To a stirred suspension of activated zinc dust (0.07 g, 0.92 mmol) in THF (5 mL) was added benzyl bromide (0.16 g, 0.92 mmol) and the reaction mixture was heated to reflux for 15 minutes until the zinc disappeared. After cooling to r.t., a solution of *Intermediate 2* (0.22 g, 0.61 mmol) and Pd(PPh₃)₂Cl₂ (0.04 g, 0.06 mmol) in THF (2 mL) was added and the reaction mixture was heated to reflux for 18 h. The reaction mixture was then partitioned between brine (100 mL) and EtOAc (100 mL). The aqueous layer was further extracted with EtOAc (2 x 100 mL) and the combined organics were washed with brine (200 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 0-40% EtOAc in hexanes) gave the *title compound* as a white solid (0.05 g, 25 %). δ_{H} (CDCl₃) 7.33-7.28 (3H, m), 7.25-7.09 (2H, m), 3.93 (2H, s), 3.78-3.72 (4H, m), 3.00-2.97 (4H, m), 2.57-2.47 (4H, m), 2.12-2.04 (2H, m). LCMS (ES⁺) 328.0 (M+H)⁺.

EXAMPLE 6

2-(Morpholin-4-yl)-3-(phenylethynyl)-5,6-dihydro-1-benzothiophen-7(4H)-one

To a stirred solution of *Intermediate 2* (0.25 g, 0.69 mmol), Pd(PPh₃)₂Cl₂ (0.03 g, 0.04 mmol) and phenylacetylene (0.08 g, 0.76 mmol) in diisopropylamine (5 mL) was added CuI (0.01 g, 0.07 mmol). The reaction mixture was then heated to 60°C for 3 h after which time it was partitioned between EtOAc (100 mL) and brine (200 mL). The aqueous phase was extracted with further EtOAc (2 x 100 mL) and the combined organic phases were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 10-40% EtOAc in hexanes) gave the *title compound* as an off-white solid (0.15 g, 66%). δ_{H} (DMSO-d₆) 7.56-7.42 (5H, m), 3.87-3.83 (4H, m), 3.72-

3.69 (4H, m), 2.85 (2H, t, *J* 6.0 Hz), 2.57-2.50 (2H, m), 2.18-2.04 (2H, m). LCMS (ES+) 338.0 (M+H)⁺.

EXAMPLE 7

5

2-(Morpholin-4-yl)-3-(2-phenylethyl)-5,6-dihydro-1-benzothiophen-7(4H)-one

To a stirred solution of *Example 6* (0.10 g, 0.31 mmol) in EtOH (10 mL) was added Pd (10 wt % on carbon, 0.03 g) and ammonium formate (0.39 g, 6.20 mmol). The reaction mixture was then heated at reflux for 18 h, cooled, filtered and concentrated *in vacuo*. The crude residue was partitioned between EtOAc (100 mL) and brine (200 mL) and the aqueous phase was extracted with further EtOAc (2 x 100 mL). The combined organic phases were then dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 1:6 EtOAc/hexanes) gave the *title compound* as an off-white solid (0.07 g, 60%). δ_H (DMSO-d₆) 7.36-7.31 (2H, m), 7.26-7.21 (3H, m), 3.78-3.75 (4H, m), 2.92-2.89 (4H, m), 2.87-2.81 (4H, m), 2.73-2.70 (2H, m), 2.55-2.48 (2H, m), 2.09-2.03 (2H, m). LCMS (ES+) 342.0 (M+H)⁺.

EXAMPLE 8

2-(Morpholin-4-yl)-7-oxo-*N*-phenyl-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide

To a stirred solution of *Intermediate 4* (0.07 g, 0.20 mmol) in DMSO (5 mL) was added morpholine (0.10 g, 0.10 mL, 1.15 mmol) and the reaction mixture was heated at 70°C for 18 h. After cooling, water (20 mL) was added and the resultant precipitate was collected *via* filtration, washed with water and dried *in vacuo* to give the *title compound* as an off-white solid (0.07 g, 93%). δ_H (DMSO-d₆) 10.34 (1H, s), 7.71-7.68 (2H, m), 7.37-7.31 (2H, m), 7.09 (1H, t, *J* 7.3 Hz), 3.70-3.67 (4H, m), 3.29-3.22 (4H, m), 2.76-2.73 (2H, m), 2.47-2.43 (2H, m), 2.05-2.02 (2H, m). δ¹³C (DMSO-d₆) 189.7, 164.5, 163.1, 153.8, 139.2, 129.2 (2 x CH), 124.1, 121.6, 119.8 (2 x CH), 118.6, 65.7 (2 x CH₂), 51.9 (2 x CH₂), 37.5, 25.3, 24.0. LCMS (ES+) 357.0 (M+H)⁺.

30

EXAMPLE 9

2-[(3*S*)-3-(1*H*-Indol-3-ylmethyl)morpholin-4-yl]-5,6-dihydro-1-benzothiophen-7(4*H*)-one

To a stirred solution of *Intermediate 5* (0.23 g, 0.58 mmol) in THF (2 mL) was added LiOH (0.09 g, 2.00 mmol) in water (1 mL) and the reaction mixture was heated at 70°C for 4 days. The volatiles were then removed *in vacuo* and the residue was re-dissolved in hot water (2 mL). To the solution was added aqueous 2M HCl (3 mL) and the reaction mixture was stirred at r.t. for 48 h. The resultant precipitate was collected *via* filtration and triturated with DCM and MeCN to give the *title compound* as a pale yellow solid (0.06 g, 31%). δ_{H} (DMSO- d_6) 10.94 (1H, br. s), 7.59 (1H, d, J 7.7 Hz), 7.35 (1H, d, J 7.7 Hz), 7.16-7.03 (2H, m), 6.12 (1H, s), 4.00-3.96 (2H, m), 3.76-3.60 (2H, m), 3.57-3.25 (5H, m), 2.85 (1H, dd, J 14.2 and 3.9 Hz), 2.70-2.66 (2H, m), 2.49-2.35 (2H, m), 2.02-1.98 (2H, m). $\delta^{13}\text{C}$ (DMSO- d_6) 188.3, 165.1, 156.3, 136.6, 127.7, 124.2, 121.4, 119.4, 118.9, 118.3, 111.9, 110.5, 104.0, 66.7, 65.9, 58.4, 44.8, 37.3, 26.1, 24.2, 21.9. LCMS (ES+) 367.0 (M+H)⁺.

EXAMPLE 10

5,5-Dimethyl-2-[(3*S*)-3-(1*H*-indol-3-ylmethyl)morpholin-4-yl]-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile

To a stirred solution of *Intermediate 12* (0.24 g, 0.84 mmol) in DMSO (1 mL) was added DIPEA (0.22 g, 0.30 mL, 1.76 mmol) and *Intermediate 9* (0.20 g, 0.93 mmol) and the reaction mixture was heated to 190°C for 2 h in a sealed tube under microwave irradiation. After cooling, the reaction mixture was partitioned between brine (100 mL) and EtOAc (100 mL). The aqueous phase was further extracted with EtOAc (2 x 100 mL) and the combined organics were washed with brine (200 mL), dried (MgSO₄), filtered and the solvents removed *in vacuo*. Purification by column chromatography (SiO₂, 1:1 EtOAc/hexanes) gave the *title compound* as a white solid (0.08 g, 23%). δ_{H} (DMSO- d_6) 8.16 (1H, br. s), 7.75-7.72 (1H, m), 7.37-7.31 (1H, m), 7.24-7.15 (3H, m), 4.38-4.32 (1H, m), 4.18-4.09 (1H, m), 3.92-3.88 (1H, m), 3.79-3.68 (3H, m), 3.64 (1H, dd, J 3.0 and 1.0 Hz), 3.60 (1H, dd, J 3.0 and 1.0 Hz), 3.15 (1H, dd, J 14.0 and 9.0 Hz), 2.71-2.69 (2H, m), 2.40 (2H, s), 1.05 (6H, s). LCMS (ES+) 420.0 (M+H)⁺.

EXAMPLE 11

5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile

To a stirred solution of *Intermediate 12* (18.3 g, 64.4 mmol) in DMSO (150 mL) was slowly added morpholine (14.6 g, 14.6 mL, 168.0 mmol) and the reaction mixture was heated to 100°C for 30 minutes. After cooling, the reaction mixture was diluted with water (450 mL) with rigorous stirring and the resultant precipitate was filtered, washed with water and dried to give the *title compound* as a pale green solid (14.4 g, 77%). δ_{H} (DMSO- d_6) 3.77 (4H, m), 3.64 (4H, m), 2.64 (2H, s), 2.35 (2H, s), 1.05 (6H, s). LCMS (ES+) 291.0 (M+H)⁺.

EXAMPLE 12

5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide

To a stirred solution of *Example 11* (10.0 g, 34.5 mmol) in glacial AcOH (100 mL) at 120°C was added concentrated H₂SO₄ (40 mL). After stirring for 4 h, a small aliquot (5 mL) was removed and partitioned between EtOAc (50 mL) and aqueous 2M NaOH (20 mL). The organic phase was washed with brine (20 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The resulting residue was triturated with 1:1 EtOAc/Et₂O and the solid collected by filtration to give the *title compound* (0.2 g) as a white solid. δ_{H} (DMSO- d_6) 7.67 (1H, br. s), 7.49 (1H, br. s), 3.72 (4H, m), 3.21 (4H, m), 2.64 (2H, s), 2.31 (2H, s), 1.01 (6H, s). LCMS (ES+) 308.9 (M+H)⁺; LCMS (ES-) 307.0 (M-H)⁻.

EXAMPLE 13

5,5-Dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

To a stirred solution of *Example 11* (10.0 g, 34.5 mmol) in glacial AcOH (100 mL) at 120°C was added concentrated H₂SO₄ (40 mL). After stirring for 24 h the reaction mixture was cooled to r.t. prior to pouring into a well-stirred mixture of EtOAc (950 mL) and water (950 mL) at 0°C. The resulting emulsion was filtered through Celite[®] and the organic phase was separated, washed with brine (3 x 100 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 1:1 EtOAc/hexanes) gave the *title compound* (5.3 g, 58%) as a white powder. δ_{H} (DMSO- d_6)

6.15 (1H, s), 3.72 (4H, m), 3.25 (4H, m), 2.58 (2H, s), 2.26 (2H, s), 1.01 (6H, s). LCMS (ES+) 266.0 (M+H)⁺.

EXAMPLE 14

5

5,5-Dimethyl-3-fluoro-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

To a stirred solution of *Example 13* (0.20 g, 0.75 mmol) in THF (10 mL) at 20°C was added Selectfluor[®] (0.53 g, 1.50 mmol) portionwise. The reaction mixture was then heated to reflux for 24 h before it was cooled and filtered. The filtrate was concentrated
10 *in vacuo* and the resulting solid was purified by column chromatography (SiO₂, 1:1 EtOAc/hexanes) to give the *title compound* (0.11 g, 50%) as a white powder. δ_{H} (CDCl₃) 3.86 (4H, m), 3.32 (4H, m), 2.59 (2H, s), 2.43 (2H, s), 1.13 (6H, s). LCMS (ES+) 285.0 (M+H)⁺.

15

EXAMPLE 15 (METHOD B)

3-Chloro-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

To a stirred solution of *Example 13* (0.20 g, 0.75 mmol) in THF (10 mL) was added NCS (0.11 g, 0.82 mmol) portionwise. After stirring for 30 minutes the reaction
20 mixture was diluted with EtOAc (100 mL), washed with aqueous sat. Na₂CO₃ (3 x 25 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 1:1 EtOAc/hexanes) gave the *title compound* (0.18 g, 80%) as a white powder. δ_{H} (DMSO-d₆) 3.76 (4H, m), 3.24 (4H, m), 2.61 (2H, s), 2.40 (2H, s), 1.05 (6H, s). LCMS (ES+) 300.0 (M+H)⁺.

25

EXAMPLE 16

3-Bromo-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 13* according to *Method B*, using
30 NBS in place of NCS, and was isolated as a white powder (74%). δ_{H} (DMSO-d₆) 3.83 (4H, m), 3.61 (4H, m), 2.63 (2H, s), 2.47 (2H, s), 1.04 (6H, s). LCMS (ES+) 345.3 (M+H)⁺.

EXAMPLE 17**5,5-Dimethyl-3-iodo-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one**

The *title compound* was prepared from *Example 13* according to *Method B*, using
5 NIS in place of NCS, and was isolated as a white powder (90%). δ_{H} (DMSO- d_6) 3.76 (4H, m), 3.16 (4H, m), 2.60 (2H, s), 2.41 (2H, s), 1.05 (6H, s). LCMS (ES+) 391.7 (M+H)⁺.

EXAMPLE 18**5,5-Dimethyl-2-(morpholin-4-yl)-3-(phenylthio)-5,6-dihydro-1-benzothiophen-7(4H)-one**

To a stirred solution of *Example 13* (0.20 g, 0.75 mmol) in THF (10 mL) was
added, dropwise, a solution of benzenesulfonyl chloride (0.13 g, 0.90 mmol) in THF (2
mL). After stirring for 30 minutes, finely powdered NaHCO₃ (10.00 g) was added and
15 the reaction mixture was filtered and concentrated *in vacuo*. Purification by column
chromatography (SiO₂, 1:1 EtOAc/hexanes) gave the *title compound* (0.21 g, 75%) as a
white powder. δ_{H} (DMSO- d_6) 7.31 (2H, m), 7.17 (1H, m), 7.04 (2H, m), 3.62 (4H, m),
3.45 (4H, m), 2.51 (2H, s), 2.37 (2H, s), 0.95 (6H, s). LCMS (ES+) 374.0 (M+H)⁺.

EXAMPLE 19**3-[(Dimethylamino)methyl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one**

A stirred solution of *Example 13* (0.20 g, 0.75 mmol) and Eschenmoser's salt
25 (0.50 g, 2.70 mmol) in THF (20 mL) was heated to reflux for 2 h. The reaction mixture
was then cooled to r.t., filtered through Celite[®] and the filtrate was concentrated *in vacuo*.
Purification by column chromatography (SiO₂, 20:1 EtOAc/MeOH) gave the *title*
compound (0.08 g, 31%) as a white powder. δ_{H} (DMSO- d_6) 3.73 (4H, m), 3.32 (2H, s),
3.18 (4H, m), 2.67 (2H, s), 2.35 (2H, s), 2.13 (6H, s), 1.02 (6H, s). LCMS (ES+) 323.0
30 (M+H)⁺.

EXAMPLE 20 (METHOD C)

5,5-Dimethyl-3-[(1-methyl-1*H*-imidazol-5-yl)ethynyl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

To a stirred solution of *Example 17* (1.63 g, 4.17 mmol) and 5-ethynyl-1-methyl-1*H*-imidazole (0.66 g, 6.26 mmol) in diisopropylamine (150 mL) at 60°C was added

- 5 Pd(PPh₃)₂Cl₂ (0.20 g, 0.28 mmol) and CuI (0.05 g, 0.26 mmol), and the reaction mixture was stirred for 45 minutes. The solvent was then removed *in vacuo* and the resulting residue was diluted with EtOAc (250 mL) and washed with sat. aqueous NaHCO₃ (3 x 100 mL). The organic phase was dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 10:1 EtOAc/MeOH) gave the *title compound* (1.43 g, 93%) as a pale yellow powder. δ_{H} (DMSO-*d*₆) 7.80 (1H, br. s), 7.31 (1H, br. s), 3.76 (4H, m), 3.66 (3H, s), 3.63 (4H, m), 2.65 (2H, s), 2.36 (2H, s), 1.05 (6H, s). LCMS (ES⁺) 370.1 (M+H)⁺.
- 10

EXAMPLE 21

15

5,5-Dimethyl-3-[(3-methoxyphenyl)ethynyl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

- The *title compound* was prepared from *Example 17* and 1-ethynyl-3-methoxybenzene according to *Method C* and was isolated as a tan powder (88%). δ_{H} (DMSO-*d*₆) 7.33 (1H, m), 7.07 (1H, m), 6.98 (2H, m), 3.79 (7H, br. s), 3.64 (4H, m), 2.69 (2H, s), 2.36 (2H, s), 1.07 (6H, s). LCMS (ES⁺) 396.1 (M+H)⁺.
- 20

EXAMPLE 22

- 25 3-{[4-(Dimethylamino)phenyl]ethynyl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

- The *title compound* was prepared from *Example 17* and 4-ethynyl-*N,N*-dimethylaniline according to *Method C* and was isolated as a tan powder (84%). δ_{H} (DMSO-*d*₆) 7.29 (2H, d, *J* 8.8 Hz), 6.71 (2H, d, *J* 8.8 Hz), 3.79 (4H, m), 3.60 (4H, m), 2.94 (6H, s), 2.66 (2H, s), 2.35 (2H, s), 1.06 (6H, s). LCMS (ES⁺) 409.1 (M+H)⁺.
- 30

EXAMPLE 23

5,5-Dimethyl-3-[(3-fluorophenyl)ethynyl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 1-ethynyl-3-fluorobenzene according to *Method C* and was isolated as a tan powder (84%). δ_{H} (DMSO- d_6) 7.49-7.23 (4H, m), 3.79 (4H, m), 3.65 (4H, m), 2.70 (2H, s), 2.36 (2H, s), 1.07 (6H, s). LCMS (ES+) 384.1 (M+H)⁺.

EXAMPLE 24

10 5,5-Dimethyl-2-(morpholin-4-yl)-3-(pyridin-3-ylethynyl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 3-ethynylpyridine according to *Method C* and was isolated as a pale yellow powder (82%). δ_{H} (DMSO- d_6) 8.71 (1H, d, *J* 1.5 Hz), 8.56 (1H, dd, *J* 4.8 and 1.5 Hz), 7.92 (1H, dt, *J* 7.9 and 1.8 Hz), 7.44 (1H, dd, *J* 7.9 and 4.8 Hz), 3.78 (4H, m), 3.66 (4H, m), 2.71 (2H, s), 2.36 (2H, s), 1.07 (6H, s). LCMS (ES+) 367.1 (M+H)⁺.

EXAMPLE 25

20 5,5-Dimethyl-2-(morpholin-4-yl)-3-[(4-nitrophenyl)ethynyl]-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 1-ethynyl-4-nitrobenzene according to *Method C* and was isolated as a yellow powder (82%). δ_{H} (DMSO- d_6) 8.26 (2H, d, *J* 8.7 Hz), 7.74 (2H, d, *J* 8.7 Hz), 3.80 (4H, m), 3.70 (4H, m), 2.72 (2H, s), 2.37 (2H, s), 1.08 (6H, s). LCMS (ES+) 411.0 (M+H)⁺.

EXAMPLE 26

30 5,5-Dimethyl-2-(morpholin-4-yl)-3-[(triethylsilyl)ethynyl]-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and triethyl(ethynyl)silane according to *Method C* and was isolated as a pale grey powder (86%). δ_{H} (CDCl₃) 3.85

(4H, m), 3.67 (4H, m), 2.72 (2H, s), 2.41 (2H, s), 1.12 (6H, s), 1.04 (9H, t, J 7.8 Hz), 0.68 (6H, q, J 7.8 Hz). LCMS (ES+) 404.0 (M+H)⁺.

EXAMPLE 27

5

3-(Cyclopropylethynyl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and ethynylcyclopropane according to *Method C* and was isolated as an off-white powder (77%). δ_{H} (DMSO- d_6)

10 3.74 (4H, m), 3.51 (4H, m), 2.56 (2H, s), 2.31 (2H, s), 1.56 (1H, m), 1.03 (6H, s), 0.89 (2H, m), 0.68 (2H, m). LCMS (ES+) 330.1 (M+H)⁺.

EXAMPLE 28

15 5,5-Dimethyl-3-(4-hydroxybut-1-yn-1-yl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and but-3-yn-1-ol according to *Method C* and was isolated as an off-white powder (89%). δ_{H} (DMSO- d_6) 4.85 (1H, t, J 5.3 Hz), 3.73 (4H, m), 3.59-3.54 (6H, m), 2.58 (4H, m), 2.57 (2H, s), 1.02 (6H, s). LCMS

20 (ES+) 334.1 (M+H)⁺.

EXAMPLE 29

25 5,5-Dimethyl-3-[(1-hydroxycyclohexyl)ethynyl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 1-ethynylcyclohexanol according to *Method C* and was isolated as an off-white powder (87%). δ_{H} (DMSO- d_6) 5.41 (1H, s), 3.74 (4H, m), 3.56 (4H, m), 2.59 (2H, s), 2.33 (2H, s), 1.82-1.79 (2H, m), 1.67-1.63 (2H, m), 1.47-1.41 (5H, m), 1.24-1.18 (1H, m), 1.03 (6H, s). LCMS (ES+)

30 388.0 (M+H)⁺.

EXAMPLE 30

3-[(1-Aminocyclohexyl)ethynyl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 1-ethynyl-cyclohexanamine according to *Method C* and was isolated as a pale yellow powder
5 (61%). δ_{H} (DMSO- d_6) 3.67 (4H, m), 3.47 (4H, m), 2.51 (2H, s), 2.24 (2H, s), 2.01 (2H, br. s), 1.70-1.67 (2H, m), 1.59-1.50 (2H, m), 1.49-1.46 (2H, m), 1.42-1.32 (3H, m), 1.29-1.26 (1H, m), 0.95 (6H, s). LCMS (ES+) 370.1 (M-NH₂)⁺.

EXAMPLE 31

10 3-[3-(Diethylamino)prop-1-yn-1-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and *N,N*-diethylprop-2-yn-1-amine according to *Method C* and was isolated as a pale yellow powder (76%). δ_{H}
15 (DMSO- d_6) 3.74 (4H, m), 3.63 (2H, s), 3.55 (4H, s), 2.58 (2H, s), 2.48 (4H, q, *J* 7.1 Hz), 2.33 (2H, s), 1.03 (6H, s), 1.02 (6H, t, *J* 7.1 Hz). LCMS (ES+) 302.1 (M-NEt₂)⁺.

EXAMPLE 32

20 5,5-Dimethyl-3-(3-hydroxy-3-methylbut-1-yn-1-yl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 2-methylbut-3-yn-2-ol according to *Method C* and was isolated as a pale yellow powder (77%). δ_{H} (DMSO- d_6)
5.42 (1H, s), 3.74 (4H, m), 3.55 (4H, m), 2.57 (2H, s), 2.33 (2H, s), 1.44 (6H, s), 1.03
25 (6H, s). LCMS (ES+) 348.1 (M+H)⁺.

EXAMPLE 33

30 5,5-Dimethyl-3-[(3-hydroxy-1-azabicyclo[2.2.2]oct-3-yl)ethynyl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 3-ethynylquinuclidin-3-ol according to *Method C* and was isolated as a pale yellow powder (86%). δ_{H} (CD₃OD)
3.84 (4H, m), 3.66 (4H, m), 3.19 (1H, d, *J* 14.0 Hz), 3.01 (1H, d, *J* 14.0 Hz), 2.88-2.79

(4H, m), 2.70 (2H, s), 2.40 (2H, s), 2.10-1.95 (3H, m), 1.81 (1H, m), 1.57-1.51 (1H, m), 1.11 (6H, s). Exchangeable proton not observed. LCMS (ES⁺) 415.1 (M+H)⁺.

EXAMPLE 34

5

5,5-Dimethyl-3-[3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 1-methyl-4-(prop-2-yn-1-yl)piperazine according to *Method C* and was isolated as a yellow powder (96%). δ_{H}
10 (DMSO-d₆) 3.74 (4H, m), 3.56 (4H, m), 3.53 (2H, s), 2.59 (2H, s), 2.33 (2H, s), 1.03 (6H, s). LCMS (ES⁺) 402.2 (M+H)⁺.

EXAMPLE 35

15 N-{3-[5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]prop-2-yn-1-yl}methanesulfonamide

The *title compound* was prepared from *Example 17* and N-(prop-2-yn-1-yl)methanesulfonamide according to *Method C* and was isolated as a tan powder (65%).
 δ_{H} (DMSO-d₆) 7.61 (1H, br, s), 4.09 (2H, s), 3.73 (4H, m), 3.56 (4H, m), 2.99 (3H, s),
20 2.60 (2H, s), 2.32 (2H, s), 1.03 (6H, s). LCMS (ES⁺) 397.0 (M+H)⁺.

EXAMPLE 36

25 3-[3-(3,4-Dihydroisoquinolin-2(1H)-yl)prop-1-yn-1-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 2-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline according to *Method C* and was isolated as a tan powder (95%). δ_{H} (DMSO-d₆) 7.14-7.07 (4H, m), 3.74 (2H, s), 3.72 (4H, m), 3.70 (2H, s), 3.55 (4H, m), 2.85 (2H, m), 2.77 (2H, m), 2.61 (2H, s), 2.32 (2H, s), 1.02 (6H, s). LCMS
30 (ES⁺) 435.2 (M+H)⁺.

EXAMPLE 37

5,5-Dimethyl-3-[(3-hydroxyphenyl)ethynyl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 3-ethynylphenol according to *Method C* and was isolated as a white powder (86%). δ_{H} (DMSO- d_6) 9.66 (1H, br. s), 7.21 (1H, t, J 7.8 Hz), 6.90 (1H, d, J 7.5 Hz), 6.85 (1H, s), 6.79 (1H, d, J 8.0 Hz), 3.78 (4H, m), 3.69 (4H, m), 2.68 (2H, m), 2.36 (2H, s), 1.06 (6H, s). LCMS (ES+) 382.1 (M+H)⁺.

EXAMPLE 38

5,5-Dimethyl-3-ethynyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

A stirred solution of *Example 26* (0.39 g, 0.96 mmol) in MeOH (12 mL) at 45°C was treated with finely powdered K₂CO₃ (0.70 g, 5.07 mmol). After stirring for 50 minutes, the reaction mixture was cooled to r.t., diluted with Et₂O (50 mL) and filtered. The filtrate was washed with water (3 x 20 mL), dried (MgSO₄), filtered and concentrated *in vacuo* at r.t. The residual solid was purified by column chromatography (SiO₂, 1:1 EtOAc/hexanes) to give the *title compound* (0.27 g, 98%) as a pale grey powder. δ_{H} (DMSO- d_6) 4.52 (1H, s), 3.74 (4H, m), 3.57 (4H, m), 2.60 (2H, s), 2.33 (2H, s), 1.03 (6H, s). LCMS (ES+) 290.1 (M+H)⁺.

EXAMPLE 39 (METHOD D)

5,5-Dimethyl-3-[(4-hydroxyphenyl)ethynyl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

To a stirred solution of *Example 38* (0.10 g, 0.35 mmol) and 4-iodophenol (0.11 g, 0.52 mmol) in diisopropylamine (7 mL) at 60°C was added Pd(PPh₃)₂Cl₂ (0.02 g, 0.03 mmol) followed by CuI (0.01 g, 0.05 mmol). After stirring for 50 minutes, the reaction mixture was concentrated *in vacuo* and the resulting residue was diluted with EtOAc (25 mL). The organics were then washed with sat. aqueous NaHCO₃ (10 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 3:1 EtOAc/hexanes) gave the *title compound* (0.11 g, 85%) as an off-white powder. δ_{H} (DMSO- d_6) 9.89 (1H, br. s), 7.31 (2H, d, J 8.2 Hz), 6.79 (2H, d, J 8.2 Hz), 3.78 (4H, m), 3.68 (4H, m), 2.67 (2H, s), 2.35 (2H, s), 1.06 (6H, s). LCMS (ES-) 380.4 (M-H)⁻.

EXAMPLE 40

3-[(2-Aminopyrimidin-5-yl)ethynyl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 38* and 2-amino-5-iodopyrimidine according to *Method D* and was isolated as a pale yellow powder (77%). δ_{H} (DMSO- d_6) 8.39 (2H, s), 7.12 (2H, br. s), 3.77 (4H, m), 3.60 (4H, m), 2.66 (2H, s), 2.34 (2H, s), 1.05 (6H, s). LCMS (ES+) 383.1 (M+H)⁺.

EXAMPLE 41

5,5-Dimethyl-3-[(1-methyl-1H-imidazol-4-yl)ethynyl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 38* and 4-iodo-1-methyl-1H-imidazole according to *Method D* and was isolated as a pale yellow powder (84%). δ_{H} (DMSO- d_6) 7.65 (1H, s), 7.50 (1H, s), 3.75 (4H, m), 3.65 (3H, s), 3.58 (4H, m), 2.62 (2H, s), 2.35 (2H, s), 1.05 (6H, s). LCMS (ES+) 370.1 (M+H)⁺.

EXAMPLE 42

5,5-Dimethyl-2-(morpholin-4-yl)-3-(pyridin-4-ylethynyl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 38* and 4-iodopyridine according to *Method D* and was isolated as a pale yellow powder (64%). δ_{H} (DMSO- d_6) 8.71 (2H, br. s), 7.52 (2H, br. s), 3.80 (4H, m), 3.68 (4H, m), 2.70 (2H, s), 2.36 (2H, s), 1.07 (6H, s). LCMS (ES+) 367.1 (M+H)⁺.

EXAMPLE 43

5,5-Dimethyl-3-(imidazo[1,2-a]pyridin-6-ylethynyl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 38* and 6-iodoimidazo[1,2-*a*]pyridine according to *Method D* and was isolated as a pale yellow powder (64%). δ_{H} (DMSO- d_6) 8.88 (1H, s), 7.96 (1H, s), 7.64 (1H, s), 7.60 (1H, d, *J* 9.3 Hz), 7.27 (1H, d, *J* 9.3 Hz), 3.80 (4H, m), 3.65 (4H, m), 2.71 (2H, s), 2.36 (2H, s), 1.08 (6H, s). LCMS (ES+) 406.0 (M+H)⁺.

EXAMPLE 44

3-({3-[(Dimethylamino)methyl]imidazo[1,2-*a*]pyridin-6-yl}ethynyl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 38* and *Intermediate 13* according to *Method D* and was isolated as a yellow powder (72%). δ_{H} (DMSO- d_6) 8.59 (1H, s), 7.60 (1H, d, *J* 9.2 Hz), 7.55 (1H, s), 7.30 (1H, dd, *J* 9.2 and 1.6 Hz), 3.81 (4H, m), 3.77 (2H, s), 3.65 (4H, m), 2.72 (2H, s), 2.37 (2H, s), 2.17 (6H, s), 1.08 (6H, s). LCMS (ES+) 463.1 (M+H)⁺.

EXAMPLE 45

3-[(6-{[2-(Dimethylamino)ethyl]amino}pyridin-3-yl)ethynyl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 38* and *Intermediate 14* according to *Method D* and was isolated as a yellow powder (64%). δ_{H} (DMSO- d_6) 8.13 (1H, s), 7.43 (1H, dd, *J* 8.6 and 1.9 Hz), 6.85 (1H, s), 6.52 (1H, d, *J* 8.6 Hz), 3.77 (4H, m), 3.61 (4H, m), 3.36 (2H, m), 2.65 (2H, s), 2.40 (2H, t, *J* 6.5 Hz), 2.34 (2H, s), 2.18 (6H, s), 1.05 (6H, s). LCMS (ES+) 453.2 (M+H)⁺.

EXAMPLE 46

3-[(6-Chloropyridin-3-yl)ethynyl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 38* and 2-chloro-5-iodopyridine according to *Method D* and was isolated as a yellow powder (44%). δ_{H} (DMSO- d_6) 8.57

(1H, d, *J* 2.2 Hz), 7.99 (1H, dd, *J* 8.3 and 2.2 Hz), 7.58 (1H, d, *J* 8.3 Hz), 3.77 (4H, m), 3.65 (4H, m), 2.70 (2H, s), 2.36 (2H, s), 1.07 (6H, s). LCMS (ES+) 401.0 (M+H)⁺.

EXAMPLE 47

5

5,5-Dimethyl-2-(morpholin-4-yl)-3-(1*H*-pyrazol-4-ylethynyl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 38* and 4-iodo-1*H*-pyrazole according to *Method D* and was isolated as a yellow powder (33%). δ_H (DMSO-d₆) 13.18 (1H, br. s), 8.10 (1H, s), 7.70 (1H, s), 3.76 (4H, m), 3.58 (4H, m), 2.64 (2H, s), 2.34 (2H, s), 1.05 (6H, s). LCMS (ES+) 354.4 (M-H)⁺.

EXAMPLE 48

15 5,5-Dimethyl-3-({6-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]pyridin-3-yl}ethynyl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 38* and *Intermediate 15* according to *Method D* and was isolated as a pale yellow powder (32%). δ_H (DMSO-d₆) 8.16 (1H, d, *J* 2.2 Hz), 7.52 (1H, dd, *J* 8.3 and 2.2 Hz), 6.47 (1H, d, *J* 8.3 Hz), 4.77 (1H, t, *J* 5.6 Hz), 4.00 (1H, br. m), 3.72 (4H, m), 3.55 (4H, m), 3.52 (1H, m), 3.49 (1H, m), 3.24 (2H, m), 2.61 (2H, s), 2.30 (2H, s), 1.98-1.82 (4H, m), 1.01 (6H, s). LCMS (ES+) 466.0 (M+H)⁺.

EXAMPLE 49 (METHOD G)

25

5,5-Dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one

To a stirred solution of *Intermediate 18* (0.86 g, 2.50 mmol) in THF (9 mL) and water (8 mL) at r.t. was added LiOH (0.16 g, 3.80 mmol). The reaction mixture was then heated at 60°C for 48 h before it was cooled and concentrated *in vacuo*. To the residue was added aqueous 2M HCl (8 mL) and the reaction mixture was stirred at r.t. for 6 h before it was cooled and basified to pH 10 by the addition of aqueous sat. Na₂CO₃. The resulting solid was filtered and dried to give the *title compound* as a white powder (0.52

g, 80%). δ_{H} (DMSO- d_6) 7.56 (1H, s), 6.08 (1H, s), 3.72 (4H, br. m), 3.15 (4H, m), 2.64 (2H, s), 1.22 (6H, s). LCMS (ES+) 267.0 (M+H)⁺.

EXAMPLE 50

5

5,5-Dimethyl-2-(morpholin-4-yl)-3-(phenylethynyl)-5,6-dihydrothieno[2,3-c]pyridin-7(4H)-one

To a stirred solution of *Intermediate 19* (0.070 g, 0.180 mmol) in DMF (3 mL) and diisopropylamine (1 mL) was added phenylacetylene (0.093 g, 0.100 mL, 0.911 mmol), Pd(PPh₃)₂Cl₂ (0.009 g, 0.011 mmol) and CuI (0.004 g, 0.022 mmol). The reaction mixture was then heated to 90°C for 2 h before it was cooled and partitioned between EtOAc (20 mL) and water (20 mL). The organics were separated, washed with water (3 x 20 mL) and brine (20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The resultant crude solid was washed sequentially with Et₂O, EtOAc and Et₂O to give the *title compound* as a pale grey solid (0.030 g, 44%). δ_{H} (DMSO- d_6) 7.49-7.40 (6H, m), 3.80 (4H, m), 3.50 (4H, m), 2.74 (2H, s), 1.28 (6H, s). LCMS (ES+) 367.0 (M+H)⁺.

EXAMPLE 51

5,5-Dimethyl-2-(morpholin-4-yl)-4,5,6,7-tetrahydro-8H-thieno[2,3-c]azepin-8-one

The *title compound* was prepared from *Intermediate 22* according to *Method G* and was isolated as a white solid (95%). δ_{H} (DMSO- d_6) 7.53 (1H, t, *J* 5.0 Hz) 5.98 (1H, s), 3.70 (4H, m), 3.10 (4H, m), 2.87 (2H, d, *J* 5.0 Hz), 2.57 (2H, s), 0.95 (6H, s). LCMS (ES+) 281.0 (M+H)⁺.

25

EXAMPLE 52

5,5-Dimethyl-3-iodo-2-(morpholin-4-yl)-4,5,6,7-tetrahydro-8H-thieno[2,3-c]azepin-8-one

The *title compound* was prepared from *Example 51* according to *Method H* and was isolated as a white solid (48%). δ_{H} (DMSO- d_6) 8.02 (1H, t, *J* 5.0 Hz), 3.73 (4H, m), 3.03 (4H, m), 2.85 (2H, d, *J* 5.2 Hz), 2.58 (2H, s), 0.98 (6H, s). LCMS (ES+) 407.0 (M+H)⁺.

30

EXAMPLE 53**5,5-Dimethyl-2-(morpholin-4-yl)-3-(phenylethynyl)-4,5,6,7-tetrahydro-8H-thieno[2,3-c]azepin-8-one**

5 To a stirred suspension of *Example 52* (0.60 g, 1.50 mmol) in diisopropylamine (12 mL) at r.t. was added phenylacetylene (0.41 g, 0.45 mL, 4.10 mmol), Pd(PPh₃)₂Cl₂ (0.05 g, 0.08 mmol) and CuI (0.04 g, 0.20 mmol), and the reaction mixture was heated to 60°C for 12 h. The reaction mixture was then cooled, filtered and washed with EtOAc and Et₂O to give a mixture of *Example 52* and the *title compound*. The crude mixture was
10 re-suspended in diisopropylamine (15 mL) and treated with phenylacetylene (1.37 g, 1.50 mL, 13.67 mmol), Pd(PPh₃)₂Cl₂ (0.07 g, 0.11 mmol) and CuI (0.06 g, 0.28 mmol) prior to heating to 65°C for a further 60 h. The reaction mixture was then cooled, filtered and washed sequentially with water, EtOAc, water, Et₂O and DCM to give the *title compound* as an off-white powder (0.15 g, 27%). δ_H (DMSO-d₆) 7.83 (1H, t, *J* 4.7 Hz) 7.47-7.38
15 (5H, m), 3.79 (4H, m), 3.47 (4H, m), 2.89 (2H, d, *J* 5.0 Hz), 2.69 (2H, s), 0.98 (6H, s). LCMS (ES⁺) 381.0 (M+H)⁺.

EXAMPLE 54

20 **3-(Biphenyl-3-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one**

To a stirred solution of *Example 16* (0.065 g, 0.190 mmol) in DME (2 mL) and water (0.5 mL) was added Pd(OAc)₂ (0.003 g, 0.011 mmol), 1,3-bis(diphenylphosphino)propane (0.010 g, 0.024 mmol), K₃PO₄ (0.134 g, 0.630 mmol) and 3-biphenylboronic acid
25 (0.081 g, 0.410 mmol). The reaction mixture was then heated to 80°C for 19 h before it was quenched with sat. aqueous NaHCO₃ solution (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 0-30% EtOAc/heptane) gave the *title compound* (0.056 g, 71%) as a beige powder. δ_H (CDCl₃) 7.65-7.30 (9H, m),
30 3.68-3.61 (4H, m), 3.05-2.98 (4H, m), 2.51 (2H, s), 2.44 (2H, s), 1.05 (6H, s). LCMS (ES⁺) 418.3 (M+H)⁺.

EXAMPLE 555,5-Dimethyl-2-(morpholin-4-yl)-3-(3-phenylisoxazol-5-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

5 To a degassed, stirred solution of *Example 16* (0.098 g, 0.285 mmol), 3-phenylisoxazol-5-ylboronic acid (0.108 g, 0.571 mmol) and aqueous KOH (0.048 g, 0.855 mmol in 1 mL) in THF (4 mL) was added Pd(PPh₃)₄ (0.033 g, 0.029 mmol) and the reaction mixture was heated at 65°C for 12 h. Further 3-phenylisoxazol-5-ylboronic acid (0.055 g, 0.290 mmol) was added and the reaction mixture was heated for a further 12 h
10 at 85°C. The reaction was then quenched with sat. aqueous NaHCO₃ solution (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 0-30% EtOAc/heptane) gave the *title compound* (0.030 g, 26%) as a white powder. δ_{H} (DMSO-d₆) 7.99-7.94 (2H, m), 7.58-7.52 (3H, m), 7.28 (1H, s), 3.76-3.70 (4H, m),
15 3.13-3.06 (4H, m), 2.69 (2H, s), 2.40 (2H, s), 1.04 (6H, s). LCMS (ES⁺) 409.3 (M+H)⁺.

EXAMPLE 56

20 5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid

To a stirred solution of *Example 104* (0.82 g, 2.54 mmol) in a mixture of MeOH (5 mL), water (1 mL) and THF (5 mL) was added LiOH (0.16 g, 3.81 mmol). After stirring at r.t. for 5 days, the reaction mixture was concentrated *in vacuo* to give a beige solid which was dissolved in aqueous 1M HCl and extracted with EtOAc (3 x 25 mL).
25 The combined organics were dried over MgSO₄, filtered and concentrated *in vacuo* to give the *title compound* (0.68 g, 87%) as a yellow solid. δ_{H} (DMSO-d₆) 12.85 (1H, br. s), 3.75-3.70 (4H, m), 3.30-3.25 (4H, m), 2.80 (2H, s), 2.35 (2H, s), 1.00 (6H, s). LCMS (ES⁺) 310.0 (M+H)⁺.

30 **EXAMPLE 57 (METHOD D)**

5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-N-[phenyl(pyridin-2-yl)methyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide

To a stirred solution of *Example 56* (0.084 g, 0.272 mmol) in DCM (10 mL), was added EDC (0.063 g, 0.330 mmol), NEt₃ (0.080 g, 0.110 mL, 0.790 mmol), and phenyl(2-pyridyl)methylamine.HCl (0.072 g, 0.330 mmol). The reaction mixture was then stirred at r.t. for 12 h before it was concentrated *in vacuo*. Purification by column

5 chromatography (SiO₂, 0-100% EtOAc/heptane) gave the *title compound* (0.017 g, 13%) as a yellow solid. δ_H (CD₃OD) 8.65-8.60 (1H, m), 7.85-7.80 (1H, m), 7.50-7.30 (7H, m), 6.40 (1H, s), 3.60-3.55 (4H, m), 3.20-3.15 (4H, m), 2.70 (2H, s), 2.40 (2H, s), 1.10 (6H, s). Exchangeable proton not observed. LCMS (ES⁺) 476.0 (M+H)⁺.

10

EXAMPLE 58

N-Benzyl-5,5-dimethyl-2-morpholin-4-yl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide

The *title compound* was prepared from *Example 56* and benzylamine according to
15 *Method I* and was isolated as an off-white solid (26%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_H (CDCl₃) 7.75 (1H, br. s), 7.40-7.30 (5H, m), 4.60 (2H, d, *J* 5.7 Hz), 3.45-3.40 (4H, m), 3.05 (2H, s), 3.00-2.95 (4H, m), 2.45 (2H, s), 1.10 (6H, s). LCMS (ES⁺) 399.0 (M+H)⁺.

20

EXAMPLE 59

5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-*N*-(pyridin-2-ylmethyl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide

The *title compound* was prepared from *Example 56* and 2-(aminomethyl)pyridine
25 according to *Method I* and was isolated as a beige solid (34%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_H (CDCl₃) 8.70 (1H, br. s), 8.60 (1H, d, *J* 4.8 Hz), 7.75-7.65 (1H, m), 7.35-7.30 (1H, d, *J* 7.8 Hz), 7.25-7.20 (1H, m), 4.70 (2H, d, *J* 4.8 Hz), 3.85-3.78 (4H, m), 3.15-3.10 (4H, m), 3.00 (2H, s), 2.45 (2H, s), 1.10 (6H, s). LCMS (ES⁺) 400.0 (M+H)⁺.

30

EXAMPLE 60

5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-N-(pyridin-4-ylmethyl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide

The *title compound* was prepared from *Example 56* and 4-(aminomethyl)pyridine according to *Method I* and was isolated as a yellow solid (30%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.95-8.90 (1H, m), 8.54 (2H, d, J 5.8 Hz), 7.32 (2H, d, J 6.0 Hz), 4.42 (2H, d, J 6.0 Hz), 3.65-3.60 (4H, m), 3.15-3.10 (4H, m), 2.60 (2H, s), 2.35 (2H, s), 1.00 (6H, s). LCMS (ES+) 400.0 (M+H)⁺.

EXAMPLE 61

5,5-Dimethyl-N-ethyl-2-(morpholin-4-yl)-7-oxo-N-(pyridin-4-ylmethyl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide

The *title compound* was prepared from *Example 56* and *N*-(4-pyridylmethyl)-ethylamine according to *Method I* and was isolated as a yellow solid (30%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.57 (1H, d, J 6.0 Hz), 8.49 (1H, d, J 5.8 Hz), 7.38 (1H, d, J 5.8 Hz), 7.11 (1H, d, J 6.0 Hz), 4.50-4.45 (2H, m), 3.80-3.70 (2H, m), 3.60-3.50 (2H, m), 3.45-3.40 (2H, m), 3.20-3.05 (4H, m), 2.40-2.10 (4H, m), 1.15-0.95 (9H, m). LCMS (ES+) 428.0 (M+H)⁺.

EXAMPLE 62

5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylic acid

To a stirred solution of *Intermediate 18* (1.00 g, 2.96 mmol) in THF (120 mL) was added LiOH (0.19 g, 4.40 mmol) in water (30 mL) and the reaction mixture was stirred at r.t. for 3 days. A further portion of LiOH (0.19 g, 4.40 mmol) in water (30 mL) was added and stirring continued for a further 3 days. Removal of the solvent *in vacuo* and addition of aqueous 2M HCl led to a thick yellow precipitate which was filtered, washed with water and dried to give the *title compound* (0.80 g, 87%) as a pale yellow powder. δ_{H} (DMSO- d_6) 12.67 (1H, br. s), 7.54 (1H, s), 3.78-3.69 (4H, m), 3.23-3.14 (4H, m), 2.91 (2H, s), 1.25 (6H, s). LCMS (ES+) 311.1 (M+H)⁺.

EXAMPLE 63

5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-N-[phenyl(pyridin-2-yl)methyl]-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxamide

The *title compound* was prepared from *Example 62* and phenyl(2-pyridyl)methylamine hydrochloride according to *Method I* and was isolated as a pink solid (100%). δ_{H} (DMSO- d_6) 9.78 (1H, d, J 7.3 Hz), 8.66 (1H, d, J 4.7 Hz), 7.90-7.83 (1H, m), 7.68 (1H, s), 7.58 (1H, d, J 7.7 Hz), 7.48-7.25 (6H, m), 6.33 (1H, d, J 7.3 Hz), 3.78-3.64 (4H, m), 3.10-3.03 (4H, m), 2.94 (2H, s), 1.25 (6H, s). LCMS (ES+) 477.0 (M+H)⁺.

EXAMPLE 64 (METHOD J)

Methyl 4-[5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]benzoate

To a stirred solution of *Example 17* (0.050 g, 0.128 mmol), 4-(methoxycarbonylphenyl)boronic acid (0.023 g, 0.128 mmol) and K₃PO₄ (0.035 g, 0.165 mmol) in a mixture of DME (1.5 mL) and water (0.5 mL) was added Pd(PPh₃)₄ (0.020 g, 0.017 mmol) and the reaction mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 40 minutes. The crude reaction mixture was then concentrated *in vacuo* and purification by column chromatography (SiO₂, 0-100% EtOAc/heptane) gave the *title compound* (0.028 g, 53%) as a pale brown solid. δ_{H} (DMSO- d_6) 8.04 (2H, m), 7.57 (2H, m), 3.88 (3H, s), 3.57 (4H, m), 2.91 (4H, m), 2.51 (2H, s), 2.37 (2H, s), 0.98 (6H, s). LCMS (ES+) 400.2 (M+H)⁺.

EXAMPLE 65

N-{4-[5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]phenyl}acetamide

The *title compound* was prepared from *Example 17* and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acetanilide according to *Method J* and was isolated as a white solid (58%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_{H} (CD₃OD) 7.66 (2H, m), 7.33 (2H, m), 3.65 (4H, m), 3.03 (4H, m), 2.51 (2H, s), 2.43

(2H, s), 2.16 (3H, s), 1.03 (6H, s). Exchangeable proton not observed. LCMS (ES+) 399.3 (M+H)⁺.

EXAMPLE 66

5

Ethyl 3-[5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]benzoate

The *title compound* was prepared from *Example 17* and ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate according to *Method J* and was isolated as
10 a pale brown solid (11%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_{H} (CD₃OD) 8.09 (1H, s), 8.08 (1H, m), 7.64 (2H, m), 4.42 (2H, q, *J* 7.1 Hz), 3.64 (4H, m), 3.02 (4H, m), 2.53 (2H, s), 2.46 (2H, s), 1.42 (3H, t, *J* 7.1 Hz) 1.04 (6H, s). LCMS (ES+) 414.2 (M+H)⁺.

15

EXAMPLE 67

Tert-Butyl 4-{3-[5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]phenyl}piperazine-1-carboxylate

The *title compound* was prepared from *Example 17* and 3-[4-(*tert*-
20 butoxycarbonyl)piperazin-1-yl]phenylboronic acid pinacol ester according to *Method J* and was isolated as a white solid (89%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_{H} (DMSO-*d*₆) 7.34 (1H, m), 6.98 (2H, m), 6.83 (1H, d, *J* 7.5 Hz), 3.60 (8H, m), 3.16 (4H, m), 3.01 (4H, m), 2.49 (2H, s), 2.41 (2H, s), 1.47 (9H, s), 1.01 (6H, s). LCMS (ES+) 526.2 (M+H)⁺.

25

EXAMPLE 68

5,5-Dimethyl-2-(morpholin-4-yl)-3-[3-(morpholin-4-yl)phenyl]-5,6-dihydro-1-benzothiophen-7(4*H*)-one

30 The *title compound* was prepared from *Example 17* and 3-morpholinophenylboronic acid pinacol ester according to *Method J* and was isolated as an off-white solid (38%) after purification by preparative HPLC (pH 2.5). δ_{H} (CD₃OD) 7.36 (1H, t, *J* 8.0 Hz), 7.04-6.94 (2H, m), 6.86 (1H, d, *J* 8.0 Hz), 3.90-3.84 (4H, m), 3.68-3.62 (4H, m),

3.22-3.16 (4H, m), 3.08-3.02 (4H, m), 2.52 (2H, s), 2.44 (2H, s), 1.04 (6H, s). LCMS (ES+) 427.3 (M+H)⁺.

EXAMPLE 69

5

3-[3-(Aminomethyl)phenyl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, formic acid salt

The *title compound* was prepared from *Example 17* and 3-(aminomethyl)-phenylboronic acid according to *Method J* and was isolated as a yellow gum (31%) after
10 purification by preparative HPLC (pH 2.5). δ_H (CD₃OD) 8.44 (1H, s), 7.66-7.44 (4H, m), 4.22 (2H, s), 3.70-3.60 (4H, m), 3.10-2.98 (4H, m), 2.52 (2H, s), 2.48 (2H, s), 1.04 (6H, s). LCMS (ES+) 371.2 (M+H)⁺.

EXAMPLE 70

15

5,5-Dimethyl-2-(morpholin-4-yl)-3-[3-(piperidin-1-ylmethyl)phenyl]-5,6-dihydro-1-benzothiophen-7(4H)-one, formic acid salt

The *title compound* was prepared from *Example 17* and 3-(piperidinomethyl)-phenylboronic acid pinacol ester according to *Method J* and was isolated as a yellow gum
20 (14%) after purification by preparative HPLC (pH 2.5). δ_H (CD₃OD) 8.44 (1H, s), 7.66-7.48 (4H, m), 4.32 (2H, s), 3.68-3.62 (4H, m), 3.30-3.12 (4H, m), 3.08-2.98 (4H, m), 2.56 (2H, s), 2.48 (2H, s), 1.94-1.80 (4H, m), 1.76-1.62 (2H, m), 1.04 (6H, s). LCMS (ES+) 439.2 (M+H)⁺.

25

EXAMPLE 71

{3-[5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]phenyl}acetic acid

The *title compound* was prepared from *Example 17* and 3-(pinacolboronyl)-phenylacetic acid according to *Method J* and was isolated as a yellow solid (35%) after
30 purification by preparative HPLC (pH 2.5). δ_H (CD₃OD) 7.44 (1H, t, *J* 7.5 Hz), 7.36 (1H, s), 7.32-7.24 (2H, m), 3.68 (2H, s), 3.70-3.60 (4H, m), 3.08-2.98 (4H, m), 2.56 (2H, s),

2.46 (2H, s), 1.04 (6H, s). Exchangeable proton not observed. LCMS (ES+) 400.3 (M+H)⁺.

EXAMPLE 72

5

Ethyl 5-[5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]nicotinate

The *title compound* was prepared from *Example 17* and 3-ethoxycarbonylpyridin-5-ylboronic acid pinacol ester according to *Method J* and was isolated as an off-white solid (47%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane) followed by preparative HPLC (pH 2.5). δ_{H} (DMSO-d₆) 9.05 (1H, s), 8.84 (1H, s), 8.38-8.34 (1H, m), 4.38 (2H, q, *J* 8.0 Hz), 3.59-3.53 (4H, m), 2.95-2.88 (4H, m), 2.53 (2H, s), 2.41 (2H, s), 1.34 (3H, t, *J* 8.0 Hz), 0.96 (6H, s). LCMS (ES+) 415.0 (M+H)⁺.

15

EXAMPLE 73

3-(2-Chloropyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 2-chloropyridin-4-ylboronic acid according to *Method J* and was isolated as an off-white solid (47%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-d₆) 8.50 (1H, s), 7.59 (1H, s), 7.49 (1H, d, *J* 6.0 Hz), 3.64-3.58 (4H, m), 2.96-2.92 (4H, m), 2.54 (2H, s), 2.38 (2H, s), 0.97 (6H, s). LCMS (ES+) 377.3 (M+H)⁺.

25

EXAMPLE 74

3-(5-Bromopyridin-3-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 3-bromopyridin-5-ylboronic acid according to *Method J* and was isolated as an off-white solid (24%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-d₆) 8.59 (1H, d, *J* 3.0 Hz), 8.51 (1H, d, *J* 3.0 Hz), 8.16 (1H, t, *J* 3.0 Hz), 3.62-3.56 (4H, m), 2.94-2.91 (4H, m), 2.50 (2H, s), 2.37 (2H, s), 0.98 (6H, s). LCMS (ES+) 421.2 and 423.2 (M+H)⁺.

EXAMPLE 75

5,5-Dimethyl-2-(morpholin-4-yl)-3-(pyridin-3-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine according to *Method J* and was isolated as a beige solid (15%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 9.05 (1H, s), 8.61 (1H, d, J 1.7 Hz), 7.88-7.82 (1H, m), 7.50 (1H, dd, J 7.7 and 4.8 Hz), 3.60-3.54 (4H, m), 2.94-2.87 (4H, m), 2.46 (2H, s), 2.37 (2H, s), 0.96 (6H, s). LCMS (ES⁺) 343.2 (M+H)⁺.

EXAMPLE 76

N-{3-[5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]phenyl}acetamide

The *title compound* was prepared from *Example 17* and 3-acetamidophenylboronic acid according to *Method J* and was isolated as a pale brown oil (27%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_{H} (CD₃OD) 7.69 (1H, t, J 2.3 Hz), 7.53-7.48 (1H, m), 7.41 (1H, t, J 7.8 Hz), 7.13-7.09 (1H, m), 3.70-3.64 (4H, m), 3.05-3.00 (4H, m), 2.53 (2H, s), 2.43 (2H, s), 2.16 (3H, s), 1.04 (6H, s). Exchangeable proton not observed. LCMS (ES⁺) 399.0 (M+H)⁺.

EXAMPLE 77

3-(3-Aminophenyl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 3-aminophenylboronic acid monohydrate according to *Method J* and was isolated as a brown solid (30%) after purification by preparative HPLC (pH 5.8). δ_{H} (CD₃OD) 7.19 (1H, t, J 8.1 Hz), 6.74-6.70 (2H, m), 6.65 (1H, d, J 7.5 Hz), 3.68-3.65 (4H, m), 3.09-3.05 (4H, m), 2.51 (2H, s), 2.42 (2H, s), 1.03 (6H, s). LCMS (ES⁺) 357.2 (M+H)⁺.

EXAMPLE 78

3-(4-Aminophenyl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 4-aminophenylboronic acid monohydrate according to *Method J* and was isolated as a pale brown solid (16%) after purification by preparative HPLC (pH 2.5). δ_{H} (CD₃OD) 7.09 (2H, d, *J* 8.5 Hz), 6.81 (2H, d, *J* 8.5 Hz), 3.68-3.63 (4H, m), 3.07-3.03 (4H, m), 2.50 (2H, s), 2.42 (2H, s), 1.03 (6H, s). Exchangeable protons not observed. LCMS (ES⁺) 357.2 (M+H)⁺.

EXAMPLE 79

3-(3-Acetylphenyl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 3-acetylphenylboronic acid according to *Method J* and was isolated as an off-white solid (73%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_{H} (CD₃OD) 8.04-8.00 (2H, m), 7.69-7.62 (2H, m), 3.66-3.62 (4H, m), 3.04-2.99 (4H, m), 2.66 (3H, s), 2.53 (2H, s), 2.46 (2H, s), 1.04 (6H, s). LCMS (ES⁺) 384.2 (M+H)⁺.

EXAMPLE 80

3-[5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]-N-methylbenzamide

The *title compound* was prepared from *Example 17* and 3-(*N*-methylamino-carbonyl)phenylboronic acid according to *Method J* and was isolated as an off-white solid (73%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_{H} (CD₃OD) 7.88-7.87 (1H, m), 7.85-7.80 (1H, m), 7.59-7.55 (2H, m), 3.65-3.60 (4H, m), 3.01-2.98 (4H, m), 2.95 (3H, s), 2.52 (2H, s), 2.43 (2H, s), 1.03 (6H, s). LCMS (ES⁺) 399.3 (M+H)⁺.

EXAMPLE 81

3-(Dibenzo[*b,d*]furan-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 17* and dibenzofuran-4-boronic acid according to *Method J* and was isolated as a pale orange powder (41%) after
5 purification by column chromatography (SiO₂, 0-30% EtOAc/heptane). δ_{H} (DMSO-*d*₆) 8.24-8.15 (2H, m), 7.73 (1H, m), 7.59-7.40 (4H, m), 3.50-3.36 (4H, m), 2.97-2.87 (4H, m), 2.44-2.29 (4H, m), 0.95 (3H, s), 0.92 (3H, s). LCMS (ES⁺) 432.2 (M+H)⁺.

EXAMPLE 82

5,5-Dimethyl-3-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 17* and 4-methyl-2-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-thiazole according to *Method J* and was
15 isolated as a white powder (33%) after purification by column chromatography (SiO₂, 0-30% EtOAc/heptane). δ_{H} (DMSO-*d*₆) 8.00-7.90 (2H, m), 7.56-7.45 (3H, m), 3.69-3.55 (4H, m), 3.15-3.01 (4H, m), 2.45-2.32 (4H, m), 2.27 (3H, s), 1.00 (6H, s). LCMS (ES⁺) 439.2 (M+H)⁺.

EXAMPLE 83

3-[4-(Benzyloxy)-3-chlorophenyl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 17* and (4-benzyloxy-3-chlorophenyl)boronic acid according to *Method J* and was isolated as an off-white solid (2%)
25 after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO-*d*₆) 7.54-7.31 (8H, m), 5.25 (2H, s), 3.61-3.53 (4H, m), 2.96-2.87 (4H, m), 2.48 (2H, s), 2.35 (2H, s), 0.97 (6H, s). LCMS (ES⁺) 482.2 and 484.1 (M+H)⁺.

EXAMPLE 84

Methyl 2-chloro-4-[5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]benzoate

The *title compound* was prepared from *Example 17* and (4-methoxycarbonyl-3-chlorophenyl)boronic acid according to *Method J* and was isolated as an off-white solid (71%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_{H} (DMSO-d₆) 7.95 (1H, d, *J* 8.1 Hz), 7.62 (1H, d, *J* 1.5 Hz), 7.47 (1H, dd, *J* 8.1 and 1.6 Hz), 3.95 (3H, s), 3.72-3.65 (4H, m), 3.07-3.00 (4H, m), 2.56 (2H, s), 2.46 (2H, s), 1.04 (6H, s). LCMS (ES+) 434.2 and 436.2 (M+H)⁺.

EXAMPLE 85

10 3-[5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]benzamide

The *title compound* was prepared from *Example 17* and (3-aminocarbonyl-phenyl)boronic acid according to *Method J* and was isolated as a brown solid (18%) after purification by preparative HPLC (pH 2.5). δ_{H} (CD₃OD) 7.97-7.85 (2H, m), 7.65-7.55 (2H, m), 3.70-3.59 (4H, m), 3.07-2.96 (4H, m), 2.53 (2H, s), 2.45 (2H, s), 1.04 (6H, s). Exchangeable protons not observed. LCMS (ES+) 385.2 (M+H)⁺.

EXAMPLE 86

20 5,5-Dimethyl-3-(4-hydroxyphenyl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 4-hydroxyphenylboronic acid according to *Method J* and was isolated as a pale yellow solid (34%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO-d₆) 9.60 (1H, s), 7.21-7.15 (2H, m), 6.87-6.80 (2H, m), 3.61-3.52 (4H, m), 2.95-2.86 (4H, m), 2.45 (2H, s), 2.34 (2H, s), 0.95 (6H, s). LCMS (ES+) 358.2 (M+H)⁺.

EXAMPLE 87

30 5-[5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]nicotinic acid

To a stirred solution of *Example 72* (0.056 g, 0.135 mmol) in EtOH (8 mL) and water (1 mL) was added LiOH (0.011 g, 0.270 mmol) and the reaction mixture was

stirred at r.t. for 1.5 h. The solvent was then removed *in vacuo* and the residue was purified by preparative HPLC (pH 2.5) to give the *title compound* (0.028 g, 54%) as a beige solid. δ_{H} (DMSO- d_6) 9.12 (1H, m), 8.83 (1H, d, J 2.1 Hz), 8.29 (1H, t, J 2.0 Hz), 3.60-3.54 (4H, m), 2.94-2.89 (4H, m), 2.50 (2H, s), 2.39 (2H, s), 0.97 (6H, s).

5 Exchangeable proton not observed. LCMS (ES+) 387.2 (M+H)⁺.

EXAMPLE 88

5,5-Dimethyl-2-(morpholin-4-yl)-3-[3-(piperazin-1-yl)phenyl]-5,6-dihydro-1-benzothiophen-7(4H)-one

10

To a stirred solution of *Example 67* (0.060 g, 0.114 mmol) in MeOH (20 mL) was added 2M HCl in Et₂O solution (1.000 mL, 2.000 mmol). After stirring for 12 h at r.t. the reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO₂, 0-10% MeOH/DCM) to give the *title compound* (0.034 g, 80%) as a yellow solid.

15 δ_{H} (CD₃OD) 7.35 (1H, m), 7.00 (2H, m), 6.87 (1H, d, J 7.5 Hz), 3.59 (4H, m), 3.40 (4H, m), 3.33 (4H, m), 2.97 (4H, m), 2.45 (2H, s), 2.37 (2H, s), 0.97 (6H, s). Exchangeable proton not observed. LCMS (ES+) 426.3 (M+H)⁺.

EXAMPLE 89 (METHOD K)

20

5,5-Dimethyl-2-(morpholin-4-yl)-3-(2-phenylpyridin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

To a stirred solution of *Example 17* (0.150 g, 0.384 mmol), Pd(PPh₃)₄ (0.050 g, 0.040 mmol) and K₃PO₄ (0.100 g, 0.470 mmol) in a mixture of water (1 mL) and DME (3 mL) was added 2-chloropyridin-4-ylboronic acid (0.060 g, 0.384 mmol) and the reaction mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. Phenylboronic acid (0.060 g, 0.492 mmol) was then added and the reaction mixture was heated again to 120°C in a sealed tube, under microwave irradiation, for 30 minutes. The reaction mixture was concentrated *in vacuo* and purified by preparative

30 HPLC (pH 2.5) to give the *title compound* (0.033 g, 21%) as an off-white solid. δ_{H} (DMSO- d_6) 8.75 (2H, d, J 4.9 Hz), 8.15 (1H, d, J 6.8 Hz), 8.06 (1H, s), 7.60-7.40 (4H, m), 3.63 (4H, m), 3.01 (4H, m), 2.62 (2H, s), 2.42 (2H, s), 1.01 (6H, s). LCMS (ES+) 419.0 (M+H)⁺.

EXAMPLE 90**5,5-Dimethyl-2-(morpholin-4-yl)-3-(5-phenylpyridin-3-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one**

The *title compound* was prepared from *Example 17*, 3-bromopyridin-5-ylboronic acid and phenylboronic acid according to *Method K* and was isolated as a white solid (14%). δ_{H} (DMSO- d_6) 8.94 (1H, d, J 2.1 Hz), 8.64 (1H, d, J 1.9 Hz), 8.16 (1H, t, J 2.2 Hz), 7.84 (2H, d, J 7.2 Hz), 7.65-7.45 (3H, m), 3.61 (4H, m), 3.00 (4H, m), 2.59 (2H, s), 2.42 (2H, s), 1.02 (6H, s). LCMS (ES+) 419.0 (M+H)⁺.

EXAMPLE 91**3-(2,3'-Bipyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one**

The *title compound* was prepared from *Example 17*, 2-chloropyridin-4-ylboronic acid and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine according to *Method K* and was isolated as a beige solid (16%). δ_{H} (DMSO- d_6) 9.37 (1H, d, J 1.9 Hz), 8.82 (1H, d, J 4.9 Hz), 8.70 (1H, dd, J 4.9 and 1.6 Hz), 8.54 (1H, m), 8.16 (1H, s), 7.59 (1H, m), 7.52 (1H, m), 3.63 (4H, m), 3.01 (4H, m), 2.64 (2H, s), 2.42 (2H, s), 1.01 (6H, s). LCMS (ES+) 420.0 (M+H)⁺.

EXAMPLE 92**3-(2-{3-[(Dimethylamino)methyl]phenyl}pyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one**

The *title compound* was prepared from *Example 17*, 2-chloropyridin-4-ylboronic acid and 3-[(*N,N*-dimethylamino)methyl]phenylboronic acid according to *Method K* and was isolated as a brown solid (11%). δ_{H} (DMSO- d_6) 8.78 (1H, d, J 5.1 Hz), 8.14 (1H, s), 8.09 (1H, s), 8.06 (1H, d, J 7.9 Hz), 7.50 (1H, t, J 7.5 Hz), 7.42 (2H, m), 3.63 (4H, m), 3.50 (2H, s), 3.01 (4H, m), 2.63 (2H, s), 2.43 (2H, s), 2.23 (6H, s), 1.01 (6H, s). LCMS (ES+) 476.0 (M+H)⁺.

EXAMPLE 93

3-(3,3'-Bipyridin-5-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

5 The *title compound* was prepared from *Example 17*, 3-bromopyridin-5-ylboronic acid and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine according to *Method K* and was isolated as a beige solid (8%). δ_{H} (DMSO- d_6) 9.20-9.00 (3H, m), 8.75-8.65 (2H, m), 8.26 (1H, m), 7.60 (1H, m), 3.61 (4H, m), 3.00 (4H, m), 2.60 (2H, s), 2.42 (2H, s), 1.02 (6H, s). LCMS (ES+) 420.0 (M+H)⁺.

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EXAMPLE 94

5,5-Dimethyl-2-(morpholin-4-yl)-3-(2-phenylpyridin-4-yl)-5,6-dihydrothieno[2,3-c]pyridin-7(4H)-one

15 The *title compound* was prepared from *Intermediate 19*, 2-chloropyridin-4-ylboronic acid and phenylboronic acid according to *Method K* and was isolated as a pink solid (11%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.73 (1H, d, *J* 5.1 Hz), 8.14 (2H, d, *J* 6.8 Hz), 8.04 (1H, s), 7.58-7.42 (5H, m), 3.64-3.57 (4H, m), 2.94-2.87 (4H, m), 2.71 (2H, s), 1.19 (6H, s). LCMS (ES+) 420.2 (M+H)⁺.

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EXAMPLE 95

3-[2-(3,5-Dimethylisoxazol-4-yl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

25 The *title compound* was prepared from *Example 17*, 2-chloropyridin-4-ylboronic acid and 3,5-dimethylisoxazol-4-ylboronic acid according to *Method K* and was isolated as a white solid (2%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.74 (1H, d, *J* 6.8 Hz), 7.52 (1H, s), 7.46 (1H, d, *J* 5.1 Hz), 3.64-3.57 (4H, m), 3.00-2.93 (4H, m), 2.63 (3H, s), 2.59 (3H, s), 2.44 (2H, s), 2.38 (2H, s), 0.98 (6H, s). LCMS (ES+) 438.2 (M+H)⁺.

30

EXAMPLE 96

3-(2,2'-Bipyridin-4-yl)-5,5-dimethyl-2-morpholin-4-yl-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17*, 2-chloropyridin-4-ylboronic acid and 2-pyridineboronic acid *N*-phenyldiethanolamine ester according to *Method K* and was isolated as an off-white solid (4%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.77 (1H, d, J 5.1 Hz), 8.72 (1H, d, J 4.7 Hz), 8.51-8.46 (1H, m), 8.44 (1H, d, J 8.1 Hz), 7.98 (1H, td, J 7.5 and 1.8 Hz), 7.53-7.46 (1H, m), 7.37-7.30 (1H, m), 3.64-3.56 (4H, m), 3.03-2.94 (4H, m), 2.58 (2H, s), 2.41 (2H, s), 0.97 (6H, s). LCMS (ES+) 420.3 (M+H)⁺.

EXAMPLE 97

5,5-Dimethyl-2-(morpholin-4-yl)-3-[3-(1H-pyrazol-4-yl)phenyl]-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17*, 3-bromophenylboronic acid and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole according to *Method K* and was isolated as an off-white solid (18%) after purification by preparative HPLC (pH 2.5). δ_{H} (CD₃OD) 8.03 (2H, s), 7.65-7.59 (2H, m), 7.48 (1H, t, J 7.7 Hz), 7.26-7.19 (1H, m), 3.67-3.60 (4H, m), 3.10-3.02 (4H, m), 2.56 (2H, s), 2.44 (2H, s), 1.05 (6H, s).

Exchangeable proton not observed. LCMS (ES+) 408.2 (M+H)⁺.

EXAMPLE 98

3-(3-Bromo-5-nitrophenyl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

To a stirred solution of *Example 17* (0.30 g, 0.77 mmol), Pd(Ph₃P)₄ (0.05 g, 0.04 mmol) and K₃PO₄ (0.20 g, 0.94 mmol) in a mixture of water (1 mL) and DME (3 mL) was added (3-bromo-5-nitrophenyl)boronic acid (0.19 g, 0.77 mmol). The reaction mixture was then heated to 140°C in a sealed tube under microwave irradiation for 1 h.

The reaction mixture was then cooled, concentrated *in vacuo* and purified by preparative HPLC (pH 2.5) to give the *title compound* as a yellow solid (0.04 g, 10%). *Example 99* was also isolated. δ_{H} (DMSO- d_6) 8.40 (1H, s), 8.27 (1H, s), 8.16 (1H, m), 3.62 (4H, m),

2.98 (4H, m), 2.59 (2H, s), 2.42 (2H, s), 1.01 (6H, s). LCMS (ES+) 465.0 and 467.0 (M+H)⁺.

EXAMPLE 99

5

3-(3'-Bromo-5,5'-dinitrobiphenyl-3-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was isolated by preparative HPLC (pH 2.5) (from the crude material produced in the synthesis of *Example 98*) as a brown solid (0.02 g, 4%). δ_{H} (DMSO-d₆) 8.67 (2H, s), 8.62 (1H, s), 8.52 (1H, s), 8.40 (1H, s), 8.37 (1H, s), 3.61 (4H, m), 3.01 (4H, m), 2.62 (2H, s), 2.43 (2H, s), 1.01 (6H, s). LCMS (ES+) 586.0 and 588.0 (M+H)⁺.

EXAMPLE 100

15

5,5-Dimethyl-3-[3-(1-methyl-1H-pyrazol-4-yl)phenyl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, formic acid salt

The *title compound* was prepared from *Example 17*, 3-bromophenylboronic acid and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole according to *Method K* and was isolated as an off-white solid (18%) after purification by preparative HPLC (pH 2.5). δ_{H} (CD₃OD) 8.04 (1H, s), 7.88 (1H, s), 7.62-7.54 (2H, m), 7.48 (1H, t, *J* 7.5 Hz), 7.22 (1H, d, *J* 7.5 Hz), 3.96 (3H, s), 3.68-3.60 (4H, m), 3.10-3.02 (4H, m), 2.58 (2H, s), 2.46 (2H, s), 1.04 (6H, s). LCMS (ES+) 422.3 (M+H)⁺.

25

EXAMPLE 101

3-{3'-[(Dimethylamino)methyl]biphenyl-3-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, formic acid salt

The *title compound* was prepared from *Example 17*, 3-bromophenylboronic acid and 3-(dimethylaminomethyl)phenylboronic acid according to *Method K* and was isolated as a yellow gum (10%) after purification by preparative HPLC (pH 2.5). δ_{H} (CD₃OD) 8.52 (1H, s), 7.84-7.68 (4H, m), 7.66-7.54 (2H, m), 7.48 (1H, d, *J* 7.5 Hz), 7.42 (1H, d, *J*

7.5 Hz), 4.12 (2H, s), 3.68-3.60 (4H, m), 3.10-3.02 (4H, m), 2.70 (6H, s), 2.56 (2H, s), 2.48 (2H, s), 1.06 (6H, s). LCMS (ES+) 475.2 (M+H)⁺.

EXAMPLE 102 (METHOD L)

5

N-(3-{4-[5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]pyridin-2-yl}phenyl)acetamide

To a stirred solution of 3-acetamidophenylboronic acid (0.028 g, 0.160 mmol), *Example 73* (0.060 g, 0.160 mmol) and K₃PO₄ (0.050 g, 0.240 mmol) in DME (1.5 mL) and water (0.5 mL) was added Pd(PPh₃)₄ (0.010 g, 0.009 mmol) and the reaction mixture was heated to 140°C in a sealed tube, under microwave irradiation, for 2 h. The solvent was then removed *in vacuo* and the residue was purified by preparative HPLC (pH 2.5) to give the *title compound* (0.058 g, 76%) as an off-white solid. δ_H (DMSO-d₆) 10.09 (1H, s), 8.75 (1H, d, *J* 5.1 Hz), 8.47 (1H, s), 7.95 (1H, s), 7.81-7.75 (1H, m), 7.68-7.61 (1H, m), 7.47-7.38 (2H, m), 3.66-3.55 (4H, m), 3.02-2.93 (4H, m), 2.59 (2H, s), 2.40 (2H, s), 2.08 (3H, s), 0.97 (6H, s). LCMS (ES+) 476.2 (M+H)⁺.

EXAMPLE 103

5,5-Dimethyl-3-[2-(3-hydroxyphenyl)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The title compound was prepared from *Example 73* and 3-hydroxyphenylboronic acid according to *Method L* and was isolated as a white solid (56%) after purification by preparative HPLC (pH 5.8). δ_H (DMSO-d₆) 9.61 (1H, s), 8.72 (1H, d, *J* 5.1 Hz), 7.92 (1H, s), 7.59-7.51 (2H, m), 7.42-7.37 (1H, m), 7.34-7.28 (1H, m), 6.89-6.82 (1H, m), 3.65-3.55 (4H, m), 3.02-2.93 (4H, m), 2.59 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES+) 435.2 (M+H)⁺.

EXAMPLE 104

30

Methyl 5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate

A mixture of *Example 17* (1.00 g, 2.56 mmol), [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II)-DCM complex (0.10 g, 0.13 mmol) and NEt₃ (4.20 g, 3.00 mL, 41.58 mmol) in MeOH (100 mL) was heated in a Parr bomb at 100 psi under an atmosphere of CO for 48 h. The reaction mixture was then filtered through Celite® and washed with MeOH. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (SiO₂, 30-50% EtOAc/heptane) to give the *title compound* (0.82 g, 99%) as a pale pink solid. δ_{H} (DMSO-d₆) 3.78 (3H, s), 3.76-3.70 (4H, m), 3.27-3.21 (4H, m), 2.77 (2H, s), 2.34 (2H, s), 1.02 (6H, s). LCMS (ES⁺) 324.3 (M+H)⁺.

EXAMPLE 105 (METHOD M)

5,5-Dimethyl-3-[(1-methyl-1*H*-imidazol-2-yl)ethynyl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

To a stirred solution of *Example 17* (0.20 g, 0.51 mmol) in diisopropylamine (1 mL) and DMF (5 mL) were added *Intermediate 23* (0.13 g, 1.03 mmol) and Pd(PPh₃)₂Cl₂ (0.02 g, 0.03 mmol), followed by CuI (0.01 g, 0.05 mmol). The reaction mixture was stirred at 60°C for 1 h, then cooled to r.t. The precipitate formed was filtered, purified by column chromatography (SiO₂, EtOAc), then triturated with DCM, Et₂O and hexanes to give the *title compound* (0.02 g, 8%) as a beige solid. δ_{H} (CDCl₃) 7.21-7.11 (1H, m), 7.06-6.96 (1H, m), 3.93-3.85 (4H, m), 3.80 (3H, s), 3.75-3.68 (4H, m), 2.72 (2H, s), 2.43 (2H, s), 1.14 (6H, s). MS (ES⁺) 370.0 (M+H)⁺.

EXAMPLE 106

5,5-Dimethyl-2-(morpholin-4-yl)-3-(piperidin-4-ylethynyl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 17* and *Intermediate 25* according to *Method M* and was isolated as an off-white solid (8%) after purification by column chromatography (SiO₂, hexanes, to EtOAc, to MeOH). δ_{H} (CDCl₃) 3.92-3.81 (4H, m), 3.64-3.56 (4H, m), 3.18-3.05 (2H, m), 2.86-2.69 (3H, m), 2.62 (2H, s), 2.41 (2H, s), 2.02-1.87 (2H, m), 2.01-1.86 (2H, m), 1.12 (6H, s). Exchangeable proton not observed. MS (ES⁺) 373.2 (M+H)⁺.

EXAMPLE 107

tert-Butyl (2S)-2-{[5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]ethynyl}pyrrolidine-1-carboxylate

5 The *title compound* was prepared from *Example 17* and *Intermediate 27* according to *Method M* and was isolated as an off-white solid (61%) after purification by column chromatography (SiO₂, 10-20% EtOAc/hexanes). δ_{H} (CDCl₃) 4.87-4.61 (1H, m), 4.00-3.77 (4H, m), 3.77-3.55 (4H, m), 3.54-3.44 (1H, m), 3.44-3.27 (1H, m), 2.62 (2H, s), 2.40 (2H, s), 2.30-1.88 (4H, m), 1.50 (9H, s), 1.12 (3H, s), 1.11 (3H, s). MS (ES⁺) 459.0
10 (M+H)⁺.

EXAMPLE 108

tert-Butyl 2-{[5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]ethynyl}piperidine-1-carboxylate

15 The *title compound* was prepared from *Example 17* and *Intermediate 30* according to *Method M* and was isolated as an off-white solid (55%) after purification by column chromatography (SiO₂, 10-20% EtOAc/hexanes). δ_{H} (CDCl₃) 5.46-5.22 (1H, m), 4.10-3.92 (1H, m), 3.95-3.75 (4H, m), 3.69-3.51 (4H, m), 3.16-2.85 (1H, m), 2.63 (2H, s), 2.41
20 (2H, s), 1.95-1.64 (5H, m), 1.58 (10H, s), 1.12 (6H, s). MS (ES⁺) 473.1 (M+H)⁺.

EXAMPLE 109

tert-Butyl 3-{[5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]ethynyl}piperidine-1-carboxylate

25 The *title compound* was prepared from *Example 17* and *Intermediate 33* according to *Method M* and was isolated as an off-white solid (56%) after purification by column chromatography (SiO₂, 10-20% EtOAc/hexanes). δ_{H} (CDCl₃) 4.20-3.92 (1H, m), 3.98-3.80 (4H, m), 3.83-3.70 (1H, m), 3.67-3.51 (4H, m), 3.16-2.94 (2H, m), 2.82-2.68 (1H, m),
30 m), 2.61 (2H, s), 2.40 (2H, s), 2.13-1.99 (1H, m), 1.84-1.70 (1H, m), 1.68-1.59 (1H, m), 1.68-1.38 (10H, m), 1.13 (6H, s). MS (ES⁺) 473.0 (M+H)⁺.

EXAMPLE 110

5,5-Dimethyl-2-(morpholin-4-yl)-3-(piperidin-2-ylethynyl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and *Intermediate 34* according to *Method M* and was isolated as a pale brown solid (10%) after purification by column chromatography (SiO₂, 0-50% MeOH/EtOAc). δ_{H} (DMSO-d₆) 3.89-3.78 (1H, m), 3.82-3.69 (4H, m), 3.64-3.45 (4H, m), 2.99-2.80 (1H, m), 2.61-2.59 (3H, m), 2.33 (2H, s), 1.82-1.60 (2H, m), 1.62-1.31 (4H, m), 1.03 (6H, s). Exchangeable proton not observed. MS (ES⁺) 373.1 (M+H)⁺.

EXAMPLE 111

5,5-Dimethyl-2-(morpholin-4-yl)-3-(piperidin-3-ylethynyl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and *Intermediate 35* according to *Method M* and was isolated as a pale brown solid (14%) after purification by column chromatography (SiO₂, 0-50% MeOH/EtOAc). δ_{H} (DMSO-d₆) 3.84-3.67 (4H, m), 3.63-3.48 (4H, m), 3.09-2.95 (1H, m), 2.84-2.71 (1H, m), 2.66-2.54 (4H, m), 2.55-2.44 (2H, m), 2.32 (2H, s), 2.02-1.85 (1H, m), 1.66-1.43 (2H, m), 1.43-1.30 (1H, m), 1.03 (6H, s). MS (ES⁺) 373.1 (M+H)⁺.

EXAMPLE 112 (METHOD Q)

5,5-Dimethyl-3-(1H-indol-5-ylethynyl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

To a stirred solution of *Example 17* (0.20 g, 0.52 mmol) and *Intermediate 37* (0.11 g, 0.78 mmol) in diisopropylamine (5 mL) and THF (5 mL) were added CuI (0.01 g, 0.05 mmol) and Pd(PPh₃)₂Cl₂ (0.02 g, 0.03 mmol). The reaction mixture was stirred at 70°C for 16 h, then cooled to r.t.. EtOAc (10 mL) and water (10 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 30% EtOAc/hexanes) gave the *title compound* (0.09 g, 43%) as a yellow solid. δ_{H} (DMSO-d₆) 11.30 (1H, br. s), 7.72 (1H, s),

7.51-7.37 (2H, m), 7.19 (1H, d, *J* 8.8 Hz), 6.47 (1H, s), 3.86-3.75 (4H, m), 3.69-3.59 (4H, m), 2.72 (2H, s), 2.36 (2H, s), 1.08 (6H, s). MS (ES⁻) 403.0 (M-H)⁻.

EXAMPLE 113

5

3-[(1,2-Dimethyl-1*H*-imidazol-4-yl)ethynyl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 17* and *Intermediate 40* according to *Method Q* and was isolated as a yellow solid (2%) after purification by column chromatography (SiO₂, 5% MeOH/DCM), followed by trituration with EtOAc and EtOH. δ_{H} (DMSO-*d*₆) 7.42 (1H, s), 3.79-3.72 (4H, m), 3.64-3.57 (4H, m), 3.55 (3H, s), 2.62 (2H, s), 2.34 (2H, s), 2.27 (3H, s), 1.04 (6H, s). MS (ES⁺) 384.0 (M+H)⁺.

EXAMPLE 114

15

5,5-Dimethyl-3-[(1-methyl-1*H*-indol-4-yl)ethynyl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 17* and *Intermediate 42* according to *Method Q* and was isolated as a beige solid (9%) after purification by column chromatography (SiO₂, 10% EtOAc/hexane). δ_{H} (DMSO-*d*₆) 7.51 (1H, d, *J* 8.2 Hz), 7.47 (1H, s), 7.25-7.14 (2H, m), 6.45 (1H, s), 3.83 (3H, s), 3.87-3.78 (4H, m), 3.74-3.66 (4H, m), 2.77 (2H, s), 2.38 (2H, s), 1.09 (6H, s). MS (ES⁺) 419.0 (M+H)⁺.

EXAMPLE 115

25

[Omitted]

EXAMPLE 116

30 3-Bromo-5,5-dimethyl-2-(morpholin-4-yl)-4,5,6,7-tetrahydro-8*H*-thieno[2,3-*c*]azepin-8-one

To a stirred solution of *Example 51* (4.0 g, 14.30 mmol) in THF (150 mL) at r.t. was added NBS (3.0 g, 17.20 mmol) portionwise over 5 minutes. The reaction mixture

was stirred at r.t. for 3 h. EtOAc (250 mL) and water (150 mL) were added. The organic layer was washed with water (3 x 100 mL), then brine (100 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 50% EtOAc/hexanes) gave the *title compound* (4.50 g, 88%) as a pale yellow solid. δ_{H} (DMSO-d₆) 8.01 (1H, s), 3.75-3.73 (4H, m), 3.09-3.06 (4H, m), 2.89 (2H, d, *J* 5.1 Hz), 2.58 (2H, s), 1.54 (6H, s). MS (ES+) 358.8 and 360.8 (M+H)⁺.

EXAMPLE 117

10 5,5-Dimethyl-2-(morpholin-4-yl)-3-phenyl-4,5,6,7-tetrahydro-8H-thieno[2,3-c]azepin-8-one

To a mixture of *Example 116* (0.15 g, 0.41 mmol), phenylboronic acid (0.08 g, 0.63 mmol), palladium acetate (0.005 g, 0.02 mmol), 1,3-bis(diphenylphosphino)propane (0.02 g, 0.04 mmol) and K₃PO₄ (0.18 g, 0.82 mmol) was added DMF (2 mL). The reaction mixture was heated at 80°C for 5 h and left standing for 16 h at r.t. Phenylboronic acid (0.08 g, 0.63 mmol), palladium acetate (0.005 g, 0.02 mmol), 1,3-bis(diphenylphosphino)propane (0.02 g, 0.04 mmol), K₃PO₄ (0.07 g, 0.33 mmol) and DMF (2 mL) were again added. The reaction mixture was heated at 90°C for 16 h, then cooled to r.t. and diluted with EtOAc (5 mL). The solid was filtered and washed with EtOAc (25 mL). The organic filtrate was washed with water (5 x 10 mL), then brine (10 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 30% EtOAc/hexanes) gave the *title compound* (0.05 g, 37%) as a white solid. δ_{H} (DMSO-d₆) 7.83 (1H, t, *J* 5.1 Hz), 7.46 (2H, t, *J* 7.4 Hz), 7.37-7.29 (3H, m), 3.49-3.47 (4H, m), 2.85 (2H, d, *J* 5.2 Hz), 2.79-2.77 (4H, m), 2.29 (2H, s), 0.86 (6H, s). MS (ES+) 357.0 (M+H)⁺.

EXAMPLE 118

30 5,5-Dimethyl-2-(morpholin-4-yl)-3-(pyridin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

To a suspension of *Example 17* (0.43 g, 1.10 mmol) in DME (10 mL) at r.t. were added pyridine-4-boronic acid (0.20 g, 1.65 mmol), K₃PO₄ (0.70 g, 3.30 mmol) and water (1 mL), followed by PdCl₂.dppf (0.02 g, 0.05 mmol). The reaction mixture was heated at

90°C for 6 h. EtOAc (50 mL) and water (20 mL) were added. The organic layer was washed with water (2 x 20 mL), then brine (20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, EtOAc) gave the *title compound* (0.03 g, 7%) as an off-white solid. δ_{H} (DMSO-d₆) 8.71 (2H, d, *J* 4.0 Hz), 7.35 (2H, d, *J* 4.0 Hz), 3.75-3.64 (4H, m), 3.08-2.95 (4H, m), 2.51 (2H, s), 2.47 (2H, s), 1.07 (6H, s). MS (ES⁺) 343.0 (M+H)⁺.

EXAMPLE 119 (METHOD S)

10 **5,5-Dimethyl-3-[(1-methyl-1*H*-imidazol-5-yl)ethynyl]-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one**

To a stirred solution of *Intermediate 19* (0.20 g, 0.51 mmol) and 5-ethynyl-1-methyl-1*H*-imidazole (0.08 mL, 0.77 mmol) in diisopropylamine (2 mL) and DMF (5 mL) were added CuI (0.01 g, 0.05 mmol) and Pd(PPh₃)₂Cl₂ (0.018 g, 0.03 mmol). The reaction mixture was stirred at 70°C for 16 h, then cooled to r.t. EtOAc (50 mL) and water (50 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (5 x 5 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude solid was washed with hot DCM and hexanes to give the *title compound* (0.12 g, 63%) as a white solid. δ_{H} (DMSO-d₆) 7.77 (1H, br. s), 7.49 (1H, s), 7.27 (1H, br. s), 3.78-3.75 (4H, m), 3.65 (3H, s), 3.49-3.46 (4H, m), 2.70 (2H, s), 1.26 (6H, s). MS (ES⁺) 371.1 (M+H)⁺.

EXAMPLE 120

25 **5,5-Dimethyl-3-[(1-methyl-1*H*-imidazol-5-yl)ethynyl]-2-(morpholin-4-yl)-4,5,6,7-tetrahydro-8*H*-thieno[2,3-*c*]azepin-8-one**

The *title compound* was prepared from *Example 52* and 5-ethynyl-1-methyl-1*H*-imidazole according to *Method S* and was isolated as a pale yellow solid (43%) after recrystallisation from MeOH. δ_{H} (DMSO-d₆) 7.84 (1H, t, *J* 4.8 Hz), 7.75 (1H, s), 7.25 (1H, s), 3.77-3.74 (4H, m), 3.66 (3H, s), 3.45-3.43 (4H, m), 2.89 (2H, d, *J* 5.0 Hz), 2.65 (2H, s), 0.95 (6H, s). MS (ES⁺) 385.1 (M+H)⁺.

EXAMPLE 121

N-{3-[5,5-Dimethyl-2-(morpholin-4-yl)-8-oxo-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*c*]azepin-3-yl]prop-2-yn-1-yl}methanesulfonamide

The *title compound* was prepared from *Example 52* and *Intermediate 43* according to *Method S* and was isolated as a white solid (15%) after trituration from hot DCM. δ_{H} (DMSO- d_6) 7.79 (1H, br. s), 7.60 (1H, br. s), 4.08 (2H, s), 3.75-3.70 (4H, m), 3.40-3.35 (4H, m), 2.99 (3H, s), 2.87 (2H, d, J 4.7 Hz), 2.60 (2H, s), 0.97 (6H, s). MS (ES⁺) 412.1 (M+H)⁺.

EXAMPLE 122

N-{3-[5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-3-yl]prop-2-yn-1-yl}methanesulfonamide

The *title compound* was prepared from *Intermediate 19* and *Intermediate 43* according to *Method S* and was isolated as an off-white solid (10%) after purification by column chromatography (SiO₂, EtOAc). δ_{H} (DMSO- d_6) 7.60 (1H, t, J 5.8 Hz), 7.42 (1H, s), 4.07 (2H, d, J 5.9 Hz), 3.75-3.73 (4H, m), 3.43-3.40 (4H, m), 2.99 (3H, s), 2.65 (2H, s), 1.23 (6H, s). MS (ES⁺) 398.0 (M+H)⁺.

EXAMPLE 123

N'-{3-[5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-3-yl]prop-2-yn-1-yl}-*N,N*-dimethylsulfamide

The *title compound* was prepared from *Intermediate 19* and *Intermediate 44* according to *Method S* and was isolated as an off-white solid (5%) after purification by column chromatography (SiO₂, 5% MeOH/EtOAc). δ_{H} (DMSO- d_6) 7.70 (1H, t, J 5.8 Hz), 7.41 (1H, s), 4.00 (2H, d, J 5.8 Hz), 3.75-3.73 (4H, m), 3.44-3.41 (4H, m), 2.70 (6H, s), 2.65 (2H, s), 1.24 (6H, s). MS (ES⁺) 427.0 (M+H)⁺.

EXAMPLE 124

N'-{3-[5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]prop-2-yn-1-yl}-*N,N*-dimethylsulfamide

The *title compound* was prepared from *Example 17* and *Intermediate 44* according to *Method S* (further addition of *Intermediate 44*, CuI and Pd(PPh₃)₂Cl₂ was required after 16 h and the reaction mixture was stirred for a further 24 h) and was isolated as a pale grey solid (40%) after purification by column chromatography (SiO₂, 50-100% EtOAc/hexanes). δ_{H} (DMSO-d₆) 7.72 (1H, d, *J* 5.8 Hz), 4.01 (2H, d, *J* 5.8 Hz), 3.75-3.72 (4H, m), 3.58-3.55 (4H, m), 2.70 (6H, s), 2.60 (2H, s), 2.33 (2H, s), 1.03 (6H, s). MS (ES⁺) 426.0 (M+H)⁺.

EXAMPLE 125

N'-{3-[5,5-Dimethyl-2-(morpholin-4-yl)-8-oxo-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*c*]azepin-3-yl]prop-2-yn-1-yl}-*N,N*-dimethylsulfamide

The *title compound* was prepared from *Example 52* and *Intermediate 44* according to *Method S* (further addition of *Intermediate 44*, CuI and Pd(PPh₃)₂Cl₂ was required after 5 h and the reaction mixture was stirred for a further 16 h) and was isolated as an off-white solid (16%) after purification by column chromatography (SiO₂, 50-100% EtOAc/hexanes). δ_{H} (DMSO-d₆) 7.78 (1H, br. s), 7.70 (1H, t, *J* 5.9 Hz), 4.00 (2H, d, *J* 5.7 Hz), 3.73-3.71 (4H, m), 3.40-3.37 (4H, m), 2.87 (2H, d, *J* 5.0 Hz), 2.70 (6H, s), 2.60 (2H, s), 0.97 (6H, s). MS (ES⁺) 441.1 (M+H)⁺.

EXAMPLE 126

5,5-Dimethyl-3-[(1-methyl-1*H*-pyrazol-4-yl)ethynyl]-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one

To a suspension of *Intermediate 19* (0.3 g, 0.76 mmol) in DMF (10 mL) were added diisopropylamine (2 mL) and a solution of *Intermediate 48* (0.11 g, 1.05 mmol) in DMF (0.5 mL), followed by CuI (0.01 g, 0.05 mmol) and Pd(PPh₃)₂Cl₂ (0.02 g, 0.03 mmol). The reaction mixture was stirred at 75°C for 16 h, then cooled to r.t. EtOAc (50 mL) and water (50 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (5 x 5 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, EtOAc), followed by washing of the purified solid with Et₂O, gave the *title compound* (0.05 g, 18%) as an off-white solid. δ_{H} (CDCl₃) 7.60 (1H,

s), 7.53 (1H, s), 5.17 (1H, s), 3.93 (3H, s), 3.89-3.87 (4H, m), 3.54-3.52 (4H, m), 2.80 (2H, s), 1.38 (6H, s). MS (ES+) 371.0 (M+H)⁺.

EXAMPLE 127

5

5,5-Dimethyl-3-[(1-methyl-1*H*-pyrazol-4-yl)ethynyl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 17* and *Intermediate 48* according to *Method S* and was isolated as an off-white solid (27%) after purification by column
10 chromatography (SiO₂, EtOAc). δ_H (DMSO) 8.04 (1H, s), 7.65 (1H, s), 3.85 (3H, s), 3.77-3.75 (4H, m), 3.60-3.57 (4H, m), 2.68 (2H, s), 2.34 (2H, s), 1.04 (6H, s). MS (ES+) 370.0 (M+H)⁺.

EXAMPLE 128

15

3-[(1-Acetylpiperidin-3-yl)ethynyl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 17* and *Intermediate 50* according to *Method S* and was isolated as an off-white solid (29%) after purification by column
20 chromatography (SiO₂, 0-5% MeOH/EtOAc). δ_H (CDCl₃), mixture of rotamers: 4.48-1.42 (9H, m), 3.89-3.83 (4H, m), 3.61-3.55 (4H, m), 2.60 (2H, s), 2.41 and 2.40 (2H, s, rotameric), 2.16 and 2.13 (3H, s, rotameric), 1.58 (6H, s). MS (ES+) 415.0 (M+H)⁺.

EXAMPLE 129

25

3-[(1-Acetylpiperidin-4-yl)ethynyl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 17* and *Intermediate 51* according to *Method S* and was isolated as an off-white solid (31%) after purification by column
30 chromatography (SiO₂, 0-2.5% MeOH/EtOAc). δ_H (CDCl₃) 4.02-3.88 (1H, m), 3.84-3.70 (4H, m), 3.63-3.61 (1H, m), 3.56-3.41 (4H, m), 3.34-3.17 (2H, m), 2.99-2.73 (1H, m), 2.51 (2H, s), 2.32 (2H, s), 2.04 (3H, s), 1.92-1.76 (2H, m), 1.68-1.53 (2H, m), 1.03 (6H, s). MS (ES+) 415.0 (M+H)⁺.

EXAMPLE 130

5 5,5-Dimethyl-3-{[1-(methylsulfonyl)piperidin-3-yl]ethynyl}-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and *Intermediate 52* according to *Method S* and was isolated as a white solid (19%) after purification by column chromatography (SiO₂, 60-80% EtOAc/hexanes). δ_{H} (CDCl₃) 3.99-3.77 (4H, m), 3.71-3.55 (5H, m), 3.48-3.39 (1H, m), 3.18-3.03 (2H, m), 3.03-2.90 (1H, m), 2.87-2.77 (3H, m), 2.65-2.56 (2H, m), 2.41 (2H, s), 2.06-1.88 (2H, m), 1.82-1.61 (2H, m), 1.13 (6H, s). MS (ES⁺) 451.0 (M+H)⁺.

EXAMPLE 131

15 5,5-Dimethyl-3-{[1-(methylsulfonyl)piperidin-4-yl]ethynyl}-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and *Intermediate 53* according to *Method S* and was isolated as a white solid (10%) after purification by column chromatography (SiO₂, first column 66% EtOAc/hexanes, second column 2% MeOH/DCM). δ_{H} (DMSO-d₆) 3.85-3.69 (4H, m), 3.64-3.48 (4H, m), 3.43-3.33 (2H, m), 3.12-2.94 (2H, m), 2.93-2.82 (1H, m), 2.88 (3H, s), 2.58 (2H, s), 2.32 (2H, s), 2.04-1.86 (2H, m), 1.75-1.56 (2H, m), 1.03 (6H, s). MS (ES⁺) 451.0 (M+H)⁺.

EXAMPLE 132

25 5,5-Dimethyl-2-(morpholin-4-yl)-3-[3-oxo-3-(pyrrolidin-1-yl)prop-1-yn-1-yl]-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and *Intermediate 54* according to *Method S* and was isolated as a white solid (10%) after purification by column chromatography (SiO₂, EtOAc). δ_{H} (CDCl₃) 4.00-.80 (4H, m), 3.77-3.67 (4H, m), 3.69-3.61 (2H, m), 3.60-3.47 (2H, m), 2.67 (2H, s), 2.42 (2H, s), 2.04-1.91 (2H, m), 1.13 (6H, s), 0.97-0.78 (2H, m). MS (ES⁺) 387.0 (M+H)⁺.

EXAMPLE 133**5,5-Dimethyl-2-(morpholin-4-yl)-3-(3-phenylprop-1-yn-1-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one**

- 5 The *title compound* was prepared from *Example 17* and 3-phenyl-1-propyne according to *Method S* and was isolated as a white solid (24%) after purification by column chromatography (SiO₂, 20-50% EtOAc/hexanes), followed by trituration with Et₂O. δ_{H} (CDCl₃) 7.40-7.34 (4H, m), 7.32-7.23 (1H, m), 3.91 (2H, s), 3.69-3.61 (4H, m), 3.54-3.45 (4H, m), 2.61 (2H, s), 2.33 (2H, s), 1.03 (6H, s). MS (ES⁺) 380.0 (M+H)⁺.

10

EXAMPLE 134 (METHOD T)**5,5-Dimethyl-3-[2-(1-methyl-1H-imidazol-5-yl)ethyl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one**

- 15 A solution of *Example 20* (0.08 g, 0.21 mmol) in MeOH (10 mL) was hydrogenated using an H-cubeTM apparatus under 30 psi of H₂ for 3 cycles, then 40 psi at 40°C for 2 cycles. The solvent was removed *in vacuo*. EtOAc (5 mL) was added. The solid formed was washed with Et₂O and filtered to give the *title compound* (0.05 g, 62%) as an off-white solid that required no further purification. δ_{H} (DMSO-d₆) 8.84 (1H, s),
20 7.33 (1H, s), 3.75 (3H, s), 3.73-3.67 (4H, m), 2.94-2.86 (4H, m), 2.87-2.77 (4H, m), 2.62 (2H, s), 2.38 (2H, s), 1.03 (6H, s). MS (ES⁺) 374.0 (M+H)⁺.

EXAMPLE 135

- 25 **5,5-Dimethyl-3-[2-(1-methyl-1H-imidazol-4-yl)ethyl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one**

- The *title compound* was prepared from *Example 41* according to *Method T* (40 psi at 40°C for 5 cycles) and was isolated as a white solid (57%) that required no further purification. δ_{H} (DMSO-d₆) 7.60 (1H, s), 6.87 (1H, s), 3.79-3.69 (4H, m), 3.59 (3H, s),
30 3.02-2.90 (4H, m), 2.81-2.70 (2H, m), 2.69-2.61 (2H, m), 2.57 (2H, s), 2.35 (2H, s), 1.01 (6H, s). MS (ES⁺) 374.0 (M+H)⁺.

EXAMPLE 136

3-[2-(1-Acetylpiperidin-4-yl)ethyl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 129* according to *Method T* (50 psi at 50°C) and was isolated as a pale yellow solid (75%) that required no further purification. δ_{H} (CDCl_3) 4.74-4.56 (1H, m), 3.86-3.84 (5H, m), 3.02-2.99 (5H, m), 2.56-2.50 (5H, m), 2.45 (2H, s), 2.11 (3H, s), 1.86-1.82 (2H, m), 1.51-1.44 (2H, m), 1.23-1.05 (3H, m), 1.12 (6H, s). MS (ES⁺) 419.0 (M+H)⁺.

EXAMPLE 137

N'-{3-[5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]propyl}-N,N-dimethylsulfamide

The *title compound* was prepared from *Example 124* according to *Method T* (50 psi at 50°C) and was isolated as a pale yellow solid (73%) that required no further purification. δ_{H} (CDCl_3) 5.75 (1H, br. s), 3.93-3.90 (4H, m), 3.04-3.02 (4H, m), 3.01-2.96 (2H, m), 2.81 (6H, s), 2.64 (2H, t, *J* 7.0 Hz), 2.58 (2H, s), 2.46 (2H, s), 1.82-1.79 (2H, m), 1.13 (6H, s). MS (ES⁺) 430.0 (M+H)⁺.

EXAMPLE 138

5,5-Dimethyl-3-[(1-methyl-1H-imidazol-4-yl)acetyl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

To a pH 2 buffer solution (100 mL) was added a solution of *Example 41* (0.16 g, 0.43 mmol) in DMSO (2 mL). The reaction mixture was stirred at r.t. for 16 h then freeze dried. The resulting semi-solid was dissolved in water (50 mL), and EtOAc (50 mL) was added. The layers were separated. The aqueous layer was extracted with DCM (4 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2 , 8% MeOH/EtOAc) gave the *title compound* (0.04 g, 21%) as an off-white solid. δ_{H} (DMSO-d_6), mixture of ketone (major form) and enol (minor form); Ketone form: 7.42 (1H, s), 7.05 (1H, s), 4.08-4.00 (2H, m), 3.82-3.75 (4H, m), 3.58 (3H, s), 3.21-3.12 (4H, m), 2.56 (2H, s), 2.34 (2H, s), 0.95 (6H, s); Enol form: 7.77 (1H, s), 6.91 (1H, s), 5.47 (1H, s), 3.72-3.64 (4H, m), 3.58 (3H, s),

3.29-3.23 (4H, m), 2.61 (2H, s), 2.32 (2H, s), 1.00 (6H, s). Exchangeable proton not visible. MS (ES+) 388.0 (M+H)⁺.

EXAMPLE 139 (METHOD U)

5

1-[5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]-2-(1-methyl-1H-imidazol-4-yl)ethane-1,2-dione

To a stirred solution of *Example 41* (0.10 g, 0.27 mmol) in DMSO (5 mL) was added aqueous 2M HCl (2mL). The reaction mixture was stirred at r.t. for 16 h. EtOAc (40 mL) and water (20 mL) were added and the layers separated. The aqueous layer was taken to pH 9 by slow addition of aqueous sat. NaHCO₃ then extracted into EtOAc (2 x 20 mL). The combined organic layers were washed with brine (20 ml), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 8% MeOH/EtOAc) gave the *title compound* (0.03 g, 30%) as a pale yellow solid. δ_H (DMSO-d₆) 8.12 (1H, s), 7.79 (1H, s), 3.75 (3H, s), 3.49-3.46 (4H, m), 3.07-3.05 (4H, m), 2.75 (2H, s), 2.42 (2H, s), 1.00 (6H, s). MS (ES+) 402.0 (M+H)⁺.

EXAMPLE 140

20 1-[5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]-2-(1-methyl-1H-imidazol-5-yl)ethane-1,2-dione

The *title compound* was prepared from *Example 20* according to *Method U* and was isolated as a pale yellow solid (16%) after purification by column chromatography (SiO₂, 8% MeOH/EtOAc). δ_H (DMSO-d₆) 8.15 (1H, s), 7.69 (1H, s), 3.97 (3H, s), 3.51-3.46 (4H, m), 3.10-3.08 (4H, m), 2.73 (2H, s), 2.43 (2H, s), 1.01 (6H, s). MS (ES+) 401.9 (M+H)⁺.

EXAMPLE 141

30 5,5-Dimethyl-3-[(Z)-2-(1-methyl-1H-imidazol-5-yl)vinyl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

A solution of *Example 20* (0.05 g, 0.14 mmol) in EtOH (5 mL) was hydrogenated using palladium on carbon (0.01 g) and a balloon at r.t. for 48 h. The reaction mixture

was then filtered through Celite[®], and the solvent removed *in vacuo* to give the *title compound* (0.02 g, 32%) that required no further purification. δ_{H} (DMSO- d_6) 7.59 (1H, s), 6.61 (1H, dd, J 11.7 and 0.6 Hz), 6.41 (1H, s), 6.30 (1H, d, J 11.7 Hz), 3.63 (3H, s), 3.64-5.52 (4H, m), 3.25-3.15 (4H, m), 2.27 (2H, s), 2.26 (2H, s), 0.89 (6H, s). MS (ES+) 372.1 (M+H)⁺.

EXAMPLE 142

5,5-Dimethyl-2-(morpholin-4-yl)-3-(phenylethynyl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and phenylacetylene according to *Method C* and was isolated as a fluffy white solid (78%) after trituration of the precipitate, formed upon completion of the reaction, with water. δ_{H} (DMSO- d_6) 7.53-7.48 (2H, m), 7.46-7.38 (3H, m), 3.83-3.75 (4H, m), 3.68-3.60 (4H, m), 2.70 (2H, s), 2.36 (2H, s), 1.07 (6H, s). MS (ES+) 366.0 (M+H)⁺.

EXAMPLE 143

3-[(4-Aminopyridin-3-yl)ethynyl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 38* and 4-amino-3-iodopyridine according to *Method C* and was isolated as an off-white solid (87%) after purification by column chromatography (SiO₂, 10% MeOH/EtOAc), followed by trituration with EtOAc. δ_{H} (DMSO- d_6) 8.20 (1H, s), 7.98 (1H, d, J 5.7 Hz), 6.62 (1H, d, J 5.7 Hz), 6.22 (2H, br. s), 3.78-3.75 (4H, m), 3.65-3.62 (4H, m), 2.74 (2H, s), 2.34 (2H, s), 1.06 (6H, s). MS (ES+) 382.0 (M+H)⁺.

EXAMPLE 144

5,5-Dimethyl-2-(morpholin-4-yl)-3-[(E)-2-phenylvinyl]-5,6-dihydro-1-benzothiophen-7(4H)-one

A mixture of *Example 16* (0.32 g, 0.93 mmol), styreneboronic acid (0.41 g, 2.79 mmol), palladium acetate (0.02 g, 0.08 mmol), 1,3-bis(diphenylphosphino)propane (0.038

g, 0.08 mmol) and K₃PO₄ (0.59 g, 3.30 mmol) in 1,4-dioxane (30 mL) was heated at 90°C for 36 h. The reaction mixture was then concentrated *in vacuo*. Purification by column chromatography (SiO₂, 0-25% EtOAc/hexanes) gave the *title compound* (0.02 g, 7%) as an off-white solid. δ_{H} (DMSO-d₆) 7.61-7.40 (2H, m), 7.40-7.37 (2H, m), 7.30-7.26 (1H, m), 6.99 (2H, s), 3.83-3.73 (4H, m), 3.18-3.08 (4H, m), 2.80 (2H, s), 2.40 (2H, s), 0.96 (6H, s). MS (ES⁺) 368.0 (M+H)⁺.

EXAMPLE 145

10 5,5-Dimethyl-3-(4-methoxyphenyl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 4-methoxyphenylboronic acid according to *Method J* and was isolated as a beige solid (40%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-d₆) 7.34-7.28 (2H, m), 7.05-7.00 (2H, m), 3.79 (3H, s), 3.60-3.54 (4H, m), 2.94-2.88 (4H, m), 2.45 (2H, s), 2.35 (2H, s), 0.95 (6H, s). LCMS (ES⁺) 372.2 (M+H)⁺.

EXAMPLE 146

20 5,5-Dimethyl-3-(3-hydroxyphenyl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 3-hydroxyphenylboronic acid according to *Method J* and was isolated as an off-white solid (71%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-d₆) 9.57 (1H, s), 7.25 (1H, t, *J* 8.1 Hz), 6.80-6.71 (3H, m), 3.61-3.54 (4H, m), 2.96-2.90 (4H, m), 2.45 (2H, s), 2.35 (2H, s), 0.96 (6H, s). LCMS (ES⁺) 358.2 (M+H)⁺.

EXAMPLE 147

30 N-{3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl}acetamide

The *title compound* was prepared from *Example 73* and 3-acetamidobenzeneboronic acid according to *Method L* and was isolated as an off-white solid (77%) after

purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 10.09 (1H, s), 8.75 (1H, d, J 5.1 Hz), 8.47 (1H, s), 7.95 (1H, s), 7.78 (1H, d, J 7.9 Hz), 7.64 (1H, dd, J 7.9, 0.9 Hz), 7.47-7.38 (2H, m), 3.64-3.58 (4H, m), 3.01-2.95 (4H, m), 2.58 (2H, s), 2.39 (2H, s), 2.08 (3H, s), 0.97 (6H, s). LCMS (ES+) 476.3 (M+H)⁺.

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EXAMPLE 148

3-(2-{4-[(Dimethylamino)methyl]phenyl}pyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, acetic acid salt

10 The *title compound* was prepared from *Example 73* and *N,N*-(dimethylamino-methyl)phenyl-4-boronic acid pinacol ester according to *Method L* and was isolated as a brown solid (82%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.73 (1H, d, J 5.1 Hz), 8.11 (2H, d, J 8.3 Hz), 8.01 (1H, s), 7.45-7.37 (3H, m), 3.64-3.55 (4H, m), 3.45 (2H, s), 3.03-2.95 (4H, m), 2.58 (2H, s), 2.39 (2H, s), 2.17 (6H, s), 1.89 (6H, s),
15 0.97 (6H, s). LCMS (ES+) 476.2 (M+H)⁺.

EXAMPLE 149

3-[3-(Benzyloxy)phenyl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

20 The *title compound* was prepared from *Example 17* and 3-benzyloxyphenyl-boronic acid according to *Method L* and was isolated as an off-white solid (3%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 7.49-7.30 (6H, m), 7.04-6.92 (3H, m), 5.16 (2H, s), 3.56-3.49 (4H, m), 2.93-2.86 (4H, m), 2.39 (2H, s), 2.34 (2H, s),
25 0.94 (6H, s). LCMS (ES+) 448.2 (M+H)⁺.

EXAMPLE 150

5,5-Dimethyl-3-[2-(4-hydroxyphenyl)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

30 The *title compound* was prepared from *Example 73* and 4-hydroxyphenylboronic acid according to *Method L* and was isolated as a brown solid (40%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 9.82 (1H, br s), 8.66 (1H, d, J 5.1 Hz), 7.99

(2H, d, J 8.9 Hz), 7.87 (1H, s), 7.29 (1H, dd, J 4.9, 1.3 Hz), 6.88 (2H, d, J 8.9 Hz), 3.64-3.54 (4H, m), 3.02-2.93 (4H, m), 2.57 (2H, s), 2.38 (2H, s), 0.97 (6H, s). LCMS (ES+) 435.3 (M+H)⁺.

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EXAMPLE 151

5,5-Dimethyl-3-[2-(4-methoxyphenyl)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, formic acid salt

The *title compound* was prepared from *Example 73* and 4-methoxyphenylboronic acid according to *Method L* and was isolated as an off-white solid (30%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.69 (1H, d, J 4.9 Hz), 8.17 (1H, s), 8.11 (2H, d, J 8.9 Hz), 7.95 (1H, s), 7.33 (1H, dd, J 5.1, 1.3 Hz), 7.07 (2H, d, J 8.9 Hz), 3.83 (3H, s), 3.63-3.55 (4H, m), 3.02-2.94 (4H, m), 2.58 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES+) 435.3 (M+H)⁺.

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EXAMPLE 152

3-{2-[3-(Dimethylamino)phenyl]pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 73* and 3-(*N,N*-dimethylamino)-phenylboronic acid according to *Method L* and was isolated as an off-white solid (50%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.73 (1H, d, J 4.9 Hz), 8.01 (1H, s), 7.49-7.28 (4H, m), 6.83 (1H, dd, J 7.9, 2.1 Hz), 3.66-3.56 (4H, m), 3.05-2.94 (10H, m), 2.60 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES+) 462.3 (M+H)⁺.

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EXAMPLE 153

N-{4-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl}acetamide

The *title compound* was prepared from *Example 73* and 4-acetamidophenylboronic acid according to *Method L* and was isolated as an off-white solid (44%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 10.12 (1H, s), 8.70 (1H, d, J 4.9 Hz), 8.10 (2H, d, J 8.7 Hz), 7.96 (1H, s), 7.72 (2H, d, J 8.7 Hz), 7.35 (1H, dd, J 5.1,

1.3 Hz), 3.64-3.56 (4H, m), 3.03-2.94 (4H, m), 2.58 (2H, s), 2.39 (2H, s), 2.08 (3H, s), 0.97 (6H, s). LCMS (ES+) 476.3 (M+H)⁺.

EXAMPLE 154

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3-{2-[4-(Dimethylamino)phenyl]pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 73* and 4-(*N,N*-dimethylamino)-phenylboronic acid according to *Method L* and was isolated as a green-blue solid (10%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.63 (1H, d, *J* 4.9 Hz), 8.01 (2H, d, *J* 9.0 Hz), 7.86 (1H, s), 7.22 (1H, dd, *J* 5.1, 1.3 Hz), 6.81 (2H, d, *J* 9.0 Hz), 3.56-3.64 (4H, m), 3.04-2.95 (10H, m), 2.58 (2H, s), 2.38 (2H, s), 0.97 (6H, s). LCMS (ES+) 462.3 (M+H)⁺.

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EXAMPLE 155

5,5-Dimethyl-3-{2-[3-(hydroxymethyl)phenyl]pyridin-4-yl}-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 73* and 3-(hydroxymethyl)-phenylboronic acid according to *Method L* and was isolated as a white solid (50%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.75 (1H, d, *J* 4.9 Hz), 8.12 (1H, s), 8.04-7.97 (2H, m), 7.51-7.38 (3H, m), 5.29 (1H, t, *J* 5.8 Hz), 4.60 (2H, d, *J* 5.8 Hz), 3.65-3.55 (4H, m), 3.04-2.94 (4H, m), 2.58 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES+) 449.2 (M+H)⁺.

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EXAMPLE 156

5,5-Dimethyl-3-(3-methoxyphenyl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 3-methoxyphenylboronic acid according to *Method J* and was isolated as a pale yellow solid (56%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_{H} (CD₃OD)

7.43-7.35 (1H, m), 6.97-6.91 (3H, m), 3.84 (3H, s), 3.71-3.61 (4H, m), 3.09-3.00 (4H, m), 2.51 (2H, s), 2.43 (2H, s), 1.03 (6H, s). LCMS (ES⁺) 372.3 (M+H)⁺.

EXAMPLE 157

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5,5-Dimethyl-3-(3-ethoxyphenyl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 3-ethoxyphenylboronic acid according to *Method J* and was isolated as a white solid (44%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_{H} (CDCl₃) 7.36-7.29 (1H, m), 6.92-6.84 (3H, m), 4.06 (2H, q, *J* 7.0 Hz), 3.70-3.62 (4H, m), 3.04-2.96 (4H, m), 2.46 (2H, s), 2.42 (2H, s), 1.45 (3H, t, *J* 7.0 Hz), 1.03 (6H, s). LCMS (ES⁺) 386.3 (M+H)⁺.

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EXAMPLE 158

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3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzaldehyde

The *title compound* was prepared from *Example 73* and 3-formylphenylboronic acid according to *Method L* and was isolated as an off-white solid (10%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-*d*₆) 10.14 (1H, s), 8.80 (1H, d, *J* 4.9 Hz), 8.73-8.71 (1H, m), 8.52-8.47 (1H, m), 8.16 (1H, d, *J* 0.4 Hz), 8.00 (1H, d, *J* 7.5 Hz), 7.76 (1H, t, *J* 7.7 Hz), 7.48 (1H, dd, *J* 5.3, 1.5 Hz), 3.65-3.56 (4H, m), 3.04-2.96 (4H, m), 2.59 (2H, s), 2.39 (2H, s), 0.98 (6H, s). LCMS (ES⁺) 447.2 (M+H)⁺.

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EXAMPLE 159

3-{2-[3-(Aminomethyl)phenyl]pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

A solution of *Example 224* (115 mg, 0.21 mmol) in methanol (8.0 mL) was treated with a 2N solution of HCl in Et₂O (4.0 mL, 2.0 mmol). After stirring for 19 h at room temperature, the solvent was removed *in vacuo*. The orange residue was purified by preparative HPLC (pH 2.5), then partitioned between 1M NaOH solution (3 mL) and EtOAc (10 mL). The organic phase was purified by column chromatography (SiO₂, 2%

30

NH₄OH, 20% MeOH in EtOAc) to give the *title compound* (35 mg, 49%) as an off-white solid. δ_{H} (CD₃OD) 8.76-8.71 (1H, m), 8.07-8.03 (1H, m), 8.00-7.93 (2H, m), 7.60-7.45 (3H, m), 4.02 (2H, s), 3.73-3.63 (4H, m), 3.13-3.04 (4H, m), 2.63 (2H, s), 2.48 (2H, s), 1.06 (6H, s). LCMS (ES+) 448.3 (M+H)⁺.

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EXAMPLE 160

3-{2-[3-(Aminomethyl)phenyl]pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, formic acid salt

10 The *title compound* was prepared from *Example 73* and 3-(aminomethyl)phenylboronic acid hydrochloride according to *Method L* and was isolated as a clear glass (15%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-d₆) 8.75 (1H, d, *J* 5.1 Hz), 8.29 (1H, s), 8.19 (1H, s), 8.10-8.02 (2H, m), 7.55-7.40 (3H, m), 3.97 (2H, s), 3.65-3.56 (4H, m), 3.03-2.95 (4H, m), 2.57 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES+) 448.4
15 (M+H)⁺.

EXAMPLE 161

3-[2-(1-Benzothien-3-yl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

20 The *title compound* was prepared from *Example 73* and 1-benzothiophen-3-ylboronic acid according to *Method L* and was isolated as a clear glass (8%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-d₆) 8.78-8.84 (2H, m), 8.43 (1H, s), 8.07-8.12 (1H, m), 7.98 (1H, s), 7.43-7.54 (3H, m), 3.59-3.66 (4H, m), 2.97-3.05 (4H, m), 2.62 (2H, s), 2.40 (2H, s), 0.99 (6H, s). LCMS (ES+) 475.2 (M+H)⁺.
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EXAMPLE 162

3-[2-(1-Benzofuran-2-yl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, formic acid salt

30 The *title compound* was prepared from *Example 73* and benzo[*b*]furan-2-boronic acid according to *Method L* and was isolated as a clear glass (3%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-d₆) 8.76 (1H, d, *J* 5.1 Hz), 8.30 (1H, s), 8.04

(1H, s), 7.79-7.65 (3H, m), 7.48-7.29 (3H, m), 3.65-3.58 (4H, m), 3.05-2.98 (4H, m), 2.60 (2H, s), 2.41 (2H, s), 0.98 (6H, s). LCMS (ES+) 459.3 (M+H)⁺.

EXAMPLE 163

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3-[2-(Benzyloxy)phenyl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 2-benzyloxyphenyl-boronic acid according to *Method J* and was isolated as a white solid (44%) after
10 purification by preparative HPLC (pH 2.5). δ_H (CD₃OD) 7.43-7.18 (8H, m), 7.10-7.03 (1H, m), 5.13 (2H, s), 3.61-3.48 (4H, m), 3.09-2.98 (4H, m), 2.44-2.26 (4H, m), 0.98 (3H, s), 0.93 (3H, s). LCMS (ES+) 448.2 (M+H)⁺.

EXAMPLE 164

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5,5-Dimethyl-2-(morpholin-4-yl)-3-(1-naphthyl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 1-naphthaleneboronic acid according to *Method J* and was isolated as an off-white solid (31%) after purification by
20 preparative HPLC (pH 2.5). δ_H (CDCl₃) 7.95-7.87 (2H, m), 7.67-7.61 (1H, m), 7.58-7.45 (3H, m), 7.41-7.37 (1H, m), 3.51-3.33 (4H, m), 2.98-2.85 (4H, m), 2.42 (2H, s), 0.96 (3H, s), 2.16 (2H, q, *J* 16.8 Hz), 0.97 (3H, s). LCMS (ES+) 392.3 (M+H)⁺.

EXAMPLE 165

25 3-(Dibenzo[*b,d*]thien-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and dibenzothiophene-4-boronic acid according to *Method J* and was isolated as an off-white solid (48%) after
30 purification by preparative HPLC (pH 2.5). δ_H (CDCl₃) 8.23-8.16 (2H, m), 7.89-7.83 (1H, m), 7.59-7.46 (3H, m), 7.37-7.32 (1H, m), 3.60-3.44 (4H, m), 3.05-2.97 (4H, m), 2.42 (2H, s), 2.30 (2H, m), 0.99 (6H, s). LCMS (ES+) 448.3 (M+H)⁺.

EXAMPLE 166

5,5-Dimethyl-3-{2-[4-(hydroxymethyl)phenyl]pyridin-4-yl}-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 73* and 4-(hydroxymethyl)-phenylboronic acid according to *Method L* and was isolated as an off-white solid (61%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.72 (1H, d, *J* 5.1 Hz), 8.11 (2H, d, *J* 8.3 Hz), 8.01 (1H, s), 7.45 (2H, d, *J* 8.3 Hz), 7.36-7.41 (1H, m), 5.27 (1H, t, *J* 5.7 Hz), 4.57 (2H, d, *J* 5.5 Hz), 3.65-3.55 (4H, m), 3.04-2.94 (4H, m), 2.58 (2H, s), 2.38 (2H, s), 0.97 (6H, s). LCMS (ES⁺) 449.3 (M+H)⁺.

EXAMPLE 167

3-[2-(1-Benzothien-2-yl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 73* and benzo[*b*]thiophene-2-boronic acid according to *Method L* and was isolated as an off-white solid (7%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.68 (1H, d, *J* 5.1 Hz), 8.28 (1H, s), 8.19 (1H, s), 8.04-7.99 (1H, m), 7.92-7.87 (1H, m), 7.45-7.39 (3H, m), 3.67-3.59 (4H, m), 3.06-2.98 (4H, m), 2.61 (2H, s), 2.40 (2H, s), 0.98 (6H, s). LCMS (ES⁺) 475.2 (M+H)⁺.

EXAMPLE 168

5,5-Dimethyl-3-[2-(1H-indol-6-yl)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 73* and indole-6-boronic acid according to *Method L* and was isolated as an off-white solid (42%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 11.30 (1H, s), 8.71 (1H, d, *J* 4.9 Hz), 8.21 (1H, s), 7.99 (1H, s), 7.83-7.76 (1H, m), 7.68-7.61 (1H, m), 7.49-7.44 (1H, m), 7.35-7.29 (1H, m), 6.48 (1H, s), 3.67-3.57 (4H, m), 3.06-2.96 (4H, m), 2.61 (2H, s), 2.40 (2H, s), 0.98 (6H, s). LCMS (ES⁺) 458.2 (M+H)⁺.

EXAMPLE 169

N-{3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzyl}methanesulfonamide

The *title compound* was prepared from *Example 73* and 3-(methanesulfonyl-aminomethyl)phenylboronic acid according to *Method L* and was isolated as an off-white solid (39%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.76 (1H, d, J 4.9 Hz), 8.16 (1H, s), 8.08-8.02 (2H, m), 7.69-7.62 (1H, m), 7.55-7.40 (3H, m), 4.26 (2H, d, J 6.2 Hz), 3.64-3.56 (4H, m), 3.02-2.95 (4H, m), 2.90 (3H, s), 2.58 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES+) 526.2 (M+H)⁺.

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EXAMPLE 170

3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]-N,N-dimethylbenzamide

The *title compound* was prepared from *Example 73* and 3-(N,N-dimethylaminocarbonyl)phenylboronic acid according to *Method L* and was isolated as an off-white solid (33%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.76 (1H, d, J 5.1 Hz), 8.26-8.21 (1H, m), 8.18 (1H, s), 8.10 (1H, s), 7.59 (1H, t, J 7.7 Hz), 7.52-7.47 (1H, m), 7.44 (1H, dd, J 4.9, 1.1 Hz), 3.64-3.55 (4H, m), 3.08-2.93 (10H, m), 2.59 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES+) 490.2 (M+H)⁺.

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EXAMPLE 171 (METHOD AA)

N-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-1-phenylmethanesulfonamide

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A solution of *Example 78* (50 mg, 0.14 mmol) in anhydrous DMF (2.0 mL) was treated with α -toluenesulfonyl chloride (40 mg, 0.21 mmol) and triethylamine (0.06 mL, 0.42 mmol). The reaction mixture was stirred at room temperature for 18 h, then quenched by the addition of a few drops of water and the solvent removed *in vacuo*. The *title compound* was obtained as a pale orange solid (26 mg, 36%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl₃) 7.41-7.28 (7H, m), 7.20-7.14 (2H, m), 6.28 (1H, s), 4.42 (2H, s), 3.72-3.63 (4H, m), 3.03-2.94 (4H, m), 2.46 (4H, d, J 7.5 Hz), 1.06 (6H, s). LCMS (ES+) 511.1 (M+H)⁺.

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EXAMPLE 172

N-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-3,5-dimethylisoxazole-4-sulfonamide

The *title compound* was prepared from *Example 78* and 3,5-dimethylisoxazole-4-sulfonyl chloride according to *Method AA* and was isolated as a pale yellow solid (9%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 7.36-7.30 (2H, m), 7.19-7.14 (2H, m), 6.78 (1H, s), 3.68-3.60 (4H, m), 2.99-2.91 (4H, m), 2.53 (3H, s), 2.43 (2H, s), 2.40 (2H, s), 2.32 (3H, s), 1.03 (6H, s). LCMS (ES⁺) 516.1 (M+H)⁺.

EXAMPLE 173

5,5-Dimethyl-3-(2-methoxyphenyl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 17* and 2-methoxyphenylboronic acid according to *Method J* and was isolated as a clear oil (14%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 7.40-7.33 (1H, m), 7.25-7.20 (1H, m), 7.05-6.96 (2H, m), 3.81 (3H, s), 3.66-3.58 (4H, m), 3.05-2.96 (4H, m), 2.51-2.33 (3H, m), 2.25-2.15 (1H, m), 1.05 (3H, s), 0.98 (3H, s). LCMS (ES⁺) 372.2 (M+H)⁺.

EXAMPLE 174

3-[3'-(Dimethylamino)biphenyl-3-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 17*, 3-bromophenylboronic acid and 3-(*N,N*-dimethylamino)phenylboronic acid according to *Method K* and was isolated as a white solid (31%) after purification by preparative HPLC (pH 5.8). δ_{H} (CD_3OD) 7.66-7.60 (2H, m), 7.59-7.51 (1H, m), 7.39-7.28 (2H, m), 7.02-6.95 (2H, m), 6.86-6.80 (1H, m), 3.71-3.62 (4H, m), 3.12-3.04 (4H, m), 3.02 (6H, s), 2.59 (2H, s), 2.46 (2H, s), 1.05 (6H, s). LCMS (ES⁺) 461.3 (M+H)⁺.

EXAMPLE 175

5,5-Dimethyl-3-(isoquinolin-5-yl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, acetic acid salt

The *title compound* was prepared from *Example 17* and isoquinoline-5-boronic acid according to *Method J* and was isolated as a white solid (31%) after purification by preparative HPLC (pH 5.8). δ_{H} (CD_3OD) 9.36 (1H, s), 8.49 (1H, d, J 6.0 Hz), 8.22 (1H, dd, J 7.9, 0.9 Hz), 7.88-7.77 (2H, m), 7.58 (1H, d, J 6.0 Hz), 3.52-3.35 (4H, m), 3.05-2.89 (4H, m), 2.45 (2H, d, J 5.5 Hz), 2.41-2.10 (2H, m), 1.01 (3H, s), 0.96 (3H, s). LCMS (ES+) 393.2 (M+H)⁺.

EXAMPLE 176

3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzonitrile

The *title compound* was prepared from *Example 73* and 3-cyanophenylboronic acid according to *Method L* and was isolated as an off-white solid (52%) after purification by preparative HPLC (pH 5.8). δ_{H} ($\text{DMSO}-d_6$) 8.79 (1H, d, J 5.1 Hz), 8.59 (1H, s), 8.51 (1H, m), 8.18 (1H, s), 7.94 (1H, m), 7.74 (1H, t, J 7.9 Hz), 7.49 (1H, dd, J 4.9, 1.3 Hz), 3.64-3.54 (4H, m), 3.04-2.94 (4H, m), 2.58 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES+) 444.3 (M+H)⁺.

EXAMPLE 177

4-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzonitrile

The *title compound* was prepared from *Example 73* and 4-cyanophenylboronic acid according to *Method L* and was isolated as an off-white solid (33%) after purification by preparative HPLC (pH 2.5). δ_{H} ($\text{DMSO}-d_6$) 8.81 (1H, d, J 5.1 Hz), 8.36 (2H, d, J 8.5 Hz), 8.18 (1H, s), 7.99 (2H, d, J 8.5 Hz), 7.51 (1H, dd, J 4.9, 1.3 Hz), 3.64-3.54 (4H, m), 3.02-2.94 (4H, m), 2.59 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES+) 444.2 (M+H)⁺.

EXAMPLE 178

5,5-Dimethyl-2-(morpholin-4-yl)-3-[3-(pyridin-3-yl)phenyl]-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17*, 3-bromophenylboronic acid and pyridine-3-boronic acid 1,3-propanediol cyclic ester according to *Method K* and was isolated as a white solid (25%) after purification by preparative HPLC (pH 5.8). δ_{H} (CDCl_3) 8.89 (1H, d, J 1.9 Hz), 8.64 (1H, dd, J 4.7, 1.5 Hz), 7.95-7.89 (1H, m), 7.63-7.60 (1H, m), 7.59-7.55 (2H, m), 7.45-7.38 (2H, m), 3.70-3.62 (4H, m), 3.05-2.98 (4H, m), 2.51 (2H, s), 2.45 (2H, s), 1.05 (6H, s). LCMS (ES+) 419.2 (M+H)⁺.

EXAMPLE 179

5',5'-Dimethyl-2'-(morpholin-4-yl)-5',6'-dihydro-2,3'-bi-1-benzothiophen-7'(4H)-one

The *title compound* was prepared from *Example 17* and thianaphthene-2-boronic acid according to *Method J* and was isolated as an off-white solid (10%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-d_6) 8.02-7.96 (1H, m), 7.93-7.86 (1H, m), 7.47 (1H, s), 7.44-7.35 (2H, m), 3.71-3.62 (4H, m), 3.11-3.03 (4H, m), 2.63 (2H, s), 2.40 (2H, s), 0.99 (6H, s). LCMS (ES+) 398.2 (M+H)⁺.

EXAMPLE 180

3-(1-Benzofuran-2-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 2-benzofuranboronic acid according to *Method J* and was isolated as an off-white solid (5%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-d_6) 7.71-7.66 (1H, m), 7.62 (1H, d, J 7.5 Hz), 7.37-7.25 (2H, m), 7.04 (1H, s), 3.74-3.65 (4H, m), 3.12-3.03 (4H, m), 2.68 (2H, s), 2.39 (2H, s), 1.01 (6H, s). LCMS (ES+) 382.2 (M+H)⁺.

EXAMPLE 181

N-{4-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzyl}methanesulfonamide, formic acid salt

The *title compound* was prepared from *Example 73* and 4-(methanesulfonyl-aminomethyl)phenylboronic acid according to *Method L* and was isolated as a brown solid (52%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.74 (1H, d, J 4.9 Hz), 8.15 (2H, d, J 8.1 Hz), 8.04 (1H, s), 7.68-7.60 (2H, m), 7.49 (2H, d, J 8.3 Hz), 7.43-7.37 (1H, m), 4.27-4.22 (2H, m), 3.65-3.56 (4H, m), 3.03-2.96 (4H, m), 2.90 (3H, s), 2.59 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES+) 526.2 (M+H)⁺.

EXAMPLE 182

10 3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]-N-methylbenzamide

The *title compound* was prepared from *Example 73* and 3-(N-methylamino-carbonyl)phenylboronic acid according to *Method L* and was isolated as a pale yellow solid (24%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.78 (1H, d, J 4.9 Hz), 8.64-8.57 (2H, m), 8.30 (1H, d, J 7.7 Hz), 8.13 (1H, s), 7.92 (1H, d, J 7.9 Hz), 7.61 (1H, t, J 7.7 Hz), 7.44 (1H, dd, J 4.9, 1.1 Hz), 3.64-3.56 (4H, m), 3.04-2.95 (4H, m), 2.83 (3H, d, J 4.5 Hz), 2.59 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES+) 476.4 (M+H)⁺.

20 EXAMPLE 183

N-{4-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzyl}acetamide

The *title compound* was prepared from *Example 73* and 4-(acetamidomethyl)-phenylboronic acid according to *Method L* and was isolated as a yellow solid (59%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.73 (1H, d, J 5.1 Hz), 8.42 (1H, t, J 5.8 Hz), 8.11 (2H, d, J 8.3 Hz), 8.02 (1H, s), 7.44-7.34 (3H, m), 4.32 (2H, d, J 5.8 Hz), 3.65-3.55 (4H, m), 3.05-2.93 (4H, m), 2.59 (2H, s), 2.39 (2H, s), 1.90 (3H, s), 0.97 (6H, s). LCMS (ES+) 490.4 (M+H)⁺.

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EXAMPLE 184

4-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]-N-methylbenzamide

The *title compound* was prepared from *Example 73* and 4-(*N*-methylamino-carbonyl)phenylboronic acid according to *Method L* and was isolated as a pale yellow solid (46%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.77 (1H, d, *J* 5.1 Hz), 8.60-8.51 (1H, m), 8.25 (2H, d, *J* 8.5 Hz), 8.12 (1H, s), 7.97 (2H, d, *J* 8.5 Hz), 7.45 (1H, dd, *J* 5.1, 1.3 Hz), 3.64-3.55 (4H, m), 3.03-2.94 (4H, m), 2.81 (3H, d, *J* 4.5 Hz), 2.59 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES⁺) 476.4 (M+H)⁺.

EXAMPLE 185

5,5-Dimethyl-3-(3-isobutoxyphenyl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 3-isobutoxyphenylboronic acid according to *Method J* and was isolated as an off-white solid (58%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 7.41-7.33 (1H, m), 6.97-6.88 (3H, m), 3.77 (2H, d, *J* 6.6 Hz), 3.63-3.52 (4H, m), 2.98-2.88 (4H, m), 2.47 (2H, s), 2.35 (2H, s), 2.10-1.97 (1H, m), 0.99 (6H, d, *J* 6.8 Hz), 0.96 (6H, s). LCMS (ES⁺) 414.3 (M+H)⁺.

EXAMPLE 186

3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzamide

The *title compound* was prepared from *Example 73* and 3-(aminocarbonyl)-phenylboronic acid according to *Method L* and was isolated as an off-white solid (51%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.78 (1H, d, *J* 5.1 Hz), 8.62 (1H, s), 8.31 (1H, d, *J* 7.9 Hz), 8.15 (2H, s), 7.96 (1H, d, *J* 7.5 Hz), 7.61 (1H, t, *J* 7.7 Hz), 7.51-7.41 (2H, m), 3.65-3.55 (4H, m), 3.05-2.94 (4H, m), 2.59 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES⁺) 462.4 (M+H)⁺.

EXAMPLE 187

4-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzamide

The *title compound* was prepared from *Example 73* and 4-(aminocarbonyl)-phenylboronic acid according to *Method L* and was isolated as a pale yellow solid (31%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.78 (1H, d, J 5.1 Hz), 8.24 (2H, d, J 8.5 Hz), 8.12 (1H, s), 8.07 (1H, s), 8.01 (2H, d, J 8.3 Hz), 7.45 (2H, d, J 3.6 Hz), 3.65-3.56 (4H, m), 3.05-2.94 (4H, m), 2.60 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES+) 462.2 (M+H)⁺.

EXAMPLE 188

3-{2-[2-(Aminomethyl)-4-fluorophenyl]pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, formic acid salt

The *title compound* was prepared from *Example 73* and 2-(aminomethyl)-4-fluorophenylboronic acid hydrochloride according to *Method L* and was isolated as an off-white solid (25%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.74 (1H, d, J 5.1 Hz), 8.28 (1H, s), 7.64 (1H, s), 7.58 (1H, dd, J 8.5, 6.0 Hz), 7.53-7.46 (2H, m), 7.27 (1H, td, J 8.5, 2.6 Hz), 3.87 (2H, s), 3.67-3.56 (4H, m), 3.03-2.93 (4H, m), 2.58 (2H, s), 2.39 (2H, s), 0.98 (6H, s). LCMS (ES+) 466.2 (M+H)⁺.

EXAMPLE 189

3-{2-[2-(Aminomethyl)-5-fluorophenyl]pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, formic acid salt

The *title compound* was prepared from *Example 73* and 2-(aminomethyl)-5-fluorophenylboronic acid hydrochloride according to *Method L* and was isolated as a brown solid (49%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.76 (1H, d, J 5.1 Hz), 8.33 (1H, s), 7.76 (1H, s), 7.66 (1H, dd, J 8.5, 6.0 Hz), 7.55 (1H, dd, J 5.3, 1.5 Hz), 7.43 (1H, dd, J 10.0, 2.6 Hz), 7.35 (1H, td, J 8.5, 2.6 Hz), 3.88 (2H, s), 3.65-3.55 (4H, m), 3.03-2.92 (4H, m), 2.59 (2H, s), 2.39 (2H, s), 0.98 (6H, s). LCMS (ES+) 466.1 (M+H)⁺.

EXAMPLE 190

3-Amino-4-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzonitrile

The *title compound* was prepared from *Example 73* and 2-amino-4-cyanophenylboronic acid hydrochloride according to *Method L* and was isolated as an off-white solid (45%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.73 (1H, d, J 5.1 Hz), 7.91 (1H, s), 7.79 (1H, d, J 8.3 Hz), 7.45 (1H, dd, J 5.1, 1.1 Hz), 7.17 (1H, d, J 1.7 Hz), 7.08 (2H, s), 7.01 (1H, dd, J 8.1, 1.7 Hz), 3.65-3.56 (4H, m), 3.03-2.93 (4H, m), 2.57 (2H, s), 2.38 (2H, s), 0.97 (6H, s). LCMS (ES⁺) 459.2 (M+H)⁺.

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EXAMPLE 191

3-[2-(2-Aminophenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 73* and 2-aminophenylboronic acid according to *Method L* and was isolated as a pale yellow solid (47%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.67 (1H, d, J 5.1 Hz), 7.80 (1H, s), 7.62-7.57 (1H, m), 7.35 (1H, dd, J 4.9, 0.8 Hz), 7.15-7.08 (1H, m), 6.79 (1H, d, J 7.9 Hz), 6.73-6.61 (3H, m), 3.66-3.56 (4H, m), 3.03-2.94 (4H, m), 2.58 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES⁺) 434.4 (M+H)⁺.

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EXAMPLE 192

5,5-Dimethyl-3-{4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl}-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

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The *title compound* was prepared from *Example 17* and 4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-[4-(trifluoromethyl)phenyl]-1,3-thiazole according to *Method J*, heating for 40 minutes at 130°C, and was isolated as a yellow solid (30%) after purification by column chromatography (SiO₂, 0-50% EtOAc/heptane). δ_{H} (DMSO- d_6) 8.17 (2H, d, J 8.5 Hz), 7.88 (2H, d, J 8.5 Hz), 3.67-3.59 (4H, m), 3.13-3.04 (4H, m), 2.41 (2H, s), 2.38 (2H, s), 2.30 (3H, s), 0.99 (6H, s). LCMS (ES⁺) 507.2 (M+H)⁺.

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EXAMPLE 193**5,5-Dimethyl-3-(4-methoxybiphenyl-3-yl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one**

5 A mixture of *Example 17* (50 mg, 0.13 mmol), 5-bromo-2-methoxyphenylboronic acid (30 mg, 0.13 mmol), 2M aqueous sodium carbonate solution (0.14 mL, 0.28 mmol) and Pd(PPh₃)₄ (4.4 mg, 0.004 mmol) in DME (0.3 mL) and water (0.1 mL) was heated to 150°C in a sealed tube, under microwave irradiation, for 10 minutes. Phenylboronic acid (16 mg, 0.13 mmol) was then added and the reaction mixture was heated again to 150°C
10 in a sealed tube, under microwave irradiation, for 5 minutes. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC (pH 2.5) to give the *title compound* (3.2 mg, 6%) as a cream solid. δ_{H} (CDCl₃) 7.64-7.56 (3H, m), 7.53-7.31 (4H, m), 7.05 (1H, d, *J* 8.5 Hz), 3.85 (3H, s), 3.65-3.59 (4H, m), 3.07-3.00 (4H, m), 2.51-2.21 (4H, m), 1.07 (3H, s), 0.99 (3H, s). LCMS (ES⁺) 448.2 (M+H)⁺.

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EXAMPLE 194**3-{2-[4-(Aminomethyl)phenyl]pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, formic acid salt**

20 The *title compound* was prepared from *Example 73* and 4-(aminomethyl)phenylboronic acid hydrochloride according to *Method L* and was isolated as a pale yellow solid (36%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-*d*₆) 8.74 (1H, d, *J* 5.1 Hz), 8.32 (1H, s), 8.21-8.01 (4H, m), 7.54 (2H, d, *J* 8.3 Hz), 7.41 (2H, dd, *J* 4.9, 1.1 Hz), 3.95 (2H, s), 3.64-3.55 (4H, m), 3.04-2.94 (4H, m), 2.59 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES⁺) 448.4 (M+H)⁺.

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EXAMPLE 195**N-{3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzyl}acetamide**

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 The *title compound* was prepared from *Example 73* and 3-(acetamidomethyl)-phenylboronic acid according to *Method L* and was isolated as a yellow solid (61%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-*d*₆) 8.75 (1H, d, *J* 5.1 Hz), 8.43

(1H, t, *J* 5.7 Hz), 8.08-7.97 (3H, m), 7.47 (1H, t, *J* 7.7 Hz), 7.41 (1H, dd, *J* 5.1, 1.3 Hz), 7.37-7.32 (1H, m), 4.35 (2H, d, *J* 6.0 Hz), 3.64-3.56 (4H, m), 3.02-2.94 (4H, m), 2.58 (2H, s), 2.39 (2H, s), 1.89 (3H, s), 0.97 (6H, s). LCMS (ES+) 490.4 (M+H)⁺.

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EXAMPLE 196

4-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]-*N,N*-dimethylbenzamide

The *title compound* was prepared from *Example 73* and 4-(*N,N*-dimethylaminocarbonyl)phenylboronic acid according to *Method L* and was isolated as a yellow solid (9%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-*d*₆) 8.77 (1H, d, *J* 5.1 Hz), 8.21 (2H, d, *J* 8.3 Hz), 8.07 (1H, s), 7.54 (2H, d, *J* 8.1 Hz), 7.44 (1H, dd, *J* 4.9, 1.1 Hz), 3.63-3.56 (4H, m), 3.06-2.94 (10H, m), 2.59 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES+) 490.4 (M+H)⁺.

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EXAMPLE 197

5,5-Dimethyl-3-[2-(isoquinolin-5-yl)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 73* and 5-isoquinolineboronic acid according to *Method L* and was isolated as a brown solid (64%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-*d*₆) 9.43 (1H, s), 8.87 (1H, d, *J* 5.1 Hz), 8.54 (1H, d, *J* 6.0 Hz), 8.26 (1H, d, *J* 8.1 Hz), 8.10 (1H, d, *J* 6.0 Hz), 7.99 (1H, dd, *J* 7.0, 0.9 Hz), 7.89-7.80 (1H, m), 7.74 (1H, s), 7.59 (1H, dd, *J* 5.1, 1.5 Hz), 3.68-3.57 (4H, m), 3.06-2.96 (4H, m), 2.64 (2H, s), 2.39 (2H, s), 1.00 (6H, s). LCMS (ES+) 470.4 (M+H)⁺.

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EXAMPLE 198

3-(2-{2-[(Dimethylamino)methyl]phenyl}pyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

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The *title compound* was prepared from *Example 73* and 2-(*N,N*-dimethylaminomethyl)phenylboronic acid according to *Method L* and was isolated as a yellow glass (30%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO-*d*₆) 8.72 (1H, d,

J 5.1 Hz), 8.18 (1H, s), 7.59 (1H, s), 7.56-7.38 (4H, m), 3.64-3.53 (6H, m), 3.03-2.95 (4H, m), 2.55 (2H, s), 2.38 (2H, s), 2.06 (6H, s), 0.97 (6H, s). LCMS (ES+) 476.4 (M+H)⁺.

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EXAMPLE 199

3-Amino-4-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzoic acid, acetic acid salt

The *title compound* was prepared from *Example 73* and 2-amino-4-carboxy-phenylboronic acid according to *Method L* and was isolated as a brown solid (6%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.69 (1H, d, *J* 5.1 Hz), 7.84 (1H, s), 7.62 (1H, d, *J* 8.3 Hz), 7.41-7.34 (2H, m), 7.15 (1H, dd, *J* 8.1, 1.5 Hz), 6.75 (2H, br s), 3.66-3.57 (4H, m), 3.03-2.95 (4H, m), 2.58 (2H, s), 2.39 (2H, s), 1.89 (6H, s), 0.97 (6H, s). LCMS (ES+) 478.4 (M+H)⁺.

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EXAMPLE 200

4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)benzoic acid

The *title compound* was prepared from *Example 17* and 4-carboxyphenylboronic acid according to *Method J* and was isolated as a pale yellow solid (23%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl₃) 8.19 (2H, d, *J* 8.2 Hz), 7.51 (2H, d, *J* 8.2 Hz), 3.72-3.64 (4H, m), 3.03-2.94 (4H, m), 2.48 (2H, s), 2.45 (2H, s), 1.04 (6H, s). LCMS (ES+) 386.2 (M+H)⁺.

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EXAMPLE 201

3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)benzoic acid

The *title compound* was prepared from *Example 17* and 3-carboxyphenylboronic acid according to *Method J* and was isolated as a pale yellow solid (19%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl₃) 8.16 (1H, s), 8.09 (1H, d, *J* 7.3

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Hz), 7.67-7.54 (2H, m), 3.71-3.63 (4H, m), 3.03-2.94 (4H, m), 2.48 (2H, s), 2.46 (2H, s), 1.05 (6H, s). LCMS (ES+) 386.2 (M+H)⁺.

EXAMPLE 202 (METHOD AB)

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5,5-Dimethyl-3-{3-[(3-methoxybenzyl)oxy]phenyl}-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

A solution of *Example 146* (50 mg, 0.14 mmol) in DMF (5.0 mL) was treated with potassium carbonate (23 mg, 0.16 mmol) and 3-methoxybenzyl bromide (22 μ L, 0.15 mmol) and the reaction mixture was stirred for 18 h at room temperature. The solvent was removed *in vacuo* and the residue purified by preparative HPLC (pH 2.5) to give the *title compound* (41.5 mg, 62%) as an off-white solid. δ_{H} (CDCl₃) 7.39-7.28 (2H, m), 7.06-6.84 (6H, m), 5.09 (2H, s), 3.82 (3H, s), 3.65-3.57 (4H, m), 3.02-2.92 (4H, m), 2.41 (2H, s), 2.39 (2H, s), 1.01 (6H, s). LCMS (ES+) 478.2 (M+H)⁺.

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EXAMPLE 203

5,5-Dimethyl-2-(morpholin-4-yl)-3-[3-(pyridin-4-ylmethoxy)phenyl]-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 146* and 4-picolyl chloride hydrochloride according to *Method AB*, followed by heating to 100°C in a sealed tube under microwave irradiation for 30 minutes. The *title compound* was isolated as an off-white solid (37%) after purification by preparative HPLC (pH 2.5). δ_{H} (CD₃OD) 8.60-8.55 (2H, m), 7.56 (2H, d, *J* 6.0 Hz), 7.42 (1H, t, *J* 7.9 Hz), 7.10-7.04 (1H, m), 7.02-6.96 (2H, m), 5.27 (2H, s), 3.66-3.58 (4H, m), 3.06-2.98 (4H, m), 2.41 (4H, s), 1.00 (6H, s). LCMS (ES+) 449.2 (M+H)⁺.

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EXAMPLE 204 (METHOD AC)

5,5-Dimethyl-3-(3-{[(5-methyl-2-furyl)methyl]amino}phenyl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, acetic acid salt

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To a stirred solution of *Example 77* (42 mg, 0.12 mmol) and 5-methylfurfural (13 mg, 0.12 mmol) in DCM (5.0 mL) was added sodium triacetoxymethylborohydride (38 mg, 0.18

mmol) and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue purified by preparative HPLC (pH 2.5) to give the *title compound* (19.5 mg, 32%) as an orange gum. δ_{H} (CDCl_3) 7.22 (1H, t, J 7.7 Hz), 6.71-6.59 (3H, m), 6.12 (1H, d, J 3.0 Hz), 4.27 (2H, s), 5.93-5.89 (1H, m), 3.67-3.60 (4H, m), 3.03-2.96 (4H, m), 2.43 (2H, s), 2.41 (2H, s), 2.28 (3H, s), 1.02 (6H, s). LCMS (ES+) 451.2 ($\text{M}+\text{H}$)⁺.

EXAMPLE 205

10 5,5-Dimethyl-2-(morpholin-4-yl)-3-{3-[(pyridin-4-ylmethyl)amino]phenyl}-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 77* and 4-pyridinecarboxaldehyde according to *Method AC* and was isolated as an off-white solid (7 mg, 13%) after purification by preparative HPLC (pH 2.5). δ_{H} (CD_3OD) 8.51-8.46 (2H, m), 7.51-7.46 (2H, m), 7.19 (1H, t, J 7.7 Hz), 6.68-6.63 (1H, m), 6.60 (1H, dd, J 7.3, 1.1 Hz), 6.45-6.42 (1H, m), 4.46 (2H, s), 3.60-3.53 (4H, m), 3.02-2.96 (4H, m), 2.37 (2H, s), 2.31 (2H, s), 0.96 (6H, s). LCMS (ES+) 448.2 ($\text{M}+\text{H}$)⁺.

EXAMPLE 206

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3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]-N-methoxy-N-methylbenzamide

The *title compound* was prepared from *Example 73* and 3-(*N,O*-dimethyl-hydroxylaminocarbonyl)phenylboronic acid according to *Method L* and was isolated as an off-white solid (7%) after purification by preparative HPLC (pH 5.8). δ_{H} ($\text{DMSO}-d_6$) 8.77 (1H, d, J 5.1 Hz), 8.37 (1H, s), 8.27 (1H, d, J 7.7 Hz), 8.10 (1H, s), 7.69-7.57 (2H, m), 7.44 (1H, dd, J 5.1, 1.3 Hz), 3.64-3.55 (7H, m), 3.33 (3H, s), 3.02-2.94 (4H, m), 2.60 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES+) 506.2 ($\text{M}+\text{H}$)⁺.

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EXAMPLE 207

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(morpholin-4-ylcarbonyl)phenyl]pyridin-4-yl}-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 73* and 3-(morpholin-4-yl-carbonyl)phenylboronic acid according to *Method L* and was isolated as a white solid (48%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.76 (1H, d, J 5.1 Hz), 8.25 (1H, d, J 7.9 Hz), 8.18 (1H, s), 8.10 (1H, s), 7.60 (1H, t, J 7.5 Hz), 7.52-7.43 (2H, m), 3.73-3.37 (12H, m), 3.03-2.94 (4H, m), 2.59 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES+) 532.3 (M+H)⁺.

EXAMPLE 208

10 3-[2-(3-Acetylphenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 73* and 3-acetylphenylboronic acid according to *Method L* and was isolated as an off-white solid (39%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.79 (1H, d, J 5.1 Hz), 8.69 (1H, s), 8.44-8.38 (1H, m), 8.17 (1H, s), 8.08-8.03 (1H, m), 7.69 (1H, t, J 7.7 Hz), 7.47 (1H, dd, J 5.1, 1.3 Hz), 3.65-3.55 (4H, m), 3.04-2.95 (4H, m), 2.68 (3H, s), 2.61 (2H, s), 2.40 (2H, s), 0.98 (6H, s). LCMS (ES+) 461.4 (M+H)⁺.

EXAMPLE 209

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3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]-N-methoxybenzamide

The *title compound* was prepared from *Example 73* and 3-(*O*-methyl-hydroxylaminocarbonyl)phenylboronic acid according to *Method L* and was isolated as an off-white solid (36%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 11.89 (1H, s), 8.78 (1H, d, J 5.1 Hz), 8.50 (1H, s), 8.32 (1H, d, J 8.1 Hz), 8.12 (1H, s), 7.84 (1H, d, J 7.7 Hz), 7.63 (1H, t, J 7.7 Hz), 7.45 (1H, dd, J 5.1, 1.3 Hz), 3.74 (3H, s), 3.64-3.56 (4H, m), 3.03-2.95 (4H, m), 2.59 (2H, s), 2.40 (2H, s), 0.98 (6H, s). LCMS (ES+) 492.4 (M+H)⁺.

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EXAMPLE 210

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(pyrrolidin-1-ylcarbonyl)phenyl]pyridin-4-yl}-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 73* and 3-(pyrrolidin-1-yl-carbonyl)phenylboronic acid according to *Method L* and was isolated as a white solid (44%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.76 (1H, d, J 5.1 Hz), 8.29 (1H, s), 8.27-8.21 (1H, m), 8.10 (1H, s), 7.62-7.57 (2H, m), 7.44 (1H, dd, J 4.9, 1.1 Hz), 3.63-3.56 (4H, m), 3.55-3.41 (4H, m), 3.03-2.94 (4H, m), 2.59 (2H, s), 2.39 (2H, s), 1.96-1.77 (4H, m), 0.97 (6H, s). LCMS (ES⁺) 516.5 (M+H)⁺.

EXAMPLE 211

3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]-*N,N*-dimethyl-5-fluorobenzamide

The *title compound* was prepared from *Example 73* and 3-(*N,N*-dimethylamino-carbonyl)-5-fluorophenylboronic acid according to *Method L* and was isolated as an off-white solid (49%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.77 (1H, d, J 5.1 Hz), 8.17 (1H, s), 8.10-8.03 (2H, m), 7.48 (1H, dd, J 5.1, 1.3 Hz), 7.36 (1H, ddd, J 8.7, 2.4, 1.3 Hz), 3.62-3.54 (4H, m), 3.06-2.92 (10H, m), 2.58 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES⁺) 508.5 (M+H)⁺.

EXAMPLE 212 (METHOD AD)

3-(2-Anilinopyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

A mixture of *Example 73* (50 mg, 0.133 mmol), sodium *tert*-butoxide (32 mg, 0.332 mmol), tributylphosphine tetrafluoroborate (7.6 mg, 0.027 mmol), palladium(II) acetate (8.9 mg, 0.013 mmol) and aniline (60 μ L, 0.66 mmol) in THF (3.0 mL) was heated to 140°C in a sealed tube under microwave irradiation for 1 h. The solvent was removed *in vacuo* and the residue purified by preparative HPLC (pH 2.5) to give the *title compound* (23 mg, 40%) as a brown solid. δ_{H} (DMSO- d_6) 9.13 (1H, s), 8.22 (2H, dd, J 3.2, 1.3 Hz), 7.71 (2H, d, J 8.5 Hz), 7.32-7.23 (2H, m), 6.94-6.86 (1H, m), 6.84-6.78 (2H, m), 3.68-3.58 (4H, m), 3.04-2.96 (4H, m), 2.54 (2H, s), 2.39 (2H, s), 0.99 (6H, s). LCMS (ES⁺) 434.3 (M+H)⁺.

EXAMPLE 213

5,5-Dimethyl-3-[2-(N-methyl-N-phenylamino)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-
5 dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 73* and *N*-methylaniline according to *Method AD*, heating for 2 h, and was isolated as an off-white solid (32%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.24 (1H, d, J 5.3 Hz), 7.51-7.43 (2H, m), 7.40-7.34 (2H, m), 7.32-7.25 (1H, m), 6.75 (1H, dd, J 5.3, 1.3 Hz),
10 6.39 (1H, s), 3.60-3.52 (4H, m), 3.43 (3H, s), 2.94-2.87 (4H, m), 2.39 (2H, s), 2.33 (2H, s), 0.95 (6H, s). LCMS (ES $^{+}$) 448.3 (M+H) $^{+}$.

EXAMPLE 214

15 *N*-[2-(Dimethylamino)ethyl]-3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzamide, formic acid salt

The *title compound* was prepared from *Example 73* and 3-[2-(*N,N*-dimethylamino)ethylaminocarbonyl]phenylboronic acid according to *Method L* and was isolated as an off-white solid (52%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6)
20 8.78 (1H, d, J 4.9 Hz), 8.65-8.55 (2H, m), 8.30 (1H, d, J 7.5 Hz), 8.17 (1H, s), 8.13 (1H, s), 7.93 (1H, d, J 7.9 Hz), 7.62 (1H, t, J 7.7 Hz), 7.47-7.42 (1H, m), 3.64-3.56 (4H, m), 3.46-3.38 (4H, m), 3.03-2.95 (4H, m), 2.59 (2H, s), 2.40 (2H, s), 2.25 (6H, s), 0.98 (6H, s). LCMS (ES $^{+}$) 533.3 (M+H) $^{+}$.

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EXAMPLE 215

Methyl 4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)-
2,4'-bipyridine-2'-carboxylate

A mixture of *Example 217* (160 mg, 0.35 mmol), [1,1'-bis(diphenylphosphino)-
30 ferrocene]dichloropalladium(II) (catalytic amount), methanol (20 mL) and triethylamine (0.5 mL) was heated at 100°C in a Parr vessel under 100 psi pressure of carbon monoxide for 18 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane) to give the *title compound* (80 mg, 48%)

as an off-white solid. δ_{H} (CDCl_3) 8.90 (1H, d, J 5.1 Hz), 8.85 (1H, d, J 4.9 Hz), 8.75 (1H, d, J 1.1 Hz), 8.21 (1H, dd, J 4.9, 1.7 Hz), 8.02 (1H, s), 7.41 (1H, dd, J 4.9, 1.3 Hz), 4.07 (3H, s), 3.73-3.66 (4H, m), 3.07-3.00 (4H, m), 2.55 (2H, s), 2.47 (2H, s), 1.06 (6H, s). LCMS (ES+) 478.2 (M+H)⁺.

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EXAMPLE 216

5,5-Dimethyl-2-(morpholin-4-yl)-3-(2-phenoxyphenyl)-5,6-dihydro-1-benzothiophen-7(4H)-one

10 The title compound was prepared from Example 17 and 2-phenoxyphenylboronic acid according to Method J, heating for 140 minutes, and was isolated as a white solid (32%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 7.36-7.23 (4H, m), 7.21-7.14 (1H, m), 7.08-7.00 (2H, m), 6.89-6.84 (2H, m), 3.70-3.59 (4H, m), 3.05-2.99 (4H, m), 2.37 (2H, s), 2.48-2.30 (2H, m), 1.01 (3H, s), 0.94 (3H, s). LCMS (ES+) 434.3
15 (M+H)⁺.

EXAMPLE 217

3-(2'-Chloro-2,4'-bipyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

20 The title compound was prepared from Example 73 and 2-chloropyridine-4-boronic acid according to Method J and was isolated as a white solid (88%) after purification by column chromatography (SiO_2 , 0-100% EtOAc/heptane). δ_{H} (CDCl_3) 8.82 (1H, d, J 4.9 Hz), 8.54 (1H, d, J 5.3 Hz), 8.01 (1H, s), 7.89-7.83 (2H, m), 7.41-7.37 (1H, m), 3.71-3.64 (4H, m), 3.04-2.97 (4H, m), 2.52 (2H, s), 2.47 (2H, s), 1.06 (6H, s). LCMS (ES+) 454.2 (M+H)⁺.

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EXAMPLE 218 (METHOD AE)

N-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]ethanesulfonamide

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To a solution of Example 77 (50 mg, 0.14 mmol) in DCM (5.0 mL) was added pyridine (35 μL , 0.42 mmol) and ethanesulfonyl chloride (20 μL , 0.21 mmol) and the

reaction mixture was stirred at room temperature for 4 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 5.8) to give the *title compound* (30 mg, 48%) as a cream solid. δ_{H} (CDCl_3) 7.40 (1H, t, J 7.9 Hz), 7.26 (1H, s), 7.18-7.10 (2H, m), 6.55 (1H, m), 3.70-3.62 (4H, m), 3.19 (2H, q, J 7.3 Hz), 3.01-2.93 (4H, m), 2.46 (2H, s), 2.43 (2H, s), 1.42 (3H, t, J 7.3 Hz), 1.04 (6H, s). LCMS (ES+) 449.4 (M+H)⁺.

EXAMPLE 219

10 *N*-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]benzenesulfonamide

The *title compound* was prepared from *Example 77* and benzenesulfonyl chloride according to *Method AE* and was isolated as a beige solid (45%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 7.84-7.78 (2H, m), 7.61-7.54 (1H, m), 7.51-7.43 (2H, m), 7.35-7.28 (1H, m), 7.13-7.02 (3H, m), 6.69 (1H, s), 3.60-3.53 (4H, m), 2.93-2.86 (4H, m), 2.41 (2H, s), 2.32 (2H, s), 1.01 (6H, s). LCMS (ES+) 497.4 (M+H)⁺.

EXAMPLE 220

20 *N*-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-1-phenylmethanesulfonamide

The *title compound* was prepared from *Example 77* and α -toluenesulfonyl chloride according to *Method AE* and was isolated as a cream solid (43%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 7.44-7.28 (6H, m), 7.18-7.10 (2H, m), 7.06-7.01 (1H, m), 6.28 (1H, s), 4.40 (2H, s), 3.71-3.64 (4H, m), 3.02-2.95 (4H, m), 2.47 (2H, s), 2.45 (2H, s), 1.06 (6H, s). LCMS (ES+) 511.5 (M+H)⁺.

EXAMPLE 221

30 *N*-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-3,5-dimethylisoxazole-4-sulfonamide

The *title compound* was prepared from *Example 77* and 3,5-dimethylisoxazole-4-sulfonyl chloride according to *Method AE* and was isolated as a cream solid (58%) after

purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 7.42-7.35 (1H, m), 7.25-7.20 (1H, m), 7.09-7.03 (2H, m), 6.71 (1H, s), 3.68-3.60 (4H, m), 2.97-2.89 (4H, m), 2.50 (3H, s), 2.43 (2H, s), 2.34 (2H, s), 2.31 (3H, s), 1.03 (6H, s). LCMS (ES+) 516.5 (M+H)⁺.

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EXAMPLE 222**3-(Dibenzo[*b,d*]thien-2-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one**

A mixture of *Example 17* (50 mg, 0.13 mmol), dibenzo[*b,d*]thiophene-2-ylboronic acid (44 mg, 0.19 mmol), sodium carbonate (27 mg, 0.26 mmol) and palladium(II) acetate (1.0 mg, 0.004 mmol) in acetone (1.35 mL) and water (1.50 mL) was stirred at 35°C for 80 minutes. Water (5 mL) was added and the mixture was extracted with EtOAc (2 x 35 mL). The combined organic phases were dried (magnesium sulfate); the solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2 , 0-40% EtOAc/heptane) to give the *title compound* (35 mg, 61%) as an off-white solid. δ_{H} ($\text{DMSO}-d_6$) 8.49-8.44 (1H, m), 8.42 (1H, d, *J* 1.5 Hz), 8.12 (1H, d, *J* 8.3 Hz), 8.09-8.04 (1H, m), 7.59-7.50 (3H, m), 3.59-3.51 (4H, m), 3.01-2.93 (4H, m), 2.55 (2H, s), 2.39 (2H, s), 0.96 (6H, s). LCMS (ES+) 448.3 (M+H)⁺.

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EXAMPLE 223**4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)-2,4'-bipyridine-2'-carboxylic acid**

Sodium hydroxide (11 mg, 0.27 mmol) was added to a mixture of *Example 215* (65 mg, 0.14 mmol) in EtOH (5 mL) and water (1 mL) and the reaction mixture was stirred at room temperature for 2 h. Water (5 mL) was added; the reaction mixture was adjusted to pH 6 with 1*N* aqueous hydrochloric acid and then extracted with EtOAc (2 x 15 mL). The combined organic layers were dried (magnesium sulfate) and the solvent was removed *in vacuo* to give the *title compound* (60 mg, 92%) as a yellow solid. δ_{H} (CDCl_3) 8.91-8.78 (3H, m), 8.37 (1H, d, *J* 4.3 Hz), 8.04 (1H, s), 7.43 (1H, d, *J* 4.9 Hz), 3.74-3.62 (4H, m), 3.09-2.97 (4H, m), 2.54 (2H, s), 2.48 (2H, s), 1.06 (6H, s). LCMS (ES+) 464.0 (M+H)⁺.

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EXAMPLE 224

tert-Butyl {3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzyl} carbamate

5 The *title compound* was prepared from *Example 73* and 3-(*N*-*tert*-butoxycarbonyl-aminomethyl)phenylboronic acid according to *Method L* and was isolated as an off-white solid (79%) after purification by column chromatography (SiO₂, 30-100% EtOAc/heptane). δ_H (DMSO-*d*₆) 8.75 (1H, d, *J* 4.9 Hz), 8.04 (1H, s), 8.02-7.96 (2H, m), 7.51-7.43 (2H, m), 7.40 (1H, d, *J* 4.9 Hz), 7.35-7.30 (1H, m), 4.25-4.19 (2H, m), 3.63-3.55
10 (4H, m), 3.02-2.93 (4H, m), 2.57 (2H s), 2.39 (2H, s), 1.40 (9H, s), 0.97 (6H, s). LCMS (ES⁺) 548.1 (M+H)⁺.

EXAMPLE 225

15 5,5-Dimethyl-3-[2-(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl)pyridin-4-yl]-2-
(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, formic acid salt

The *title compound* was prepared from *Example 73* and 4-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2*H*-1,4-benzoxazine according to *Method L* and was isolated as a brown solid (47%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.62 (1H, d, J 4.9 Hz), 8.21 (1H, s), 7.83 (1H, s), 7.61 (1H, dd, J 8.5, 2.1 Hz), 7.48 (1H, d, J 2.1 Hz), 7.23 (1H, dd, J 5.1, 1.3 Hz), 6.78 (1H, d, J 8.5 Hz), 4.31-4.23 (2H, m), 3.64-3.54 (4H, m), 3.36-3.29 (2H, m), 3.02-2.94 (4H, m), 2.57 (2H, s), 2.38 (2H, s), 0.97 (6H, s). LCMS (ES+) 490.4 (M+H) $^{+}$.

25 **EXAMPLE 226**

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(morpholin-4-yl)phenyl]pyridin-4-yl}-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 73* and 3-(morpholin-4-yl)phenylboronic acid according to *Method L* and was isolated as a pale yellow solid (54%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.72 (1H, d, J 4.9 Hz), 8.04 (1H, s), 7.72-7.66 (1H, m), 7.58 (1H, d, J 7.5 Hz), 7.42-7.34 (2H, m), 7.06 (1H, dd, J 8.1,

2.1 Hz), 3.83-3.73 (4H, m), 3.64-3.55 (4H, m), 3.26-3.16 (4H, m), 3.03-2.93 (4H, m), 2.59 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES⁺) 504.4 (M+H)⁺.

EXAMPLE 227

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tert-Butyl 4-{3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl}piperazine-1-carboxylate

The *title compound* was prepared from *Example 73* and 3-[4-(*tert*-butoxy-carbonyl)piperazin-1-yl]phenylboronic acid pinacol ester according to *Method L* and was isolated as a pale yellow solid (45%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.73 (1H, d, *J* 4.9 Hz), 8.04 (1H, s), 7.70 (1H, s), 7.62-7.56 (1H, m), 7.42-7.33 (2H, m), 7.10-7.03 (1H, m), 3.63-3.55 (4H, m), 3.54-3.45 (4H, m), 3.25-3.16 (4H, m), 3.03-2.94 (4H, m), 2.59 (2H, s), 2.39 (2H, s), 1.43 (9H, s), 0.97 (6H, s). LCMS (ES⁺) 603.2 (M+H)⁺.

15

EXAMPLE 228

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(2*H*-tetrazol-5-yl)phenyl]pyridin-4-yl}-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 73* and 3-(2*H*-tetrazol-5-yl)-phenylboronic acid according to *Method L* and was isolated as a yellow solid (10%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.84-8.77 (2H, m), 8.18-8.05 (3H, m), 7.62 (1H, t, *J* 7.7 Hz), 7.44 (1H, dd, *J* 4.9, 1.3 Hz), 7.08 (1H, br s), 3.67-3.56 (4H, m), 3.05-2.95 (4H, m), 2.60 (2H, s), 2.40 (2H, s), 0.98 (6H, s). LCMS (ES⁺) 487.2 (M+H)⁺.

25

EXAMPLE 229

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(morpholin-4-ylmethyl)phenyl]pyridin-4-yl}-5,6-dihydro-1-benzothiophen-7(4*H*)-one, formic acid salt

30

The *title compound* was prepared from *Example 73* and 4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]morpholine according to *Method L* and was isolated as an off-white solid (32%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6)

8.75 (1H, d, *J* 5.1 Hz), 8.21 (1H, s), 8.11 (1H, s), 8.07-8.01 (2H, m), 7.47 (1H, t, *J* 7.5 Hz), 7.43-7.37 (2H, m), 3.65-3.52 (10H, m), 3.02-2.94 (4H, m), 2.60 (2H, s), 2.43-2.34 (6H, m), 0.98 (6H, s). LCMS (ES+) 518.3 (M+H)⁺.

5

EXAMPLE 230 (METHOD AF)

3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-3-yl)pyridin-2-yl]-*N,N*-dimethylbenzamide

A mixture of *Intermediate 19* (700 mg, 1.79 mmol), 2-chloropyridine-4-boronic acid (284 mg, 1.81 mmol), K₃PO₄ (456 mg, 2.15 mmol) and Pd(PPh₃)₄ (240 mg, 0.208 mmol) in DME (22 mL) and water (6.8 mL) was heated in a sealed tube at 120°C, under microwave irradiation, for 40 minutes. The reaction was quenched with saturated aqueous NaHCO₃ solution and extracted into EtOAc (4 x 85 mL). The combined organic phases were dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane) to give a pale orange solid (235 mg). A portion of this intermediate (75 mg) was combined with 3-(*N,N*-dimethylaminocarbonyl)phenylboronic acid (43 mg, 0.22 mmol), K₃PO₄ (63 mg, 0.30 mmol) and Pd(PPh₃)₄ (13 mg, 0.011 mmol) in DME (4.0 mL) and water (1.3 mL) and was heated in a sealed tube at 140°C, under microwave irradiation, for 2 h. The reaction mixture was diluted with dilute aqueous NaHCO₃ solution (30 mL) and extracted into EtOAc (2 x 40 mL). The combined organic phases were dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane) to give the *title compound* (28 mg, 10%) as a pale yellow solid. δ_H (DMSO-*d*₆) 8.74 (1H, d, *J* 5.0 Hz), 8.24-8.16 (2H, m), 8.11 (1H, s), 7.61-7.55 (2H, m), 7.50-7.44 (2H, m), 3.63-3.56 (4H, m), 3.06-2.94 (6H, m), 2.93-2.87 (4H, m), 2.72 (2H, s), 1.19 (6H, s). LCMS (ES+) 491.3 (M+H)⁺.

EXAMPLE 231

3-(2-{3-[(Dimethylamino)methyl]phenyl}pyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one

The *title compound* was prepared from *Intermediate 19*, 2-chloropyridine-4-boronic acid and 3-(*N,N*-dimethylaminomethyl)phenylboronic acid pinacol ester

hydrochloride according to *Method AF* and was isolated as an off-white solid (6%). δ_{H} (DMSO- d_6 , 70°C) 8.73 (1H, d, J 5.0 Hz), 8.10 (1H, s), 8.04-7.99 (2H, m), 7.48 (1H, t, J 7.5 Hz), 7.42-7.36 (2H, m), 7.22 (1H, s), 3.67-3.56 (6H, m), 2.98-2.91 (4H, m), 2.69 (2H, s), 2.29 (6H, s), 1.24 (6H, s). LCMS (ES+) 477.2 (M+H)⁺.

5

EXAMPLE 232 (METHOD AG)

1-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-3-ethylurea

10 Ethyl isocyanate (11 μL , 0.14 mmol) was added to a solution of *Example 77* (50 mg 0.14 mmol) in DCM (7.0 mL) and the reaction mixture was stirred at room temperature for 42 h. Further ethyl isocyanate (11 μL , 0.14 mmol) was added and the reaction mixture was stirred for a further 96 h at room temperature. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 2.5) to give the
15 *title compound* (39 mg, 65%) as a yellow solid. δ_{H} (CDCl₃) 7.39-7.33 (2H, m), 7.30-7.26 (1H, m), 7.04-6.99 (1H, m), 6.52 (1H, s), 4.82-4.75 (1H, m), 3.69-3.61 (4H, m), 3.33 (2H, dq, J 7.2, 5.4 Hz), 3.02-2.95 (4H, m), 2.44 (2H, s), 2.42 (2H, s), 1.20 (3H, t, J 7.2 Hz), 1.02 (6H, s). LCMS (ES+) 428.3 (M+H)⁺.

20

EXAMPLE 233

1-Cyclopentyl-3-[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]urea

The *title compound* was prepared from *Example 77* and cyclopentyl isocyanate
25 according to *Method AG* and was isolated as a yellow solid (33 mg, 50%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl₃) 7.38-7.33 (2H, m), 7.31-7.27 (1H, m), 7.02-6.97 (1H, m), 6.49 (1H, s), 4.75 (1H, d, J 7.0 Hz), 4.19-4.07 (1H, m), 3.69-3.60 (4H, m), 3.02-2.94 (4H, m), 2.44 (2H, s), 2.41 (2H, s), 2.10-1.96 (2H, m), 1.75-1.54 (4H, m), 1.49-1.36 (2H, m), 1.02 (6H, s). LCMS (ES+) 468.3 (M+H)⁺.

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EXAMPLE 234

1-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-3-phenylurea

Phenyl isocyanate (15 μ L, 0.14 mmol) was added to a solution of *Example 77* (50 mg, 0.14 mmol) in DCM (7.0 mL) and the reaction mixture was stirred at room temperature for 18 h. The precipitate was filtered off, washed with Et₂O and dried *in vacuo* to give the *title compound* (32 mg, 48%) as a yellow solid. δ_{H} (CDCl₃) 7.51-7.09 (10H, m), 7.03-6.98 (1H, m), 3.68-3.59 (4H, m), 3.02-2.94 (4H, m), 2.43 (4H, s), 1.01 (6H, s). LCMS (ES⁺) 476.3 (M+H)⁺.

EXAMPLE 235

N-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]morpholine-4-carboxamide

To a solution of *Example 77* (50 mg, 0.14 mmol) in DCM (10 mL) was added 4-morpholinecarbonyl chloride (20 μ L, 0.154 mmol) followed by triethylamine (40 μ L, 0.31 mmol) and the reaction mixture was stirred at room temperature for 42 h. Further 4-morpholinecarbonyl chloride (40 μ L, 0.308 mmol) was added and the reaction mixture was stirred for an additional 96 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 2.5) to give the *title compound* (11 mg, 17%) as a cream solid. δ_{H} (DMSO-d₆) 8.59 (1H, s), 7.52 (1H, s), 7.47-7.40 (1H, m), 7.32 (1H, t, *J* 7.7 Hz), 6.94 (1H, d, *J* 7.3 Hz), 3.65-3.53 (8H, m), 3.47-3.39 (4H, m), 2.98-2.89 (4H, m), 2.44 (2H, s), 2.36 (2H, s), 0.96 (6H, s). LCMS (ES⁺) 470.3 (M+H)⁺.

EXAMPLE 236

2-{3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenoxy}acetamide

A mixture of *Example 103* (37 mg, 0.085 mmol), 2-chloroacetamide (10 mg, 0.107 mmol) and potassium carbonate (14 mg, 0.101 mmol) in DMF (5.0 mL) was stirred at room temperature for 18 h, then heated in a sealed tube at 100°C, under microwave irradiation, for 1 h. Further 2-chloroacetamide (10 mg, 0.107 mmol) was added and heating was continued for an additional 50 minutes. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC to give the *title compound* (21mg,

50%) as a yellow gum. δ_{H} (CDCl_3) 8.76 (1H, d, J 5.1 Hz), 7.80 (1H, s), 7.72 (1H, d, J 1.9 Hz), 7.63 (1H, m), 7.46 (1H, t, J 7.9 Hz), 7.30-7.26 (2H, m), 7.03 (1H, dd, J 8.3, 2.6 Hz), 6.61 (1H, br s), 5.81 (1H, br s), 4.62 (2H, s), 3.71-3.64 (4H, m), 3.05-2.99 (4H, m), 2.53 (2H, s), 2.46 (2H, s), 1.05 (6H, s). LCMS (ES+) 492.3 ($\text{M}+\text{H}$)⁺.

5

EXAMPLE 237

5,5-Dimethyl-2-(morpholin-4-yl)-3-[2'-(morpholin-4-ylcarbonyl)-2,4'-bipyridin-4-yl]-5,6-dihydro-1-benzothiophen-7(4H)-one

10 A mixture of *Example 223* (55 mg, 0.12 mmol), morpholine (12 mL, 0.14 mmol), EDC (46 mg, 0.24 mmol) and 1-hydroxybenzotriazole hydrate (3 mg, 0.02 mmol) in DCM (10 mL) was stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 2.5) to give the *title compound* (31 mg, 49%) as a yellow oil. δ_{H} (CDCl_3) 8.82 (1H, dd, J 5.1, 0.6 Hz), 8.73 (1H, dd, J 5.1, 0.4 Hz), 8.30 (1H, d, J 1.1 Hz), 8.04 (1H, dd, J 5.1, 1.7 Hz), 7.91 (1H, s), 7.38 (1H, dd, J 4.9, 1.3 Hz), 3.90-3.81 (4H, m), 3.77-3.71 (4H, m), 3.70-3.65 (4H, m), 3.05-2.98 (4H, m), 2.51 (2H, s), 2.47 (2H, s), 1.05 (6H, s). LCMS (ES+) 533.3 ($\text{M}+\text{H}$)⁺.

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EXAMPLE 238

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tert-Butyl *N*-{3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzyl}-*N*-methylcarbamate

Sodium hydride (60% dispersion in mineral oil, 24 mg, 0.59 mmol) was added to a solution of *Example 224* (320 mg, 0.59 mmol) in DMF (10 mL) and the mixture was stirred for 30 minutes at room temperature. Methyl iodide (37 μL , 0.59 mmol) was added and the reaction mixture was stirred for 16.5 h at room temperature. The solvent was removed *in vacuo* from a 3 mL portion of the reaction mixture and purified by preparative HPLC (pH 2.5) to give the *title compound* (18 mg, 18%) as an off-white solid. δ_{H} (DMSO- d_6) 8.74 (1H, d, J 5.1 Hz), 8.09-7.99 (3H, m), 7.51 (1H, t, J 7.9 Hz), 7.40 (1H, dd, J 4.9, 1.1 Hz), 7.34-7.29 (1H, m), 4.47 (2H, s), 3.65-3.53 (4H, m), 3.03-2.94 (4H, m), 2.81 (3H, s), 2.57 (2H, s), 2.39 (2H, s), 1.42 (9H, s), 0.97 (6H, s). LCMS (ES+) 562.5 ($\text{M}+\text{H}$)⁺.

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EXAMPLE 239

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(piperazin-1-yl)phenyl]pyridin-4-yl}-5,6-dihydro-1-benzothiophen-7(4H)-one

5 A solution of *Example 227* (2.44 g, 4.05 mmol) in DCM (30 mL) was treated dropwise with a solution of HCl in Et₂O (2M, 12 mL, 24 mmol) and the reaction mixture stirred for 72 h at room temperature. The precipitate was filtered off, washed with Et₂O, then dissolved in dilute sodium bicarbonate solution (30 mL) and extracted with DCM (3 x 100 mL). The combined organic phases were dried (magnesium sulfate) and the solvent
10 was removed *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-10% MeOH/DCM, containing 1% NH₄OH solution) to give the *title compound* (1.24 g, 61%) as a pale yellow solid. δ_{H} (CD₃OD) 8.70 (1H, dd, *J* 5.1, 0.8 Hz), 7.94 (1H, m), 7.65-7.61 (1H, m), 7.49-7.39 (3H, m), 7.16-7.11 (1H, m), 3.73-3.66 (4H, m), 3.35-3.27 (4H, m), 3.14-3.04 (8H, m), 2.65 (2H, s), 2.48 (2H, s), 1.06 (6H, s). LCMS (ES⁺) 503.4
15 (M+H)⁺.

EXAMPLE 240

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(piperazin-1-yl)phenyl]pyridin-4-yl}-5,6-dihydro-1-benzothiophen-7(4H)-one, acetic acid salt

20 A mixture of *Example 73* (77 mg, 0.2 mmol), 3-[4-(*tert*-butoxycarbonyl)-piperazin-1-yl]phenylboronic acid pinacol ester (79 mg, 0.2 mmol), potassium phosphate (70 mg, 0.33 mmol) and Pd(PPh₃)₄ (30 mg, 0.026 mmol) in DME (4.0 mL) and water (1.0 mL) was heated in a sealed tube at 140°C, under microwave irradiation, for 4 h. The
25 solvent was removed *in vacuo*, redissolved in MeOH (5.0 mL) and treated with a solution of HCl in Et₂O (2M, 2.5 mL, 5.0 mmol), then stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 5.8) to give the *title compound* (84 mg, 68%) as an off-white solid. δ_{H} (DMSO-*d*₆) 8.72 (1H, d, *J* 5.1 Hz), 8.03 (1H, s), 7.66 (1H, s), 7.57-7.50 (1H, m), 7.42-7.30 (2H, m), 7.03 (1H, dd, *J* 8.1, 2.1 Hz), 3.65-3.54 (4H, m), 3.19-3.10 (4H, m), 3.02-2.94 (4H, m), 2.91-2.82 (4H, m), 2.59 (2H, s), 2.39 (2H, s), 1.88 (6H, s), 0.97 (6H, s). LCMS (ES⁺) 503.4
30 (M+H)⁺.

EXAMPLE 241

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(piperidin-1-ylcarbonyl)phenyl]pyridin-4-yl}-5,6-dihydro-1-benzothiophen-7(4H)-one

- 5 The *title compound* was prepared from *Example 73* and 3-(piperidin-1-yl-carbonyl)phenylboronic acid according to *Method L* and was isolated as a white solid (63%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.76 (1H, d, *J* 5.1 Hz), 8.23 (1H, d, *J* 8.1 Hz), 8.14 (1H, s), 8.10 (1H, s), 7.59 (1H, t, *J* 7.7 Hz), 7.47-7.42 (2H, m), 3.67-3.55 (6H, m), 3.37-3.33 (2H, m), 3.01-2.93 (4H, m), 2.59 (2H, s), 2.39 (2H, s), 1.68-1.43 (6H, m), 0.97 (6H, s). LCMS (ES+) 530.5 (M+H)⁺.
- 10

EXAMPLE 242

N,N-Diethyl-3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzamide

- 15 The *title compound* was prepared from *Example 73* and 3-(*N,N*-diethylamino-carbonyl)phenylboronic acid according to *Method L* and was isolated as an off-white solid (59%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.76 (1H, d, *J* 5.1 Hz), 8.22 (1H, d, *J* 7.9 Hz), 8.14-8.08 (2H, m), 7.58 (1H, t, *J* 7.7 Hz), 7.47-7.40 (2H, m), 3.63-3.53 (4H, m), 3.52-3.40 (2H, m), 3.29-3.17 (2H, m), 3.02-2.94 (4H, m), 2.59 (2H, s), 2.39 (2H, s), 1.23-1.02 (6H, m), 0.97 (6H, s). LCMS (ES+) 518.5 (M+H)⁺.
- 20

EXAMPLE 243

3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]-*N*-ethyl-*N*-methylbenzamide

- 25 The *title compound* was prepared from *Example 73* and 3-(*N*-ethyl-*N*-methylaminocarbonyl)phenylboronic acid according to *Method L* and was isolated as an off-white solid (55%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.76 (1H, d, *J* 5.1 Hz), 8.22 (1H, d, *J* 8.1 Hz), 8.15 (1H, s), 8.10 (1H, s), 7.59 (1H, t, *J* 7.7 Hz), 7.49-7.41 (2H, m), 3.63-3.55 (4H, m), 3.54-3.45 (1H, m), 3.30-3.20 (1H, m), 3.03-2.90 (7H, m), 2.59 (2H, s), 2.39 (2H, s), 1.21-1.04 (3H, m), 0.97 (6H, s). LCMS (ES+) 504.5 (M+H)⁺.
- 30

EXAMPLE 244

5,5-Dimethyl-3-(2-{3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyridin-4-yl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, formic acid salt

The *title compound* was prepared from *Example 73* and 2-{3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane according to *Method L* and was isolated as a yellow glass (80%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 8.76 (1H, d, J 5.1 Hz), 8.24 (1H, d, J 7.9 Hz), 8.15 (2H, m), 8.10 (1H, s), 7.59 (1H, t, J 7.5 Hz), 7.49-7.43 (2H, m), 3.73-3.54 (6H, m), 3.44-3.34 (2H, m), 3.03-2.94 (4H, m), 2.59 (2H, s), 2.44-2.25 (6H, m), 2.21 (3H, s), 0.97 (6H, s). LCMS (ES+) 545.5 (M+H)⁺.

EXAMPLE 245

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[2-(morpholin-4-ylcarbonyl)phenyl]pyridin-4-yl}-5,6-dihydro-1-benzothiophen-7(4H)-one, acetic acid salt

The *title compound* was prepared from *Example 73* and 2-(morpholin-4-ylcarbonyl)phenylboronic acid according to *Method L* and was isolated as a brown solid (15%) after purification by preparative HPLC (pH 5.8). δ_{H} (CD₃OD) 8.73 (1H, d, J 5.1 Hz), 7.83-7.75 (2H, m), 7.66-7.55 (2H, m), 7.52-7.42 (2H, m), 3.77-3.50 (8H, m), 3.44-3.33 (4H, m), 3.11-3.02 (4H, m), 2.64 (2H, s), 2.48 (2H, s), 1.95 (6H, s), 1.07 (6H, s). LCMS (ES+) 532.5 (M+H)⁺.

EXAMPLE 246

2-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzamide

The *title compound* was prepared from *Example 73* and 2-(aminocarbonyl)-phenylboronic acid according to *Method L* and was isolated as a yellow solid (40%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.64 (1H, d, J 4.7 Hz), 8.34 (2H, br s), 7.62-7.53 (3H, m), 7.49-7.38 (2H, m), 7.36-7.32 (1H, m), 3.61-3.52 (4H, m), 3.00-2.90 (4H, m), 2.55 (2H, s), 2.36 (2H, s), 0.98 (6H, s). LCMS (ES+) 462.4 (M+H)⁺.

EXAMPLE 247

N-{2-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl}acetamide

The *title compound* was prepared from *Example 73* and 2-(acetylamino)-phenylboronic acid according to *Method L* and was isolated as an off-white solid (57%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 11.77 (1H, br s), 8.79 (1H, d, J 5.1 Hz), 8.23 (1H, dd, J 7.7, 0.6 Hz), 7.88 (1H, s), 7.83 (1H, dd, J 7.9, 1.3 Hz), 7.51-7.40 (2H, m), 7.28-7.21 (1H, m), 3.64-3.56 (4H, m), 3.02-2.94 (4H, m), 2.57 (2H, s), 2.39 (2H, s), 2.07 (3H, s), 0.97 (6H, s). LCMS (ES+) 476.4 (M+H)⁺.

EXAMPLE 248 (METHOD AH)

3-(2-{3-[(3-Aminopyrrolidin-1-yl)carbonyl]phenyl}pyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, formic acid salt

A mixture of *Example 254* (100 mg, 0.22 mmol), 3-(*tert*-butoxycarbonylamino)-pyrrolidine (48 mg, 0.26 mmol) and EDC (83 mg, 0.43 mmol) in DCM (5.0 mL) was stirred at room temperature for 18 h. The reaction mixture was partitioned between water (20 mL) and DCM (20 mL). The aqueous phase was extracted with further DCM (20 mL). A solution of HCl in Et₂O (2M, 0.5 mL, 1.0 mmol) was added to the combined organic phases and the solution was stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 2.5) and then column chromatography (SiO₂, 20% MeOH/DCM) to give the *title compound* (44.2 mg, 35%) as a pale yellow solid. δ_{H} (CDCl₃) 8.73 (1H, d, J 5.1 Hz), 8.39 (1H, s), 8.27-8.16 (1H, m), 8.07-7.99 (1H, m), 7.84-7.78 (1H, m), 7.62-7.47 (2H, m), 7.33-7.27 (1H, m), 4.03-3.73 (4H, m), 3.70-3.52 (5H, m), 3.06-2.96 (4H, m), 2.52 (2H, s), 2.44 (2H, s), 2.34-2.09 (2H, m), 1.03 (6H, s). LCMS (ES+) 531.3 (M+H)⁺.

EXAMPLE 249

N-[2-(Dimethylamino)ethyl]-3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]-*N*-methylbenzamide, formic acid salt

The *title compound* was prepared from *Example 254* and *N,N,N'*-trimethylethylenediamine according to *Method I* and was isolated as a clear gum (22%) after purification by preparative HPLC (pH 2.5). δ_{H} (CD_3OD) 8.75 (1H, d, J 5.1 Hz), 8.48 (1H, s), 8.24-8.13 (2H, m), 8.03 (1H, s), 7.70-7.57 (2H, m), 7.49 (1H, dd, J 5.1, 1.5 Hz), 3.99-3.86 (2H, m), 3.72-3.63 (4H, m), 3.13 (3H, s), 3.11-3.02 (4H, m), 2.90 (6H, s), 2.64 (2H, s), 2.48 (2H, s), 1.05 (6H, s). LCMS (ES+) 547.2 (M+H)⁺.

EXAMPLE 250

5,5-Dimethyl-3-[2-(3-{[(3*S*)-3-hydroxypyrrolidin-1-yl]carbonyl}phenyl)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 254* and (*R*)-(+)-3-hydroxypyrrolidine according to *Method I* and was isolated as a pale yellow solid (75%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 8.76 (1H, dd, J 5.1, 1.9 Hz), 8.19 (1H, d, J 12.1 Hz), 8.08 (1H, t, J 7.7 Hz), 7.81 (1H, s), 7.66-7.51 (2H, m), 7.32-7.27 (1H, m), 4.64-4.44 (1H, m), 3.92-3.62 (7H, m), 3.60-3.48 (1H, m), 3.07-2.98 (4H, m), 2.91-2.77 (1H, br s), 2.53 (2H, s), 2.46 (2H, s), 2.17-1.94 (2H, m), 1.05 (6H, s). LCMS (ES+) 532.4 (M+H)⁺.

EXAMPLE 251

N-(2,3-Dihydroxypropyl)-3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzamide

The *title compound* was prepared from *Example 254* and 3-amino-1,2-propanediol according to *Method I* and was isolated as a pale yellow solid (20%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 8.76 (1H, d, J 5.1 Hz), 8.51 (1H, s), 8.13 (1H, d, J 7.9 Hz), 7.93 (1H, d, J 7.9 Hz), 7.87 (1H, s), 7.59 (1H, t, J 7.7 Hz), 7.40-7.30 (2H, m), 3.97-3.89 (1H, m), 3.74-3.59 (8H, m), 3.06-2.98 (4H, m), 2.52 (2H, s), 2.42 (2H, s), 1.04 (6H, s). LCMS (ES+) 536.3 (M+H)⁺.

EXAMPLE 252

3'-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N,N,5'-trimethylbiphenyl-3-carboxamide

A mixture of *Example 17* (100 mg, 0.26 mmol), 3-bromo-5-methylphenylboronic acid (60 mg, 0.26 mmol), K₃PO₄ (70 mg, 0.33 mmol) and Pd(PPh₃)₄ (50 mg, 0.04 mmol) in DME (3.0 mL) and water (1.0 mL) was heated in a sealed tube at 120°C, under microwave irradiation, for 50 minutes. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-50% EtOAc/heptane). The intermediate so obtained was combined with 3-(*N,N*-dimethylaminocarbonyl)-phenylboronic acid (30 mg, 0.16 mmol), K₃PO₄ (35 mg, 0.17 mmol) and Pd(PPh₃)₄ (20 mg, 0.02 mmol) in DME (1.5 mL) and water (0.5 mL) and was heated in a sealed tube to 120°C, under microwave irradiation, for 1 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 2.5) to give the *title compound* (27 mg, 35%) as an off-white solid. δ_{H} (CDCl₃) 7.69-7.62 (2H, m), 7.52-7.46 (1H, m), 7.42-7.36 (3H, m), 7.16 (1H, s), 3.67-3.60 (4H, m), 3.15 (3H, s), 3.08-2.97 (7H, m), 2.49 (2H, s), 2.46 (3H, s), 2.44 (2H, s), 1.04 (6H, s). LCMS (ES⁺) 503.4 (M+H)⁺.

EXAMPLE 253

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(piperazin-1-ylcarbonyl)phenyl]pyridin-4-yl}-5,6-dihydro-1-benzothiophen-7(4*H*)-one, formic acid salt

The *title compound* was prepared from *Example 254* and 1-(*tert*-butoxycarbonyl)-piperazine according to *Method AH* and was isolated as a white solid (71%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl₃) 8.77 (1H, d, *J* 4.9 Hz), 8.38 (1H, s), 8.16-8.06 (2H, m), 7.81 (1H, s), 7.59 (1H, t, *J* 7.7 Hz), 7.52-7.47 (1H, m), 7.31 (1H, dd, *J* 4.9, 1.3 Hz), 4.16-3.72 (4H, br m), 3.71-3.62 (4H, m), 3.28-3.07 (4H, br m), 3.06-2.97 (4H, m), 2.53 (2H, s), 2.46 (2H, s), 1.05 (6H, s). LCMS (ES⁺) 531.3 (M+H)⁺.

EXAMPLE 254

3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzoic acid

A mixture of *Example 73* (300 mg, 0.80 mmol), 3-ethoxycarbonylphenylboronic acid (155 mg, 0.80 mmol), K₃PO₄ (250 mg, 1.18 mmol) and Pd(PPh₃)₄ (150 mg, 0.13

mmol) in DME (80 mL) and water (20 mL) was heated at reflux for 18 h. Water (50 mL) was added and the organic phase was removed *in vacuo*. The remaining aqueous phase was basified to pH 10 with dilute sodium hydroxide solution and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* and purified
5 by column chromatography (SiO₂, 0-100% EtOAc/heptane) to give the *title compound* (67 mg, 18%) as a yellow solid. δ_{H} (CDCl₃) 8.92 (1H, dd, *J* 5.1, 0.4 Hz), 8.88 (1H, t, *J* 1.5 Hz), 8.30-8.20 (2H, m), 7.93 (1H, d, *J* 0.6 Hz), 7.65 (1H, t, *J* 7.7 Hz), 7.35 (1H, dd, *J* 5.1, 1.3 Hz), 3.75-3.66 (4H, m), 3.09-3.01 (4H, m), 2.56 (2H, s), 2.48 (2H, s), 1.07 (6H, s). LCMS (ES⁺) 463.3 (M+H)⁺.

10

EXAMPLE 255

N,N-Diethyl-2-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzamide

15 The *title compound* was prepared from *Example 73* and 2-(*N,N*-diethylamino-carbonyl)phenylboronic acid according to *Method L* and was isolated as a pale yellow solid (25%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO-*d*₆) 8.66 (1H, d, *J* 5.1 Hz), 7.82 (1H, dd, *J* 7.7, 1.7 Hz), 7.72 (1H, s), 7.59-7.47 (2H, m), 7.41 (1H, dd, *J* 5.1, 1.5 Hz), 7.35-7.30 (1H, m), 3.62-3.52 (4H, m), 3.34-3.28 (4H, m), 2.98-2.90 (4H, m),
20 2.57 (2H, s), 2.39 (2H, s), 1.02-0.83 (12H, m). LCMS (ES⁺) 518.5 (M+H)⁺.

EXAMPLE 256

Ethyl {[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]amino}(oxo)acetate

25

Ethyl oxalyl chloride (0.20 mL, 1.69 mmol) and triethylamine (0.24 mL, 1.69 mmol) were added to a solution of *Example 77* (400 mg, 1.12 mmol) in DCM (20 mL) and the reaction mixture was stirred at room temperature for 18 h. Water (20 mL) was added and the mixture was extracted with DCM (100 mL). The organic phase was dried
30 (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by column chromatography (SiO₂, 40-50% EtOAc/heptane) to give the *title compound* (330 mg, 64%) as a cream solid. δ_{H} (CDCl₃) 8.93 (1H, s), 7.77-7.72 (1H, m), 7.57-7.51 (1H, m), 7.44 (1H, t, *J* 7.7 Hz), 7.20 (1H, dt, *J* 7.5, 1.3 Hz), 4.45 (2H, q, *J* 7.2 Hz), 3.71-3.62

(4H, m), 3.03-2.95 (4H, m), 2.47 (2H, s), 2.43 (2H, s), 1.45 (3H, t, J 7.2 Hz), 1.04 (7H, s).
LCMS (ES+) 457.3 (M+H)⁺.

EXAMPLE 257

5

3-(6-Aminobiphenyl-3-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 272* and phenylboronic acid according to *Method L*, heating at 150°C for 2 h, and was obtained as an off-white solid
10 (56%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 7.52-7.41 (4H, m), 7.40-7.32 (1H, m), 7.07 (1H, d, J 8.5 Hz), 7.00 (1H, s), 6.84 (1H, d, J 8.3 Hz), 5.01-4.92 (1H, m), 3.64-3.51 (4H, m), 3.02-2.89 (4H, m), 2.50 (2H, s), 2.34 (2H, s), 0.97 (6H, s). LCMS (ES+) 433.3 (M+H)⁺.

15

EXAMPLE 258 (METHOD A1)

N,N-Dimethyl-3-[4-(2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzamide

A mixture of *Intermediate 2* (1.00 g, 2.75 mmol), 2-chloropyridine-4-boronic acid
20 (0.43 g, 2.75 mmol), K₃PO₄ (0.70 g, 3.30 mmol) and Pd(PPh₃)₄ (400 mg, 0.35 mmol) in DME (30 mL) and water (10 mL) was heated at 70°C for 5 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane). A sample (50 mg) of the intermediate so obtained was combined with 3-(*N,N*-dimethylaminocarbonyl)phenylboronic acid (28 mg, 0.14 mmol), K₃PO₄ (35 mg, 0.17
25 mmol) and Pd(PPh₃)₄ (20 mg, 0.017 mmol) in DME (1.5 mL) and water (0.5 mL) and was heated in a sealed tube at 120°C, under microwave irradiation, for 1 h. The solvent was removed *in vacuo* and the residue purified by preparative HPLC (pH 2.5) to give the
title compound (56 mg, 67%) as a yellow glass. δ_{H} (CD₃OD) 8.73 (1H, dd, J 5.3, 0.8 Hz), 8.19-8.09 (2H, m), 8.01 (1H, dd, J 1.3, 0.8 Hz), 7.63 (1H, td, J 7.5, 0.6 Hz), 7.57-7.52
30 (1H, m), 7.49 (1H, dd, J 5.1, 1.5 Hz), 3.72-3.63 (4H, m), 3.16 (3H, s), 3.12-3.01 (7H, m), 2.74 (2H, t, J 6.0 Hz), 2.63-2.55 (2H, m), 2.18-2.07 (2H, m). LCMS (ES+) 462.3 (M+H)⁺.

EXAMPLE 259

3-(2-{3-[(Dimethylamino)methyl]phenyl}pyridin-4-yl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, formic acid salt

- 5 The *title compound* was prepared from *Intermediate 2* and 3-(*N,N*-dimethylamino-methyl)phenylboronic acid according to *Method AI* and was obtained as a pale yellow glass (61%) after purification by preparative HPLC (pH 2.5). δ_{H} (CD₃OD) 8.75 (1H, dd, *J* 5.1, 0.8 Hz), 8.21 (1H, s), 8.15 (1H, dt, *J* 7.0, 1.7 Hz), 8.00 (1H, d, *J* 0.6 Hz), 7.70-7.60 (2H, m), 7.51 (1H, dd, *J* 5.1, 1.5 Hz), 4.39 (2H, s), 3.72-3.63 (4H, m), 3.12-3.03 (4H, m),
10 2.87 (6H, s), 2.74 (2H, t, *J* 5.8 Hz), 2.63-2.56 (2H, m), 2.18-2.07 (2H, m). LCMS (ES+) 448.2 (M+H)⁺.

EXAMPLE 260 (METHOD AJ)

- 15 3-(6-{3-[(Dimethylamino)methyl]phenyl}pyridin-2-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

- A mixture of *Example 17* (100 mg, 0.26 mmol), 6-chloropyridine-2-boronic acid (61 mg, 0.26 mmol), K₃PO₄ (100 mg, 0.47 mmol) and Pd(PPh₃)₄ (20 mg, 0.017 mmol) in DME (3 mL) and water (1 mL) was heated in a sealed tube at 120°C, under microwave
20 irradiation, for 20 minutes. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-60% EtOAc/heptane). A sample of the intermediate so obtained (50 mg) was combined with 3-[(*N,N*-dimethylamino)methyl]-phenylboronic acid pinacol ester (40 mg, 0.13 mmol), K₃PO₄ (50 mg, 0.24 mmol) and Pd(PPh₃)₄ (10 mg, 0.009 mmol) in DME (3 mL) and water (1 mL) and the mixture was
25 heated in a sealed tube at 140°C, under microwave irradiation, for 2 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 20-100% EtOAc/heptane then 10% MeOH/EtOAc) to give the *title compound* (32 mg, 29%) as a beige solid. δ_{H} (DMSO-*d*₆) 8.15 (1H, s), 8.02-7.88 (3H, m), 7.63 (1H, dd, *J* 7.2, 0.8 Hz), 7.47 (1H, t, *J* 7.5 Hz), 7.39-7.34 (1H, m), 3.67-3.59 (4H, m), 3.49 (2H, s), 3.01-2.93
30 (4H, m), 2.75 (2H, s), 2.41 (2H, s), 2.19 (6H, s), 1.01 (6H, s). LCMS (ES+) 476.5 (M+H)⁺.

EXAMPLE 261

3-[6-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]-N,N-dimethylbenzamide

The *title compound* was prepared from *Example 17* and 3-(N,N-dimethyl-aminocarbonyl)phenylboronic acid according to *Method AJ* and was obtained as a yellow solid (40%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_{H} (DMSO-d₆) 8.23-8.16 (2H, m), 8.01-7.96 (2H, m), 7.67 (1H, t, *J* 4.1 Hz), 7.59 (1H, t, *J* 7.7 Hz), 7.50-7.46 (1H, m), 3.66-3.59 (4H, m), 3.10-2.85 (10H, m), 2.71 (2H, s), 2.41 (2H, s), 0.98 (6H, s). LCMS (ES⁺) 476.5 (M+H)⁺.

EXAMPLE 262

3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzyl methanesulfonate

Triethylamine (140 μL , 1.0 mmol) and methanesulfonyl chloride (68 μL , 0.88 mmol) were added to a solution of *Example 155* (359 mg, 0.80 mmol) in DCM (40 mL) and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 20-100% EtOAc/heptane) to give the *title compound* (288 mg, 68%) as a yellow solid. δ_{H} (DMSO-d₆) 8.77 (1H, d, *J* 4.9 Hz), 8.26 (1H, d, *J* 0.4 Hz), 8.21-8.15 (1H, m), 8.07 (1H, s), 7.63-7.52 (2H, m), 7.44 (1H, d, *J* 4.9 Hz), 5.37 (2H, s), 3.63-3.55 (4H, m), 3.28 (3H, s), 3.02-2.93 (4H, m), 2.59 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES⁺) 527.2 (M+H)⁺.

EXAMPLE 263 (METHOD AK)

5,5-Dimethyl-3-(2-{3-[(methylamino)methyl]phenyl}pyridin-4-yl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, acetic acid salt

Example 262 (46 mg, 0.087 mmol) was combined with methylamine hydrochloride (67 mg, 1.0 mmol), triethylamine (140 μL , 1.0 mmol) and THF (3 mL) in a sealed tube and the mixture was stirred at room temperature for 16 h. A solution of methylamine in THF (2M, 1.0 mL, 2.0 mmol) was added and the mixture was then heated at 120°C, under microwave irradiation, for 1 h. The solvent was removed *in vacuo* and

the residue was purified by preparative HPLC (pH 5.8) to give the *title compound* (16 mg, 31%) as a yellow solid. δ_{H} (DMSO- d_6) 8.74 (1H, d, J 4.9 Hz), 8.12 (1H, s), 8.06-7.96 (2H, m), 7.49-7.36 (3H, m), 3.74 (2H, s), 3.64-3.54 (4H, m), 3.03-2.92 (4H, m), 2.58 (2H, s), 2.39 (2H, s), 2.29 (3H, s), 1.86 (6H, s), 0.97 (6H, s). LCMS (ES+) 462.3 (M+H)⁺.

5

EXAMPLE 264 (METHOD AL)

N-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]benzamide

10 To a solution of *Example 77* (50 mg, 0.14 mmol) in DCM (5.0 mL) was added benzoic acid (21 mg, 0.17 mmol), EDC (54 mg, 0.28 mmol) and 1-hydroxybenzotriazole (3.0 mg, 0.03 mmol) and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 2.5) to give the *title compound* (32 mg, 50%) as a cream solid. δ_{H} (CDCl₃) 7.92-7.86 (3H, m), 7.73 (1H, t, J 1.9 Hz), 7.62-7.49 (4H, m), 7.44 (1H, t, J 7.9 Hz), 7.17-7.12 (1H, m), 15 3.71-3.64 (4H, m), 3.05-2.98 (4H, m), 2.49 (2H, s), 2.43 (2H, s), 1.04 (6H, s). LCMS (ES+) 461.3 (M+H)⁺.

EXAMPLE 265

20

tert-Butyl *N*-(1-{3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzoyl}piperidin-4-yl)-*N*-methylcarbamate

The *title compound* was prepared from *Example 254* and 4-[*N*-(*tert*-butoxycarbonyl)-*N*-methylamino]piperidine according to *Method I* and was isolated as a white solid (14%) after purification by preparative HPLC (pH 5.8). δ_{H} (CD₃OD) 8.75 (1H, m), 8.19-8.11 (2H, m), 8.02 (1H, s), 7.65 (1H, t, J 7.5 Hz), 7.58-7.53 (1H, m), 7.48 (1H, dd, J 5.1, 1.5 Hz), 4.87-4.75 (1H, m), 4.25-4.08 (1H, m), 3.97-3.84 (1H, m), 3.72-3.63 (4H, m), 3.30-3.19 (1H, m), 3.14-3.03 (4H, m), 3.00-2.86 (1H, m), 2.80 (3H, s), 2.64 (2H, s), 2.47 (2H, s), 1.91-1.59 (4H, m), 1.48 (9H, s), 1.05 (6H, s). LCMS (ES+) 659.2 (M+H)⁺.

30

EXAMPLE 266

3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]-N-methyl-N-(1-methylpyrrolidin-3-yl)benzamide, formic acid salt

The title compound was prepared from *Example 254* and *N,N'*-dimethyl-3-aminopyrrolidine (21 mg, 0.18 mmol) according to *Method I* and was isolated as a yellow glass (40%) after purification by preparative HPLC (pH 2.5). δ_{H} (CD_3OD) 8.75 (1H, dd, *J* 5.1, 0.6 Hz), 8.35 (2H, s), 8.20-8.14 (2H, m), 8.02 (1H, d, *J* 0.6 Hz), 7.67 (1H, t, *J* 7.7 Hz), 7.62-7.56 (1H, m), 7.49 (1H, dd, *J* 5.1, 1.5 Hz), 4.82-4.68 (1H, m), 3.95-3.72 (2H, m), 3.72-3.63 (4H, m), 3.61-3.43 (1H, m), 3.30-3.20 (1H, m), 3.14 (3H, s), 3.10-3.04 (4H, m), 3.03-2.87 (3H, m), 2.67-2.55 (3H, m), 2.52-2.34 (3H, m), 1.05 (6H, s). LCMS (ES+) 559.4 (M+H)⁺.

EXAMPLE 267

3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]-N-methyl-N-(1-methylpiperidin-4-yl)benzamide, formic acid salt

The title compound was prepared from *Example 254* and 1-methyl-4-(methylamino)piperidine (26 μL , 0.18 mmol) according to *Method I* and was isolated as a white solid (25%) after purification by preparative HPLC (pH 2.5). δ_{H} (CD_3OD) 8.75 (1H, d, *J* 5.1 Hz), 8.20-8.11 (2H, m), 8.03 (1H, s), 7.66 (1H, t, *J* 7.7 Hz), 7.59-7.53 (1H, m), 7.48 (1H, dd, *J* 5.3, 1.5 Hz), 4.79-4.59 (1H, m), 3.76-3.65 (4H, m), 3.64-3.42 (2H, m), 3.29-3.12 (2H, m), 3.12-3.04 (4H, m), 3.04-2.95 (3H, br s), 2.94-2.72 (3H, br s), 2.64 (2H, s), 2.47 (2H, s), 2.35-2.16 (2H, m), 2.16-1.99 (2H, m), 1.05 (6H, s). LCMS (ES+) 573.3 (M+H)⁺.

EXAMPLE 268 (METHOD AM)

3-(2-{3-[(4-Aminopiperidin-1-yl)carbonyl]phenyl}pyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

A solution of HCl in Et_2O (2M, 3.3 mL, 6.6 mmol) was added to a solution of *Example 273* (0.21 g, 0.33 mmol) in DCM (6 mL) and the reaction mixture was stirred at room temperature for 18 h. The precipitate was filtered off and washed with Et_2O . The solid was partitioned between DCM (100 mL) and dilute sodium hydrogencarbonate solution (50 mL). The organic phase was dried (magnesium sulfate) and the solvent was

removed *in vacuo* to give the *title compound* (104 mg, 59%) as a yellow solid. δ_{H} (CD₃OD) 8.74 (1H, dd, *J* 5.1, 0.6 Hz), 8.18-8.13 (1H, m), 8.12-8.09 (1H, m), 8.02 (1H, s), 7.65 (1H, t, *J* 7.7 Hz), 7.56-7.51 (1H, m), 7.48 (1H, dd, *J* 5.1, 1.5 Hz), 4.72-4.56 (1H, m), 3.89-3.75 (1H, m), 3.73-3.64 (4H, m), 3.25-3.16 (1H, m), 3.14-3.05 (4H, m), 3.03-2.90 (2H, m), 2.64 (2H, s), 2.48 (2H, s), 2.08-1.93 (1H, m), 1.91-1.77 (1H, m), 1.52-1.30 (2H, m), 1.06 (6H, s). LCMS (ES⁺) 545.3 (M+H)⁺.

EXAMPLE 269

10 3-(2,6-Dichloropyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17* and 2,6-dichloropyridyl-4-boronic acid pinacol ester according to *Method J* and was isolated as an off-white solid (45%) after purification by column chromatography (SiO₂, 0-50% EtOAc/heptane). δ_{H} (CDCl₃) 7.35 (2H, s), 3.77-3.70 (4H, m), 3.05-2.96 (4H, m), 2.51 (2H, s), 2.46 (2H, s), 1.07 (6H, s). LCMS (ES⁺) 411.3, 413.2 (M+H)⁺.

EXAMPLE 270

20 5,5-Dimethyl-3-[2-(3-{[4-(methylamino)piperidin-1-yl]carbonyl}phenyl)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 265* according to *Method AM* and was isolated as a white solid (51%). δ_{H} (CD₃OD) 8.74 (1H, dd, *J* 5.1, 0.6 Hz), 8.18-8.13 (1H, m), 8.12-8.09 (1H, m), 8.01 (1H, s), 7.65 (1H, t, *J* 7.7 Hz), 7.56-7.51 (1H, m), 7.48 (1H, dd, *J* 5.3, 1.5 Hz), 4.71-4.60 (1H, m), 3.90-3.78 (1H, m), 3.73-3.64 (4H, m), 3.29-3.17 (1H, m), 3.13-3.05 (4H, m), 3.05-2.93 (1H, m), 2.80-2.67 (1H, m), 2.64 (2H, s), 2.48 (2H, s), 2.42 (3H, s), 2.16-2.04 (1H, m), 1.99-1.86 (1H, m), 1.47-1.26 (2H, m), 1.06 (6H, s). LCMS (ES⁺) 559.3 (M+H)⁺.

30 EXAMPLE 271 (METHOD AN)

5,5-Dimethyl-3-(2-{2-[(4-methylpiperazin-1-yl)methyl]phenyl}pyridin-4-yl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, acetic acid salt

A mixture of 2-formylphenylboronic acid (100 mg, 0.67 mmol), 1-methyl-piperazine (90 μ L, 0.80 mmol) and activated molecular sieves (100 mg) in methanol (3.0 mL) was stirred at room temperature for 4 h. Sodium borohydride (30 mg, 0.79 mmol) was then added and stirring was continued for 1 h. The solvent was removed *in vacuo* and the residue was taken up in DME (3.0 mL) and water (1.0 mL), to which was added K_3PO_4 (50 mg, 0.24 mmol), $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) and *Example 73* (50 mg, 0.13 mmol). The reaction mixture was heated at 140°C, under microwave irradiation, for 2 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 5.8) to give the *title compound* (40 mg, 52%) as an off-white solid. δ_H (DMSO- d_6) 8.71 (1H, d, J 5.1 Hz), 7.81 (1H, s), 7.54-7.48 (1H, m), 7.47-7.37 (4H, m), 3.63-3.56 (4H, m), 3.51 (2H, s), 3.02-2.93 (4H, m), 2.56 (2H, s), 2.38 (2H, s), 2.31-1.99 (11H, m), 1.89 (3H, s), 0.97 (6H, s). LCMS (ES+) 531.6 (M+H)⁺.

EXAMPLE 272

3-(4-Amino-3-bromophenyl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

N-Bromosuccinimide (70 mg, 0.39 mmol) was added to a solution of *Example 78* (140 mg, 0.39 mmol) in THF (10 mL) and the reaction mixture was stirred at room temperature for 35 minutes. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 10-70% EtOAc/heptane) to give the *title compound* (136 mg, 79%) as a yellow solid. δ_H (DMSO- d_6) 7.37 (1H, d, J 1.9 Hz), 7.09 (1H, dd, J 8.3, 1.7 Hz), 6.86 (1H, d, J 8.3 Hz), 3.64-3.54 (4H, m), 2.97-2.88 (4H, m), 2.47 (2H, s), 2.34 (2H, s), 0.96 (6H, s). LCMS (ES+) 435.3, 437.2 (M+H)⁺.

EXAMPLE 273

tert-Butyl (1-{3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)]pyridin-2-yl}benzoyl)piperidin-4-yl)carbamate

The *title compound* was prepared from *Example 254* and 4-(*tert*-butoxycarbonylamino)piperidine according to *Method I* and was obtained as an off-white solid (14%) after purification by preparative HPLC (pH 2.5). δ_H (CD₃OD) 8.74 (1H, dd, J 5.1, 0.6 Hz), 8.19-8.13 (1H, m), 8.12-8.08 (1H, m), 8.01 (1, d, J 0.6 Hz), 7.64 (1H, t, J 7.5 Hz),

7.56-7.46 (2H, m), 4.63-4.48 (1H, m), 3.85-3.60 (6H, m), 3.29-3.18 (1H, m), 3.17-3.01 (5H, m), 2.64 (2H, s), 2.48 (2H, s), 2.08-1.81 (2H, m), 1.61-1.35 (11H, m), 1.05 (6H, s). LCMS (ES+) 645.2 (M+H)⁺.

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EXAMPLE 274

N-Benzyl-N-[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]propanamide

Sodium hydride (60% dispersion in oil, 2.8 mg, 0.07 mmol) was added to a solution of *Example 278* (24 mg, 0.06 mmol) in DMF (1.0 mL) and the reaction mixture was stirred at room temperature for 5 minutes. Benzyl bromide (7 µL, 0.06 mmol) was then added and stirring was continued for 18.5 h. The reaction mixture was filtered and purified by preparative HPLC (pH 2.5) to give the *title compound* (10 mg, 33%) as a yellow solid. δ_H (CDCl₃) 7.42 (1H, t, *J* 7.7 Hz), 7.25-7.14 (6H, m), 7.10-7.03 (1H, m), 6.93-6.87 (1H, m), 4.95 (2H, s), 3.59-3.51 (4H, m), 2.92-2.83 (4H, m), 2.41 (2H, s), 2.25 (2H, s), 2.21-2.10 (2H, m), 1.12 (3H, t, *J* 7.5 Hz), 1.01 (6H, s). LCMS (ES+) 503.6 (M+H)⁺.

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EXAMPLE 275

tert-Butyl 4- {[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]carbamoyl}piperidine-1-carboxylate

The *title compound* was prepared from *Example 77* and *N-(tert-butoxycarbonyl)-isonipecotic acid* according to *Method AL* and was obtained as a cream solid (55%) after purification by preparative HPLC (pH 2.5). δ_H (CDCl₃) 7.59-7.55 (1H, m), 7.49-7.43 (1H, m), 7.42-7.35 (1H, m), 7.31-7.27 (1H, m), 7.12-7.06 (1H, m), 4.30-4.13 (2H, m), 3.70-3.61 (4H, m), 3.03-2.95 (4H, m), 2.88-2.74 (2H, m), 2.45 (2H, s), 2.44-2.35 (3H, m), 1.99-1.87 (2H, m), 1.84-1.68 (2H, m), 1.47 (9H, s), 1.03 (6H, s). LCMS (ES+) 568.2 (M+H)⁺.

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EXAMPLE 276

N-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-2-phenylacetamide

The *title compound* was prepared from *Example 77* and phenylacetic acid according to *Method AL* and was obtained as a cream solid (65%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 7.55-7.51 (1H, m), 7.47-7.27 (7H, m), 7.11-7.03 (2H, m), 3.78 (2H, s), 3.66-3.59 (4H, m), 3.00-2.93 (4H, m), 2.45 (2H, s), 2.41 (2H, s), 1.02 (6H, s). LCMS (ES+) 475.3 (M+H)⁺.

EXAMPLE 277

N-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-1H-indole-3-carboxamide

The *title compound* was prepared from *Example 77* and indole-3-carboxylic acid according to *Method AL* and was obtained as a cream solid (20%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 8.76 (1H, br s), 8.10-8.04 (1H, m), 7.93 (1H, d, *J* 2.8 Hz), 7.79 (1H, s), 7.74 (1H, t, *J* 1.7 Hz), 7.64-7.58 (1H, m), 7.53-7.47 (1H, m), 7.44 (1H, t, *J* 7.9 Hz), 7.36-7.30 (2H, m), 7.14-7.09 (1H, m), 3.72-3.64 (4H, m), 3.06-2.98 (4H, m), 2.51 (2H, s), 2.43 (2H, s), 1.04 (6H, s). LCMS (ES+) 500.3 (M+H)⁺.

EXAMPLE 278

N-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]propanamide

The *title compound* was prepared from *Example 77* and propionic acid according to *Method AL* and was obtained as a cream solid (76%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 7.59 (1H, br s), 7.47-7.34 (2H, m), 7.17 (1H, s), 7.08 (1H, d, *J* 7.3 Hz), 3.70-3.62 (4H, m), 3.03-2.95 (4H, m), 2.50-2.38 (6H, m), 1.27 (3H, t, *J* 7.5 Hz), 1.03 (6H, s). LCMS (ES+) 413.3 (M+H)⁺.

EXAMPLE 279

N-[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]isonicotinamide

The *title compound* was prepared from *Example 77* and isonicotinic acid according to *Method AL* and was obtained as a cream solid (37%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 8.86-8.81 (2H, m), 8.05 (1H, br s), 7.78-7.71 (3H, m), 7.62-7.57 (1H, m), 7.47 (1H, t, J 7.9 Hz), 7.19 (1H, d, J 7.7 Hz), 3.72-3.64 (4H, m), 3.05-2.97 (4H, m), 2.49 (2H, s), 2.42 (2H, s), 1.03 (6H, s). LCMS (ES+) 462.3 (M+H)⁺.

EXAMPLE 280

10 *N*-[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]cyclopentanecarboxamide

The *title compound* was prepared from *Example 77* and cyclopentanecarboxylic acid according to *Method AL* and was obtained as a cream solid (63%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 7.58 (1H, br s), 7.50-7.45 (1H, m), 7.37 (1H, t, J 7.7 Hz), 7.23 (1H, br s), 7.07 (1H, d, J 7.5 Hz), 3.70-3.62 (4H, m), 3.03-2.96 (4H, m), 2.78-2.65 (1H, m), 2.48 (2H, s), 2.42 (2H, s), 2.04-1.58 (8H, m), 1.03 (6H, s). LCMS (ES+) 453.4 (M+H)⁺.

EXAMPLE 281

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3-{3-[(Dimethylamino)methyl]phenyl}-5,5-dimethyl-2-morpholin-4-yl-5,6-dihydro-1-benzothiophen-7(4*H*)-one, formic acid salt

The *title compound* was prepared from *Example 17* and 3-[(*N,N*-dimethylamino)-methyl]phenylboronic acid according to *Method J* and was obtained as an off-white solid (60%) after purification by preparative HPLC (pH 2.5). δ_{H} (CD_3OD) 8.45 (1H, s), 7.62-7.55 (1H, m), 7.53-7.46 (3H, m), 4.25 (2H, s), 3.67-3.59 (4H, m), 3.05-2.95 (4H, m), 2.78 (6H, s), 2.49 (2H, s), 2.42 (2H, s), 1.01 (6H, s). LCMS (ES+) 399.3 (M+H)⁺.

EXAMPLE 282

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5,5-Dimethyl-2-(morpholin-4-yl)-3-(2-phenylpyrimidin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

A mixture of *Example 344* (70 mg, 0.19 mmol), benzamidine hydrochloride (61 mg, 0.39 mmol) and sodium ethoxide (53 mg, 0.77 mmol) in EtOH (3.0 mL) was heated at 100°C, under microwave irradiation, for 80 minutes. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane) and preparative HPLC (pH 2.5) to give the *title compound* (13 mg, 16%) as an off-white solid. δ_{H} (DMSO-d₆) 8.94 (1H, d, *J* 5.2 Hz), 8.47-8.41 (2H, m), 7.73 (1H, d, *J* 5.2 Hz), 7.59-7.53 (3H, m), 3.71-3.63 (4H, m), 3.07-3.00 (4H, m), 2.82 (2H, s), 2.43 (2H, s), 1.00 (6H, s). LCMS (ES⁺) 420.3 (M+H)⁺.

EXAMPLE 283

5,5-Dimethyl-2-(morpholin-4-yl)-3-(6-phenylpyridin-2-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17*, 6-chloropyridine-2-boronic acid and phenylboronic acid according to *Method AJ* and was obtained as an off-white solid (30%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-d₆) 8.18-8.12 (2H, m), 8.01-7.91 (2H, m), 7.62 (1H, dd, *J* 7.2, 1.3 Hz), 7.56-7.43 (3H, m), 3.67-3.57 (4H, m), 3.02-2.94 (4H, m), 2.69 (2H, s), 2.40 (2H, s), 0.98 (6H, s). LCMS (ES⁺) 419.3 (M+H)⁺.

EXAMPLE 284 (METHOD AO)

3-Acetyl-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

A solution of *Intermediate 57* (365 mg, 1.00 mmol) in aqueous hydrochloric acid (1M, 4.0 mL) and acetonitrile (10.0 mL) was stirred at room temperature for 3 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane) to give the *title compound* (270 mg, 88%) as a pale yellow solid. δ_{H} (CD₃OD) 3.91-3.85 (4H, m), 3.25-3.19 (4H, m), 2.78 (2H, s), 2.55 (3H, s), 2.43 (2H, s), 1.08 (6H, s). LCMS (ES⁺) 308.2 (M+H)⁺.

EXAMPLE 285 (METHOD AP)

tert-Butyl (1-{[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]carbamoyl}pyrrolidin-3-yl)carbamate

Triphosgene (42 mg, 0.14 mmol) and triethylamine (0.2 mL, 1.40 mmol) were added to a cooled solution of *Example 77* (10 mg, 0.28 mmol) in THF (15 mL) at -78°C.

- 5 The mixture was then allowed to warm to 0°C and stirred at this temperature for 30 minutes. The reaction mixture was then recooled to -78°C, 3-(*tert*-butoxycarbonyl-amino)pyrrolidine (78 mg, 0.42 mmol) was added, and then it was allowed to warm to 0°C and stirred for 1 h. Water (20 mL) was added and the mixture was extracted with EtOAc (75 mL). The combined organic phase was washed with brine (20 mL), dried
10 (magnesium sulfate) and the solvent was removed *in vacuo*. A sample (40 mg) of the residue was purified by preparative HPLC (pH 2.5) to give the *title compound* (21 mg) as an off-white solid. δ_{H} (CDCl₃) 7.44-7.41 (1H, m), 7.37-7.33 (2H, m), 7.03-6.98 (1H, m), 6.20 (1H, s), 4.75-4.65 (1H, m), 4.34-4.25 (1H, m), 3.82-3.73 (1H, m), 3.69-3.54 (6H, m), 3.41-3.32 (1H, m), 3.04-2.96 (4H, m), 2.47 (2H, s), 2.41 (2H, s), 2.32-2.20 (1H, m), 2.01-
15 1.89 (1H, m), 1.46 (9H, s), 1.03 (6H, s). LCMS (ES+) 569.2 (M+H)⁺.

EXAMPLE 286

tert-Butyl 4-{[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]carbamoyl}piperazine-1-carboxylate

- 20 The *title compound* was prepared from *Example 77* and 1-(*tert*-butoxycarbonyl)-piperazine according to *Method AP* and was obtained as an off-white solid (19 mg) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl₃) 7.39-7.29 (3H, m), 7.02 (1H, dt, *J* 7.0, 1.7 Hz), 6.43 (1H, s), 3.69-3.62 (4H, m), 3.52 (8H, s), 3.03-2.96 (4H, m), 2.46 (2H,
25 s), 2.41 (2H, s), 1.49 (9H, s), 1.02 (6H, s). LCMS (ES+) 569.2 (M+H)⁺.

EXAMPLE 287

(3*R*)-*N*-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-3-hydroxypyrrolidine-1-carboxamide

- 30 The *title compound* was prepared from *Example 77* and (*R*)-(+)-3-hydroxypyrrolidine according to *Method AP* and was obtained as a pale yellow solid (58%) after purification of the entire sample by preparative HPLC (pH 2.5). δ_{H} (CDCl₃) 7.46-7.42

(1H, m), 7.38-7.33 (2H, m), 7.03-6.97 (1H, m), 6.23 (1H, s), 4.63-4.57 (1H, m), 3.72-3.49 (8H, m), 3.04-2.97 (4H, m), 2.46 (2H, s), 2.41 (2H, s), 2.18-2.06 (2H, m), 1.85-1.75 (1H, m), 1.02 (6H, s). LCMS (ES+) 470.3 (M+H)⁺.

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EXAMPLE 288**3-(Biphenyl-3-yl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one**

The *title compound* was prepared from *Intermediate 2* and 3-biphenylboronic acid according to *Method J* and was obtained as an off-white solid (77%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO- d_6) 6.87-6.79 (4H, m), 6.79-6.72 (1H, m), 6.70-6.63 (2H, m), 6.60-6.53 (2H, m), 2.86-2.78 (4H, m), 2.28-2.20 (4H, m), 1.91-1.83 (2H, m), 1.80-1.72 (2H, m), 1.34-1.25 (2H, m). LCMS (ES+) 390.3 (M+H)⁺.

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EXAMPLE 289**3-Acetyl-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4H)-one**

The *title compound* was prepared from *Intermediate 58* according to *Method AO* and was obtained as a yellow solid (60%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_{H} (CD₃OD) 3.94-3.86 (4H, m), 3.21-3.13 (4H, m), 2.95 (2H, s), 2.60 (3H, s), 1.33 (6H, s). LCMS (ES+) 309.2 (M+H)⁺.

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EXAMPLE 290**Ethyl 3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzoate**

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The *title compound* was prepared from *Example 73* and 3-ethoxycarbonylphenylboronic acid according to *Method L* and was isolated as an off-white solid (5%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_{H} (CDCl₃) 8.79 (1H, dd, *J* 5.1, 0.8 Hz), 8.66-8.64 (1H, m), 8.32-8.24 (1H, m), 8.17-8.12 (1H, m), 7.89 (1H, d, *J* 0.8 Hz), 7.60 (1H, t, *J* 7.9 Hz), 7.30-7.25 (1H, m), 4.43 (2H, q, *J* 7.2 Hz), 3.73-3.65 (4H, m), 3.06-2.99 (4H, m), 2.55 (2H, s), 2.47 (2H, s), 1.43 (3H, t, *J* 7.2 Hz), 1.06 (6H, s). LCMS (ES+) 491.3 (M+H)⁺.

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EXAMPLE 291**2-(Morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile**

Tert-butyl nitrite (4.6 mL, 4.3 mmol) was added to a cooled mixture of copper(II) bromide (10.5 g, 46.9 mmol) in acetonitrile (50 mL). 2-Amino-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile (6.0 g, 31.3 mmol) was then added over a period of 1 h and the reaction mixture was then allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue was partitioned between DCM and 1M aqueous HCl. The organic phase was dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane) and the isolated product was combined with morpholine (4.5 mL) in DMSO (80 mL). The reaction mixture was heated at 100°C for 1.5 h, then water (300 mL) was immediately added with rapid stirring and the mixture was allowed to cool to room temperature overnight. The precipitate was filtered off, washed with water and dried *in vacuo* to give the *title compound* (5.65 g, 69%) as a pale brown solid. δ_{H} (DMSO-*d*₆) 3.80-3.72 (4H, m), 3.67-3.59 (4H, m), 2.73 (2H, t, *J* 6.0 Hz), 2.49-2.42 (2H, m), 2.13-2.03 (2H, m). LCMS (ES⁺) 263.2 (M+H)⁺.

EXAMPLE 292**{[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]amino}(oxo)acetic acid**

Sodium hydroxide (53 mg, 1.32 mmol) was added to a mixture of *Example 256* (300 mg, 0.66 mmol) in THF (10 mL) and water (10 mL) and the reaction mixture was stirred at room temperature for 3 h. The THF was removed *in vacuo* and the aqueous phase was diluted with water (10 mL), washed with EtOAc (20 mL) and acidified to pH 2 with 2M aqueous HCl. The aqueous phase was extracted with EtOAc (50 mL) and the organic phase was dried (magnesium sulfate) and the solvent was removed *in vacuo* to give the *title compound* (204 mg, 72%) as a yellow solid. δ_{H} (CDCl₃) 9.04 (1H, br s), 7.77-7.74 (1H, m), 7.59-7.47 (2H, m), 7.28-7.25 (1H, m), 3.72-3.66 (4H, m), 3.04-2.98 (4H, m), 2.51 (2H, s), 2.47 (2H, s), 1.06 (6H, s). LCMS (ES⁺) 429.0 (M+H)⁺.

EXAMPLE 293

N-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-5-methylisoxazole-3-carboxamide

The title compound was prepared from Example 77 and 5-methylisoxazole-3-carboxylic acid according to Method AL and was isolated as a cream solid (57%) after purification by preparative HPLC (pH 2.5). δ_H (CDCl₃) 8.57 (1H, br s), 7.73 (1H, t, *J* 1.7 Hz), 7.61-7.55 (1H, m), 7.44 (1H, t, *J* 7.7 Hz), 7.18-7.14 (1H, m), 6.55 (1H, d, *J* 0.8 Hz), 3.70-3.63 (4H, m), 3.04-2.96 (4H, m), 2.55 (3H, d, *J* 0.9 Hz), 2.48 (2H, s), 2.43 (2H, s), 1.04 (6H, s). LCMS (ES+) 466.3 (M+H)⁺.

EXAMPLE 294

N-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-N'-ethylethanediamide

The title compound was prepared from Example 292 and ethylamine (2M in THF) according to Method AL and was isolated as an off-white solid (5%) after purification by preparative HPLC (pH 2.5). δ_H (CDCl₃) 9.33 (1H, s), 7.70 (1H, t, *J* 1.7 Hz), 7.60-7.50 (2H, m), 7.44 (1H, t, *J* 7.7 Hz), 7.20-7.15 (1H, m), 3.70-3.63 (4H, m), 3.50-3.39 (2H, m), 3.03-2.96 (4H, m), 2.48 (2H, s), 2.43 (2H, s), 1.26 (3H, t, *J* 7.3 Hz), 1.04 (6H, s). LCMS (ES+) 456.3 (M+H)⁺.

EXAMPLE 295

3-{2-[3-(2,3-Dihydroxypropoxy)phenyl]pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

A mixture of Example 103 (30 mg, 0.069 mmol), 2,2-dimethyl-1,3-dioxolan-4-yl-methyl *p*-toluenesulfonate (30 mg, 0.104 mmol) and potassium carbonate (29 mg, 0.207 mmol) in DMF (5.0 mL) was heated at 80°C for 18 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane). The resulting intermediate was combined with *p*-toluenesulfonic acid monohydrate (1.0 mg, 0.004 mmol) in MeOH (1.5 mL) and water (0.5 mL) and the reaction mixture was stirred at room temperature for 18 h, then in a sealed tube at 80°C for 1 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 2.5) to give

the *title compound* (10 mg, 47%) as a clear oil. δ_{H} (CD_3OD) 8.71 (1H, d, J 5.3 Hz), 7.95 (1H, d, J 0.6 Hz), 7.65-7.56 (2H, m), 7.49-7.41 (2H, m), 7.13-7.07 (1H, m), 4.23-4.16 (1H, m), 4.14-3.99 (2H, m), 3.76-3.66 (6H, m), 3.12-3.04 (4H, m), 2.64 (2H, s), 2.48 (2H, s), 1.06 (6H, s). LCMS (ES+) 509.3 ($\text{M}+\text{H}$)⁺.

5

EXAMPLE 296

N-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-2-(morpholin-4-yl)-2-oxoacetamide

10 The *title compound* was prepared from *Example 292* and morpholine according to *Method AL* and was isolated as a cream solid (10%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 9.30 (1H, s), 7.66 (1H, t, J 1.7 Hz), 7.57-7.51 (1H, m), 7.43 (1H, t, J 7.7 Hz), 7.16 (1H, d, J 7.5 Hz), 4.38-4.31 (2H, m), 3.84-3.72 (6H, m), 3.70-3.61 (4H, m), 3.04-2.95 (4H, m), 2.48 (2H, s), 2.43 (2H, s), 1.04 (6H, s). LCMS (ES+) 498.3
15 ($\text{M}+\text{H}$)⁺.

EXAMPLE 297 (METHOD AQ)

5,5-Dimethyl-2-(morpholin-4-yl)-3-[3-(morpholin-4-ylcarbonyl)phenyl]-5,6-dihydro-1-benzothiophen-7(4*H*)-one

20 A mixture of *Example 66* (1.40 g, 3.39 mmol) and lithium hydroxide monohydrate (0.43 g, 10.17 mmol) in THF (12 mL), MeOH (8 mL) and water (4 mL) was stirred at room temperature for 1 h. Water (30 mL) was added and the resulting precipitate was filtered off and dried *in vacuo* to give a beige solid (1.15 g). A sample of this
25 intermediate lithium salt (50 mg, 0.13 mmol) was dissolved in DMF (2 mL) and stirred with morpholine (10 μL , 0.13 mmol), HBTU (52 mg, 0.13 mmol) and diisopropylethylamine (70 μL , 0.39 mmol) at room temperature for 72h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 2.5) to give the *title compound* (44 mg, 64%) as a white solid. δ_{H} (CDCl_3) 7.54-7.36 (4H, m), 3.91-3.42 (12H, m), 3.00-2.92 (4H, m), 2.48 (2H, s), 2.44 (2H, s), 1.04 (6H, s). LCMS (ES+) 455.4
30 ($\text{M}+\text{H}$)⁺.

EXAMPLE 298

N-Benzyl-3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)benzamide

The *title compound* was prepared from *Example 66* and benzylamine according to *Method AQ* and was isolated as a white solid (25%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 7.89-7.85 (1H, m), 7.75-7.70 (1H, m), 7.53-7.48 (2H, m), 7.41-7.29 (5H, m), 6.44-6.37 (1H, m), 4.68 (2H, d, J 5.7 Hz), 3.66-3.58 (4H, m), 2.99-2.91 (4H, m), 2.48 (2H, s), 2.43 (2H, s), 1.03 (6H, s). LCMS (ES+) 475.4 (M+H)⁺.

EXAMPLE 299

3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-isopropylbenzamide

The *title compound* was prepared from *Example 66* and isopropylamine according to *Method AQ* and was isolated as a white solid (52%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 7.83 (1H, d, J 0.6 Hz), 7.71-7.64 (1H, m), 7.54-7.46 (2H, m), 5.92 (1H, d, J 7.7 Hz), 4.38-4.26 (1H, m), 3.68-3.60 (4H, m), 3.00-2.91 (4H, m), 2.48 (2H, s), 2.43 (2H, s), 1.31 (3H, s), 1.28 (3H, s), 1.03 (6H, s). LCMS (ES+) 427.3 (M+H)⁺.

EXAMPLE 300

3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-(1H-imidazol-2-yl)benzamide

The *title compound* was prepared from *Example 66* and 2-aminoimidazole sulfate according to *Method AQ* and was isolated as a white solid (12%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 8.10 (1H, s), 8.03-7.97 (1H, m), 7.63-7.58 (2H, m), 6.66 (2H, s), 3.66-3.58 (4H, m), 2.99-2.91 (4H, m), 2.51 (2H, s), 2.45 (2H, s), 1.04 (6H, s). LCMS (ES+) 451.3 (M+H)⁺.

EXAMPLE 301

3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-ethylbenzamide

The *title compound* was prepared from *Example 66* and ethylamine (2M in THF) according to *Method AQ* and was isolated as a white solid (33%) after purification by preparative HPLC (pH 5.8). δ_{H} (CDCl_3) 7.83 (1H, s), 7.72-7.67 (1H, m), 7.55-7.47 (2H, m), 6.16-6.07 (1H, m), 3.68-3.61 (4H, m), 3.54 (2H, dq, J 7.2, 5.7 Hz), 3.00-2.93 (4H, m), 2.48 (1H, s), 2.43 (2H, s), 1.29 (3H, t, J 7.2 Hz), 1.03 (6H, s). LCMS (ES^+) 413.3 ($\text{M}+\text{H}$)⁺.

EXAMPLE 302

3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N,N-dimethylbenzamide

The *title compound* was prepared from *Example 66* and dimethylamine hydrochloride according to *Method AQ* and was isolated as a white solid (32%) after purification by preparative HPLC (pH 5.8). δ_{H} (CDCl_3) 7.51-7.38 (4H, m), 3.68-3.61 (4H, m), 3.15 (3H, s), 3.04 (3H, s), 3.00-2.94 (4H, m), 2.48 (2H, s), 2.43 (2H, s), 1.03 (6H, s). LCMS (ES^+) 413.4 ($\text{M}+\text{H}$)⁺.

EXAMPLE 303

N-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-4-methylpiperazine-1-carboxamide

The *title compound* was prepared from *Example 77* and 1-methylpiperazine according to *Method AP* and was isolated as a yellow solid (32%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 7.39-7.29 (3H, m), 7.03-6.98 (1H, m), 6.49 (1H, s), 3.69-3.63 (4H, m), 3.62-3.55 (4H, m), 3.04-2.96 (4H, m), 2.59-2.52 (4H, m), 2.45 (2H, s), 2.41 (2H, s), 2.39 (3H, s), 1.02 (6H, s). LCMS (ES^+) 483.2 ($\text{M}+\text{H}$)⁺.

EXAMPLE 304

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[2-(piperazin-1-ylmethyl)phenyl]pyridin-4-yl}-5,6-dihydro-1-benzothiophen-7(4H)-one, acetic acid salt

The *title compound* was prepared from piperazine and *Example 73* according to *Method AN* and was isolated as a brown solid (38%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.71 (1H, d, J 5.1 Hz), 7.74 (1H, s), 7.51-7.38 (5H, m), 3.62-3.56 (4H, m), 3.50 (2H, s), 3.02-2.95 (4H, m), 2.56 (2H, s), 2.52-2.45 (4H, m), 2.38 (2H, s), 2.18-2.09 (4H, m), 1.90 (3H, s), 0.97 (6H, s). LCMS (ES+) 517.5 (M+H)⁺.

EXAMPLE 305

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(pyrrolidin-1-ylmethyl)phenyl]pyridin-4-yl}-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from pyrrolidine and *Example 262* according to *Method AK* and was isolated as a brown solid (41%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.75 (1H, d, J 4.9 Hz), 8.17-8.11 (1H, m), 8.08-7.99 (2H, m), 7.51-7.37 (3H, m), 3.76 (2H, s), 3.65-3.55 (4H, m), 3.37-3.25 (4H, m, obscured), 3.03-2.94 (4H, m), 2.61 (2H, s), 2.39 (2H, s), 1.79-1.68 (4H, m), 0.97 (6H, s). LCMS (ES+) 502.5 (M+H)⁺.

EXAMPLE 306

5,5-Dimethyl-3-(2-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}pyridin-4-yl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, acetic acid salt

The *title compound* was prepared from 1-methylpiperazine and *Example 262* according to *Method AK* and was isolated as a brown solid (3%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.75 (1H, d, J 5.1 Hz), 8.11-8.00 (3H, m), 7.46 (1H, t, J 8.1 Hz), 7.42-7.35 (2H, m), 3.65-3.57 (4H, m), 3.54 (2H, s), 3.03-2.95 (4H, m), 2.60 (2H, s), 2.46-2.26 (10H, m), 2.14 (3H, s), 1.90 (6H, s), 0.98 (6H, s). LCMS (ES+) 531.6 (M+H)⁺.

EXAMPLE 307

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(piperazin-1-ylmethyl)phenyl]pyridin-4-yl}-5,6-dihydro-1-benzothiophen-7(4H)-one, acetic acid salt

The *title compound* was prepared from piperazine and *Example 262* according to *Method AK* and was isolated as a brown glass (49%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.75 (1H, d, J 4.9 Hz), 8.11-7.99 (3H, m), 7.46 (1H, t, J 7.5 Hz), 7.42-7.35 (2H, m), 3.64-3.58 (4H, m), 3.52 (2H, s), 3.03-2.95 (4H, m), 2.75-2.68 (4H, m), 2.60 (2H, s), 2.40 (2H, s), 2.38-2.30 (4H, m), 1.90 (6H, s), 0.97 (6H, s). LCMS (ES+) 517.5 (M+H)⁺.

EXAMPLE 308

10 5,5-Dimethyl-3-[2-(3-{{(3*S*)-3-Hydroxypyrrolidin-1-yl}methyl}phenyl)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, acetic acid salt

The *title compound* was prepared from (*R*)-(+)-3-hydroxypyrrolidine and *Example 262* according to *Method AK* and was isolated as a brown glass (64%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.75 (1H, d, J 4.9 Hz), 8.10 (1H, s), 8.05-7.98 (2H, m), 7.46 (1H, t, J 7.5 Hz), 7.42-7.36 (2H, m), 4.26-4.16 (1H, m), 3.72-3.57 (6H, m), 3.03-2.95 (4H, m), 2.76-2.69 (1H, m), 2.59 (2H, s), 2.58-2.53 (1H, m), 2.49-2.41 (1H, m), 2.39 (2H, s), 2.37-2.29 (1H, m), 2.07-1.94 (1H, m), 1.91 (6H, s), 1.60-1.49 (1H, m), 0.97 (6H, s). LCMS (ES+) 518.6 (M+H)⁺.

20

EXAMPLE 309

N-(2-Aminoethyl)-3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]-*N*-methylbenzamide, acetic acid salt

The *title compound* was prepared from *Example 254* and *N*-(*tert*-butoxycarbonyl)-2-(methylamino)ethylamine hydrochloride according to *Method AH* and was isolated as a yellow glass (20%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO- d_6) 8.78 (1H, d, J 5.1 Hz), 8.58 (1H, s), 8.30 (1H, d, J 7.9 Hz), 8.14 (1H, s), 7.94 (1H, d, J 7.7 Hz), 7.61 (1H, t, J 7.9 Hz), 7.44 (1H, dd, J 4.7, 0.9 Hz), 3.63-3.55 (4H, m), 3.45-3.37 (2H, m), 3.03-2.95 (4H, m), 2.74-2.66 (2H, m), 2.61 (2H, s), 2.39 (2H, s), 2.32 (3H, s), 1.88 (9H, s), 0.98 (6H, s). LCMS (ES+) 519.6 (M+H)⁺.

EXAMPLE 310 (METHOD AR)

N-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]piperazine-1-carboxamide, acetic acid salt

A solution of HCl in Et₂O (2M, 2.0 mL, 4.0 mmol) was added to a solution of *Example 286* (100 mg, 0.18 mmol) in DCM (8 mL) and the reaction mixture was stirred at room temperature for 3 h. Methanol (4 mL) was added followed by an additional solution of HCl in Et₂O (2M, 2.0 mL, 4.0 mmol) and stirring was continued for 18 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 5.8) to give the *title compound* (85 mg, 86%) as a yellow solid (20%) after purification by preparative HPLC (pH 5.8). δ_{H} (CDCl₃) 7.41-7.32 (3H, m), 7.07-6.99 (1H, m), 6.70-6.64 (1H, m), 3.74-3.55 (8H, m), 3.13-2.97 (8H, m), 2.46 (2H, s), 2.42 (2H, s), 2.08 (3H, s), 1.03 (6H, s). LCMS (ES⁺) 469.2 (M+H)⁺.

EXAMPLE 311

3-Amino-N-[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]pyrrolidine-1-carboxamide, acetic acid salt

The *title compound* was prepared from *Example 285* according to *Method AR* and was isolated as a yellow glass (78%) after purification by preparative HPLC (pH 5.8). δ_{H} (CDCl₃) 7.47-7.43 (1H, m), 7.40-7.32 (2H, m), 7.03-6.98 (1H, m), 6.35 (1H, br s), 3.82-3.51 (8H, m), 3.40-3.32 (1H, m), 3.05-2.97 (4H, m), 2.48 (2H, s), 2.43 (2H, s), 2.28-2.17 (1H, m), 1.94-1.85 (1H, m), 1.04 (6H, s). LCMS (ES⁺) 469.3 (M+H)⁺.

EXAMPLE 312

3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-[(1-methyl-1H-imidazol-4-yl)methyl]benzamide

The *title compound* was prepared from *Example 66* and (1-methyl-1H-imidazol-4-yl)methylamine according to *Method AQ* and was isolated as a yellow solid (39%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl₃) 7.85 (1H, s), 7.81-7.75 (1H, m), 7.63-7.56 (1H, m), 7.53-7.45 (3H, m), 6.97 (1H, s), 4.57 (2H, d, *J* 5.7 Hz), 3.73 (3H, s), 3.67-3.57 (4H, m), 3.00-2.91 (4H, m), 2.47 (2H, s), 2.43 (2H, s), 1.02 (6H, s). LCMS (ES⁺) 479.2 (M+H)⁺.

EXAMPLE 313

3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-[2-(morpholin-4-yl)ethyl]benzamide

- 5 The *title compound* was prepared from *Example 66* and 4-(2-aminoethyl)-morpholine according to *Method AQ* and was isolated as a yellow solid (15%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 7.87 (1H, s), 7.80-7.75 (1H, m), 7.57-7.51 (2H, m), 3.85-3.77 (3H, m), 3.68-3.59 (5H, m), 3.43-3.38 (1H, m), 3.01-2.94 (3H, m), 2.85-2.78 (1H, m), 2.77-2.69 (3H, m), 2.47 (2H, s), 2.44 (2H, s), 1.03 (6H, s).
10 LCMS (ES+) 498.2 (M+H)⁺.

EXAMPLE 314

N-(Cyanomethyl)-3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)benzamide

- 15 The *title compound* was prepared from *Example 66* and aminoacetonitrile hydrochloride according to *Method AQ* and was isolated as a white solid (49%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 7.86-7.80 (1H, m), 7.79-7.76 (1H, m), 7.61-7.53 (2H, m), 7.20-7.13 (1H, m), 4.44 (2H, d, J 5.8 Hz), 3.69-3.59 (4H, m),
20 3.00-2.90 (4H, m), 2.40 (2H, s), 2.33 (2H, s), 1.01 (6H, s). LCMS (ES+) 424.3 (M+H)⁺.

EXAMPLE 315

3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-(pyridin-2-ylmethyl)benzamide

- 25 The *title compound* was prepared from *Example 66* and 2-(aminomethyl)pyridine according to *Method AQ* and was isolated as a yellow solid (44%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 8.60-8.56 (1H, m), 7.93 (1H, s), 7.87-7.77 (3H, m), 7.57-7.46 (3H, m), 7.38-7.32 (1H, m), 4.83 (2H, d, J 4.7 Hz), 3.70-3.62 (4H, m),
30 3.02-2.94 (4H, m), 2.50 (2H, s), 2.44 (2H, s), 1.04 (6H, s). LCMS (ES+) 476.3 (M+H)⁺.

EXAMPLE 316

3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-(pyridin-4-ylmethyl)benzamide

The *title compound* was prepared from *Example 66* and 4-(aminomethyl)pyridine according to *Method AQ* and was isolated as a yellow solid (46%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 8.64-8.57 (2H, m), 7.90 (1H, s), 7.79-7.73 (1H, m), 7.57-7.52 (2H, m), 7.33-7.29 (2H, m), 6.67-6.60 (1H, m), 4.71 (2H, d, J 6.0 Hz), 3.67-3.60 (4H, m), 3.00-2.92 (4H, m), 2.46 (2H, s), 2.42 (2H, s), 1.03 (6H, s). LCMS (ES+) 476.3 ($\text{M}+\text{H}$)⁺.

EXAMPLE 317

3-[4-Amino-3-(6-chloropyridin-2-yl)phenyl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 272* and 6-chloropyridine-2-boronic acid pinacol ester according to *Method L*, heating at 150°C, and was isolated as a brown solid (14%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-d_6) 7.95 (1H, t, J 7.9 Hz), 7.86-7.81 (1H, m), 7.58 (1H, d, J 1.9 Hz), 7.44 (1H, d, J 7.7 Hz), 7.17 (1H, dd, J 8.3, 1.7 Hz), 6.88 (1H, d, J 8.3 Hz), 6.57-6.52 (1H, m), 3.65-3.54 (4H, m), 3.03-2.93 (4H, m), 2.50 (2H, s, obscured), 2.35 (2H, s), 0.97 (6H, s). LCMS (ES+) 468.3, 470.3 ($\text{M}+\text{H}$)⁺.

EXAMPLE 318 (METHOD AS)

3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-3-yl)pyridin-2-yl]benzoic acid, trifluoroacetic acid salt

Trifluoroacetic acid (3 mL) was added to a solution of *Example 333* (180 mg, 0.35 mmol) in DCM (10 mL) and the reaction mixture was stirred at room temperature for 90 minutes. The solvent was removed *in vacuo* and the residue was triturated with Et_2O to give the *title compound* (170 mg, 85%) as a bright yellow solid. δ_{H} (DMSO-d_6) 8.77 (1H, d, J 5.1 Hz), 8.74-8.71 (1H, m), 8.39-8.33 (1H, m), 8.16 (1H, s), 8.06-8.01 (1H, m), 7.67 (1H, t, J 7.7 Hz), 7.57 (1H, s), 7.52-7.48 (1H, m), 3.66-3.58 (4H, m), 2.97-2.87 (4H, m), 2.73 (2H, s), 1.20 (6H, s). LCMS (ES+) 464.3 ($\text{M}+\text{H}$)⁺.

EXAMPLE 319

3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-(pyridin-3-ylmethyl)benzamide

- 5 The *title compound* was prepared from *Example 66* and pyridin-3-ylmethylamine according to *Method A_Q* and was isolated as a yellow solid (32%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 8.56 (1H, d, *J* 1.7 Hz), 8.49 (1H, dd, *J* 4.9, 1.3 Hz), 7.88 (1H, s), 7.84-7.70 (3H, m), 7.56-7.49 (2H, m), 7.37-7.33 (1H, m), 4.66 (2H, d, *J* 6.0 Hz), 3.67-3.60 (4H, m), 3.01-2.94 (4H, m), 2.46 (2H, s), 2.43 (2H, s), 1.03 (6H, s).
10 LCMS (ES+) 476.3 (M+H)⁺.

EXAMPLE 320

- N-(2,3-Dihydroxypropyl)-3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)benzamide

- 15 The *title compound* was prepared from *Example 66* and 3-amino-1,2-propanediol according to *Method A_Q* and was isolated as a white solid (9%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 7.86-7.82 (1H, m), 7.79-7.74 (1H, m), 7.57-7.50 (2H, m), 6.87-6.79 (1H, m), 3.99-3.91 (1H, m), 3.77-3.59 (7H, m), 3.05-2.93 (5H, m),
20 2.45 (2H, s), 2.40 (2H, s), 1.02 (6H, s). LCMS (ES+) 459.3 (M+H)⁺.

EXAMPLE 321

- 5,5-Dimethyl-3-{2-[3-(methylsulfonyl)phenyl]pyridin-4-yl}-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

- 25 The *title compound* was prepared from *Example 73* and 3-(methanesulfonyl)-phenylboronic acid according to *Method L* and was isolated as a white solid (60%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-d_6) 8.81 (1H, d, *J* 4.9 Hz), 8.69 (1H, s), 8.50 (1H, d, *J* 7.9 Hz), 8.23 (1H, s), 8.02 (1H, d, *J* 8.1 Hz), 7.81 (1H, t, *J* 7.9 Hz),
30 7.49 (1H, dd, *J* 5.1, 1.1 Hz), 3.63-3.56 (4H, m), 3.02-2.95 (4H, m), 2.59 (2H, s), 2.40 (2H, s), 2.09 (3H, s), 0.97 (6H, s). LCMS (ES+) 497.4 (M+H)⁺.

EXAMPLE 322

tert-Butyl 4-{3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)pyridin-2-yl]benzoyl}piperazine-1-carboxylate

The *title compound* was prepared from *Example 318* and 1-(*tert*-butoxycarbonyl)-piperazine according to *Method I* and was isolated as an off-white solid (51%) after purification by column chromatography (SiO₂, 0-4.5% MeOH/DCM) and trituration with Et₂O. δ_{H} (DMSO-*d*₆) 8.74 (1H, d, *J* 5.1 Hz), 8.25 (1H, d, *J* 7.9 Hz), 8.17 (1H, s), 8.10 (1H, s), 7.64-7.54 (2H, m), 7.51-7.46 (2H, m), 3.66-3.56 (4H, m), 3.40-3.32 (8H, m, obscured), 2.95-2.87 (4H, m), 2.72 (2H, s), 1.41 (9H, s), 1.19 (6H, s). LCMS (ES+) 632.2 (M+H)⁺.

EXAMPLE 323 (METHOD AT)

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(piperazin-1-ylcarbonyl)phenyl]pyridin-4-yl}-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one

Trifluoroacetic acid (1 mL) was added to a solution of *Example 322* (40 mg, 0.06 mmol) in DCM (5 mL) and the reaction mixture was stirred at room temperature for 75 minutes. The solvent was removed *in vacuo* and the residue was triturated with Et₂O to give the *title compound* (48 mg, 100%) as a yellow-orange solid. δ_{H} (DMSO-*d*₆) 8.97-8.83 (1H, m), 8.75 (1H, d, *J* 4.9 Hz), 8.29-8.21 (2H, m), 8.10 (1H, s), 7.67-7.47 (4H, m), 3.87-3.66 (4H, m), 3.64-3.55 (4H, m), 3.28-3.10 (4H, m), 2.96-2.85 (4H, m), 2.71 (2H, s), 1.19 (6H, s). LCMS (ES+) 532.6 (M+H)⁺.

EXAMPLE 324 (METHOD AU)

5,5-Dimethyl-2-(morpholin-4-yl)-3-{6-[3-(piperazin-1-ylcarbonyl)phenyl]pyridin-2-yl}-5,6-dihydro-1-benzothiophen-7(4*H*)-one

A mixture of *Example 17* (1.00 g, 2.56 mmol), 6-chloropyridine-2-boronic acid pinacol ester (613 mg, 2.56 mmol), K₃PO₄ (1.63 g, 7.67 mmol) and Pd(PPh₃)₄ (148 mg, 0.128 mmol) in DME (6 mL) and water (2 mL) was heated in a sealed tube at 120°C, under microwave irradiation, for 20 minutes. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane). A sample of this intermediate (100 mg, 0.27 mmol) was combined with 3-(*tert*-butoxy-

carbonyl)phenylboronic acid (65 mg, 0.29 mmol), K₃PO₄ (170 mg, 0.80 mmol) and Pd(PPh₃)₄ (31 mg, 0.03 mmol) in DME (3 mL) and water (1 mL) and the mixture was heated in a sealed tube at 140°C, under microwave irradiation, for 2 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-50% EtOAc/heptane). Trifluoroacetic acid (1 mL) was added to a solution of the product in DCM (5 mL) and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue was combined with EDC.HCl (61 mg, 0.32 mmol), triethylamine (0.15 mL, 1.06 mmol) and piperazine (28 mg, 0.32 mmol) in DCM (10 mL) and the mixture was stirred at room temperature for 48 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 5.8) to give the *title compound* (20 mg, 5%) as a yellow solid. δ_H (CD₃OD) 8.24-8.17 (2H, m), 8.04-7.97 (1H, m), 7.94-7.89 (1H, m), 7.70-7.61 (2H, m), 7.56-7.52 (1H, m), 3.97-3.75 (2H, m), 3.74-3.67 (4H, m), 3.66-3.54 (2H, m), 3.12-3.06 (4H, m), 3.05-2.93 (4H, m), 2.74 (2H, s), 2.48 (2H, s), 1.98 (3H, s), 1.07 (6H, s). LCMS (ES+) 531.5 (M+H)⁺.

EXAMPLE 325

3-[2-(3-{[(3*S*)-3-Aminopyrrolidin-1-yl]carbonyl}phenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, hydrochloride salt

The *title compound* was prepared from *Example 254* and (3*S*)-(-)-3-(*tert*-butoxycarbonylamino)pyrrolidine according to *Method AH* and was isolated as a clear glass (46%) after purification by column chromatography (SiO₂, 0-20% MeOH/DCM). δ_H (CD₃OD) 8.63 (1H, d, *J* 5.3 Hz), 8.13 (1H, d, *J* 9.6 Hz), 8.09-8.02 (1H, m), 7.93-7.88 (1H, m), 7.60-7.50 (2H, m), 7.37 (1H, dd, *J* 5.1, 1.5 Hz), 3.83-3.61 (3H, m), 3.60-3.41 (6H, m), 3.00-2.92 (4H, m), 2.53 (2H, s), 2.36 (2H, s), 2.25-2.07 (1H, m), 1.91-1.76 (1H, m), 0.94 (6H, s). LCMS (ES+) 531.3 (M+H)⁺.

EXAMPLE 326

3-[2-(3-{[(3*R*)-3-Aminopyrrolidin-1-yl]carbonyl}phenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 254* and (3*R*)-(+)-3-(*tert*-butoxycarbonylamino)pyrrolidine according to *Method AH*. The reaction mixture was

basified with saturated sodium hydrogencarbonate solution and extracted into DCM. The *title compound* was isolated as an off-white solid (55%) after purification by column chromatography (SiO₂, 0-20% MeOH/DCM). δ_{H} (CDCl₃) 8.76 (1H, d, *J* 5.1 Hz), 8.21 (1H, d, *J* 1.3 Hz), 8.13-8.07 (1H, m), 7.81 (1H, s), 7.65-7.51 (2H, m), 7.30-7.28 (1H, m), 3.93-3.22 (10H, m), 3.06-2.99 (4H, m), 2.53 (2H, s), 2.46 (2H, s), 2.27-2.01 (1H, m), 1.87-1.67 (1H, m), 1.66-1.45 (2H, m), 1.05 (6H, s). LCMS (ES+) 531.2 (M+H)⁺.

EXAMPLE 327

10 3-[2-(3-{[(3*R*)-3-Aminopyrrolidin-1-yl]carbonyl}phenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, hydrochloride salt

The *title compound* was prepared from *Example 254* and (3*R*)-(+)-3-(*tert*-butoxycarbonylamino)pyrrolidine according to *Method AH* and was isolated as a clear glass (46%) after purification by column chromatography (SiO₂, 0-20% MeOH/DCM).

15 δ_{H} (CD₃OD) 8.84 (1H, d, *J* 6.0 Hz), 8.43-8.35 (1H, m), 8.26-8.19 (1H, m), 8.17-8.11 (1H, m), 8.08-7.99 (1H, m), 7.93-7.78 (2H, m), 4.11-3.96 (2H, m), 3.93-3.68 (7H, m), 3.19-3.11 (4H, m), 2.75 (2H, s), 2.51 (2H, s), 2.51-2.39 (1H, m), 2.25-2.10 (1H, m), 1.07 (6H, s). LCMS (ES+) 531.3 (M+H)⁺.

EXAMPLE 328

20 2-(Morpholin-4-yl)-3-{2-[3-(piperazin-1-yl)carbonyl]phenyl}pyridin-4-yl}-5,6-dihydro-1-benzothiophen-7(4*H*)-one, acetic acid salt

The *title compound* was prepared from *Intermediate 2*, 2-chloropyridine-4-boronic acid and 3-(*tert*-butoxycarbonyl)phenylboronic acid according to *Method AU* and was isolated as a clear glass (13%) after purification by preparative HPLC (pH 5.8). δ_{H} (CDCl₃) 8.98 (1H, d, *J* 5.7 Hz), 8.61 (1H, t, *J* 1.5 Hz), 8.28-8.21 (2H, m), 8.03 (1H, d, *J* 0.9 Hz), 7.71 (1H, t, *J* 7.9 Hz), 7.65 (1H, dd, *J* 5.7, 1.7 Hz), 3.78-3.71 (4H, m), 3.12-3.05 (4H, m), 2.78-2.71 (2H, m), 2.68-2.62 (2H, m), 2.22-2.12 (2H, m). LCMS (ES+) 503.3 (M+H)⁺.

EXAMPLE 329

N-[2-(Dimethylamino)ethyl]-*N'*-[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]ethanediamide

Isobutyl chloroformate (30 μ L, 0.23 mmol) and triethylamine (30 μ L, 0.23 mmol) were added to a solution of *Example 292* (50 mg, 0.12 mmol) in DCM (5.0 mL) and the reaction mixture was stirred at room temperature for 1 h. *N,N*-Dimethylethylenediamine (60 μ L, 0.58 mmol) was then added and the reaction mixture was stirred at room temperature for 72 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 5.8) to give the *title compound* (4 mg, 6%) as a yellow solid. δ_{H} (CDCl₃) 9.12 (1H, s), 8.41 (1H, br s), 7.55-7.46 (2H, m), 7.29 (1H, t, *J* 7.9 Hz), 7.05-7.00 (1H, m), 3.61-3.49 (6H, m), 2.90-2.77 (6H, m), 2.49 (6H, s), 2.33 (2H, s), 2.29 (2H, s), 0.90 (6H, s). LCMS (ES⁺) 499.3 (M+H)⁺.

EXAMPLE 330

N-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-*N'*-[2-{pyrrolidin-1-yl}ethyl]ethanediamide

Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (145 mg, 0.33 mmol) and 1-(2-aminoethyl)pyrrolidine (60 μ L, 0.49 mmol) were added to a solution of *Example 292* (70 mg, 0.16 mmol) in DCM (10 mL) and the reaction mixture was stirred at room temperature for 18 h. A further portion of 1-(2-aminoethyl)-pyrrolidine (60 μ L, 0.49 mmol) was added and stirring was continued for 72 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 2.5) to give the *title compound* (16 mg, 19%) as an off-white solid. δ_{H} (CDCl₃) 9.26 (1H, s), 8.43 (1H, br s), 7.74-7.69 (1H, m), 7.65-7.59 (1H, m), 7.45 (1H, t, *J* 7.7 Hz), 7.23-7.16 (1H, m), 3.78-3.64 (6H, m), 3.11-2.92 (10H, m), 2.49 (2H, s), 2.45 (2H, s), 2.07-1.96 (4H, m), 1.05 (6H, s). LCMS (ES⁺) 525.3 (M+H)⁺.

EXAMPLE 331 (METHOD AV)

3-(2-Amino-6-phenylpyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

A mixture of *Example 332* (40 mg, 0.07 mmol) in trifluoroacetic acid (10 mL) was heated under reflux for 1 h. The solvent was removed *in vacuo* and the residue was

purified by column chromatography (SiO₂, 0-100% EtOAc/heptane) to give the *title compound* (17 mg, 54%) as a white solid. δ_{H} (CD₃OD) 7.88-7.82 (2H, m), 7.68-7.62 (3H, m), 7.34 (1H, d, *J* 1.5 Hz), 7.01 (1H, d, *J* 1.5 Hz), 3.78-3.70 (4H, m), 3.21-3.13 (4H, m), 2.72 (2H, s), 2.49 (2H, s), 1.08 (6H, s). LCMS (ES⁺) 434.3 (M+H)⁺.

5

EXAMPLE 332 (METHOD AW)

3-{2-[(4-Methoxybenzyl)amino]-6-phenylpyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

10 A mixture of *Example 269* (100 mg, 0.24 mmol), 4-methoxybenzylamine (158 μ L, 1.21 mmol) and triethylamine (168 mL, 1.21 mmol) in NMP (2.0 mL) was heated at 230°C, under microwave irradiation, for 1 h. The reaction mixture was purified by column chromatography (SiO₂, 0-50% EtOAc/heptane) and triturated with water to give a pale yellow solid after drying *in vacuo*. The solid was combined with phenylboronic acid
15 (9 mg, 0.07 mmol), K₃PO₄ (30 mg, 0.14 mmol) and Pd(PPh₃)₄ (20 mg, 0.02 mmol) in DME (1.5 mL) and water (0.5 mL) and was heated in a sealed tube at 120°C, under microwave irradiation, for 1 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane) to give the *title compound* (44 mg, 39%) as a white solid. δ_{H} (CDCl₃) 8.04-8.00 (2H, m), 7.51-7.33 (5H, m), 7.12 (1H, d, *J* 0.8 Hz), 6.93-6.85 (2H, m), 6.24 (1H, d, *J* 0.8 Hz), 5.15-5.08 (1H, m),
20 4.54 (2H, d, *J* 5.7 Hz), 3.82 (3H, s), 3.66-3.58 (4H, m), 3.08-2.99 (4H, m), 2.41 (2H, s), 2.38 (2H, s), 0.99 (6H, s). LCMS (ES⁺) 554.3 (M+H)⁺.

EXAMPLE 333

25

tert-Butyl 3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-3-yl)pyridin-2-yl]benzoate

The *title compound* was prepared from *Intermediate 19*, 2-chloropyridine-4-boronic acid and 3-(*tert*-butoxycarbonyl)phenylboronic acid according to *Method AF* and
30 was isolated as an off-white solid (30%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_{H} (DMSO-*d*₆) 8.77 (1H, d, *J* 5.1 Hz), 8.64 (1H, s), 8.35 (1H, d, *J* 7.9 Hz), 8.10 (1H, s), 7.99 (1H, d, *J* 7.7 Hz), 7.65 (1H, t, *J* 7.7 Hz), 7.57 (1H, s),

7.48 (1H, dd, *J* 5.1, 1.1 Hz), 3.67-3.57 (4H, m), 2.96-2.87 (4H, m), 2.72 (2H, s), 1.59 (9H, s), 1.20 (6H, s). LCMS (ES⁺) 520.2 (M+H)⁺.

EXAMPLE 334

5
3-[2-(3-Acetylphenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one

The *title compound* was prepared from *Intermediate 19*, 2-chloropyridine-4-boronic acid and 3-acetylphenylboronic acid according to *Method AF* and was isolated as
10 a beige solid (30%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane) and preparative HPLC (pH 2.5). δ_{H} (DMSO-*d*₆) 8.77 (1H, d, *J* 5.1 Hz), 8.68 (1H, s), 8.42-8.37 (1H, m), 8.19 (1H, s), 8.07-8.02 (1H, m), 7.68 (1H, t, *J* 7.7 Hz), 7.57 (1H, s), 7.50-7.47 (1H, m), 3.66-3.58 (4H, m), 2.95-2.88 (4H, m), 2.75 (2H, s), 2.68 (3H, s), 1.20 (6H, s). LCMS (ES⁺) 462.3 (M+H)⁺.

EXAMPLE 335

3-[2-(3-[(3-*exo*)-3-Amino-8-azabicyclo[3.2.1]oct-8-yl]carbonyl}phenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

20 A mixture of *Example 254* (105 mg, 0.23 mmol), *Intermediate 63* (70 mg, 0.27 mmol), and EDC (87 mg, 0.45 mmol) in DCM (5.0 mL) was stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100%EtOAc/heptane). The resulting white solid was combined with hydrazine monohydrate (11 μ L, 0.23 mmol) and EtOH (2.0 mL) and heated in a
25 sealed tube at 100°C, under microwave irradiation, for 70 minutes. The reaction mixture was filtered and the filtrate was purified by column chromatography (SiO₂, 0-20% MeOH/DCM) to give the *title compound* (23 mg, 17%) as an off-white solid. δ_{H} (CD₃OD) 1.05 (6H, s), 1.59-1.47 (1H, m), 1.79-1.66 (1H, m), 1.95-1.79 (3H, m), 2.17-1.98 (3H, m), 2.48 (2H, s), 2.64 (2H, s), 3.12-3.04 (4H, m), 3.34-3.25 (1H, m), 3.73-3.64
30 (4H, m), 4.24-4.17 (1H, m), 4.85-4.78 (1H, m), 7.48 (1H, dd, *J* 5.1, 1.5 Hz), 7.69-7.59 (2H, m), 8.03 (1H, s), 8.21-8.15 (2H, m), 8.75 (1H, d, *J* 5.1 Hz). LCMS (ES⁺) 571 (M+H)⁺.

EXAMPLE 336

3-(3-Benzoylphenyl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

- 5 A mixture of *Example 66* (1.40 g, 3.39 mmol) and lithium hydroxide monohydrate (0.43 g, 10.17 mmol) in THF (12 mL), MeOH (8 mL) and water (4 mL) was stirred at room temperature for 1 h. Water (30 mL) was added and the resulting precipitate was filtered off and dried *in vacuo* to give a beige solid (1.15 g). A sample of this intermediate lithium salt (177 mg, 0.45 mmol) was combined with HBTU (179 mg, 0.45
- 10 mmol), *N,O*-dimethylhydroxylamine hydrochloride (44 mg, 0.45 mmol) and diisopropylethylamine (0.24 mL, 1.35 mmol) in DMF (3.0 mL) and stirred at room temperature for 40 h. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc (150 mL) and water (50 mL). The organic phase was washed with water (2 x 50 mL), dried (magnesium sulfate) and the solvent was removed *in vacuo*. The
- 15 residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane) and the resulting yellow solid was dissolved in THF (5.0 mL). This solution was added dropwise to a cooled (-78°C) solution of phenyllithium (1.9M in butyl ether, 0.76 mL, 1.44 mmol) in THF (8.0 mL) and the reaction mixture was allowed to stir at -78°C for 1 h, then at room temperature for 18 h. The reaction was quenched with aqueous ammonium chloride
- 20 solution (1.0 mL), diluted with water (15 mL) and extracted with EtOAc (2 x 70 mL). The combined organic layers were dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane) and preparative HPLC (pH 2.5) to give the *title compound* (15 mg, 7%) as a yellow solid. δ_{H} (CDCl₃) 7.79-7.89 (4H, m), 7.69-7.50 (5H, m), 3.72-3.64 (4H, m), 3.04-
- 25 2.96 (4H, m), 2.53 (2H, s), 2.47 (2H, s), 1.08 (6H, s). LCMS (ES⁺) 446.3 (M+H)⁺.

EXAMPLE 337

3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]-*N*-(piperidin-4-ylmethyl)benzamide, acetic acid salt

30

A solution of HCl in Et₂O (2M, 1.6 mL, 3.2 mmol) was added to a solution of *Example 338* (105 mg, 0.16 mmol) in DCM (5.0 mL) and the reaction mixture was stirred at room temperature for 72 h. The precipitate was filtered off and purified by preparative

HPLC (pH 5.8) to give the *title compound* (99 mg, 78%) as a yellow gum. δ_{H} (CD₃OD) 8.79-8.74 (1H, m), 8.51 (1H, t, J 1.7 Hz), 8.25-8.19 (1H, m), 8.03 (1H, d, J 0.6 Hz), 7.98-7.92 (1H, m), 7.66 (1H, t, J 7.7 Hz), 7.49 (1H, dd, J 5.1, 1.5 Hz), 3.73-3.64 (4H, m), 3.49-3.37 (4H, m), 3.13-2.93 (6H, m), 2.64 (2H, s), 2.48 (2H, s), 2.10-1.99 (3H, m), 1.94 (6H, m), 1.61-1.44 (2H, m), 1.06 (6H, s). LCMS (ES+) 559.3 (M+H)⁺.

EXAMPLE 338

tert-Butyl 4-[(3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzoyl}amino)methyl]piperidine-1-carboxylate

The *title compound* was prepared from *Example 254* and 4-(aminomethyl)-1-(*tert*-butoxycarbonyl)piperidine according to *Method I* and was obtained as a yellow solid (47%) after purification by column chromatography (SiO₂, 75-100% EtOAc/heptane). δ_{H} (CDCl₃) 8.80 (1H, d, J 5.3 Hz), 8.56 (1H, br m), 8.17-8.11 (1H, m), 7.98-7.90 (2H, m), 7.62 (1H, t, J 7.7 Hz), 7.41-7.35 (1H, m), 6.75-6.43 (1H, br m), 4.25-4.07 (2H, m), 3.77-3.66 (4H, m), 3.51-3.35 (2H, m), 3.12-3.00 (4H, m), 2.83-2.64 (2H, m), 2.57 (2H, s), 2.48 (2H, s), 1.95-1.74 (3H, m), 1.72-1.52 (2H, m), 1.47 (9H, s), 1.06 (6H, s). LCMS (ES+) 659.2 (M+H)⁺.

EXAMPLE 339

5,5-Dimethyl-3-{2-[(4-Methoxybenzyl)oxy]-6-phenylpyridin-4-yl}-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

A mixture of *Example 269* (100 mg, 0.24 mmol), 4-methoxybenzyl alcohol (138 mg, 1.0 mmol) and triethylamine (168 mL, 1.2 mmol) in NMP (2.0 mL) was heated in a sealed tube at 230°C, under microwave irradiation, for 20 minutes. Sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol) was then added and the reaction mixture was stirred at room temperature for 20 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane). The resulting white solid was combined with phenylboronic acid (19 mg, 0.16 mmol), K₃PO₄ (60 mg, 0.28 mmol) and Pd(PPh₃)₄ (40 mg, 0.035 mmol) in DME (3.0 mL) and water (1.0 mL) and was heated in a sealed tube at 120°C, under microwave irradiation, for 1 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography

(SiO₂, 0-50% EtOAc/heptane) and preparative HPLC (pH 2.5) to give the *title compound* (26 mg, 19%) as a white solid. δ_{H} (CDCl₃) 8.13-8.07 (2H, m), 7.55-7.44 (6H, m), 6.99-6.92 (2H, m), 6.67 (1H, d, *J* 0.9 Hz), 5.49 (2H, s), 3.83 (3H, s), 3.72-3.64 (4H, m), 3.10-3.00 (4H, m), 2.53 (2H, s), 2.43 (2H, s), 1.04 (6H, s). LCMS (ES+) 555.4 (M+H)⁺.

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EXAMPLE 340

3-[2-(3-Aminophenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

10 The *title compound* was prepared from *Example 73* and 3-aminophenylboronic acid according to *Method L* and was obtained as an off-white solid (19%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane) and preparative HPLC (pH 2.5). δ_{H} (CD₃OD) 8.67 (1H, d, *J* 4.9 Hz), 7.86 (1H, s), 7.42 (1H, dd, *J* 5.1, 1.5 Hz), 7.36-7.32 (1H, m), 7.30-7.23 (2H, m), 6.88-6.82 (1H, m), 3.74-3.65 (4H, m), 3.13-
15 3.04 (4H, m), 2.63 (2H, s), 2.48 (2H, s), 1.06 (6H, s). LCMS (ES+) 434.3 (M+H)⁺.

EXAMPLE 341

4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)-6-phenylpyridin-2(1H)-one

20 A solution of *Example 339* (36 mg, 0.065 mmol) in trifluoroacetic acid (10 mL) was heated at reflux for 4 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane) to give the *title compound* (12 mg, 42%) as an off-white solid. δ_{H} (CDCl₃) 7.70-7.64 (2H, m), 7.58-7.52
25 (3H, m), 6.70 (1H, d, *J* 1.3 Hz), 6.46 (1H, d, *J* 1.3 Hz), 3.77-3.70 (4H, m), 3.17-3.11 (4H, m), 2.61 (2H, s), 2.45 (2H, s), 1.07 (6H, s). LCMS (ES+) 435.3 (M+H)⁺.

EXAMPLE 342

30 5,5-Dimethyl-3-[2-(3-methylphenyl)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

 The *title compound* was prepared from *Example 73* and *m*-tolylboronic acid according to *Method L* and was obtained as an off-white solid (81%) after purification by

column chromatography (SiO₂, 10-90% EtOAc/heptane). δ_{H} (DMSO-d₆) 8.73 (1H, d, J 5.1 Hz), 7.99 (2H, d, J 6.4 Hz), 7.93 (1H, dd, J 7.7, 0.6 Hz), 7.45-7.37 (2H, m), 7.28 (1H, d, J 7.7 Hz), 3.63-3.54 (4H, m), 3.02-2.94 (4H, m), 2.58 (2H, s), 2.41 (3H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES⁺) 433.3 (M+H)⁺.

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EXAMPLE 343

3-[2-(3-Bromo-5-methylphenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

10 The *title compound* was prepared from *Example 73* and 3-bromo-5-methylboronic acid according to *Method L* and was obtained as a white solid (6%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane) and preparative HPLC (pH 2.5). δ_{H} (DMSO-d₆) 8.74 (1H, d, J 5.1 Hz), 8.13 (1H, s), 8.08 (1H, s), 7.99 (1H, d, J 0.4 Hz), 7.51 (1H, s), 7.43 (1H, dd, J 5.1, 1.5 Hz), 3.62-3.54 (4H, m), 3.02-2.94 (4H, m), 2.56 (2H, s), 2.41 (3H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES⁺) 511.3, 513.2 (M+H)⁺.

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EXAMPLE 344 (METHOD AX)

3-[(2E)-3-(Dimethylamino)prop-2-enoyl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

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A mixture of *Example 284* (418 mg, 1.36 mmol) and DMF-dimethyl acetal (10 mL, 45 mmol) was heated in a sealed tube at 140°C, under microwave irradiation, for 2 h. The solvent was removed *in vacuo* and the residue was triturated with Et₂O to give the *title compound* (322 mg, 65%) as a yellow solid. δ_{H} (CDCl₃) 7.90-7.58 (1H, br m), 5.65-5.41 (1H, br m), 3.85-3.76 (4H, m), 3.30-3.26 (4H, m), 3.20-3.11 (3H, m), 2.98-2.90 (3H, m), 2.79-2.67 (2H, m), 2.41 (2H, s), 1.08 (6H, s). LCMS (ES⁺) 363.1 (M+H)⁺.

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EXAMPLE 345

N-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]methanesulfonamide

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The *title compound* was prepared from *Example 17* and 4-(methanesulfonylamino)phenylboronic acid according to *Method L* and was obtained as an off-white solid

(63%) after purification by column chromatography (SiO₂, 10-100% EtOAc/heptane). δ_{H} (DMSO-d₆) 9.92 (1H, s), 7.39-7.25 (4H, m), 3.62-3.53 (4H, m), 3.06 (3H, s), 2.95-2.87 (4H, m), 2.47, (2H, s), 2.36 (2H, s), 0.96 (6H, s). LCMS (ES⁺) 435.2 (M+H)⁺.

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EXAMPLE 346

1-{3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl}-3-(piperidin-4-yl)urea, formic acid salt

Triethylamine (0.2 mL, 1.15 mmol) and triphosgene (42 mg, 0.12 mmol) were added to a solution of *Example 340* (100 mg, 0.23 mmol) in THF (15 mL) and the reaction mixture was stirred at 0°C for 30 minutes. The reaction mixture was then cooled to -78°C and 4-amino-1-(*tert*-butoxycarbonyl)piperidine (56 mg, 0.27 mmol) was added. The reaction mixture was then stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane). The resulting off-white solid was taken up in methanol (3.0 mL) and a solution of HCl in Et₂O (2M, 3.0 mL, 6.0 mmol) was added. The reaction mixture was stirred at room temperature for 1 h then the solvent was removed *in vacuo*. The residue was purified by preparative HPLC (pH 2.5) to give the *title compound* (39 mg, 54%) as an off-white solid. δ_{H} (CD₃OD) 8.70 (1H, d, *J* 5.3 Hz), 8.15 (1H, d, *J* 0.9 Hz), 8.44 (1H, s), 7.94 (1H, d, *J* 0.6 Hz), 7.66-7.62 (1H, m), 7.48-7.40 (3H, m), 3.96-3.84 (1H, m), 3.75-3.67 (4H, m), 3.50-3.39 (2H, m), 3.20-3.13 (2H, m), 3.12-3.06 (4H, m), 2.64 (2H, s), 2.48 (2H, s), 2.20 (2H, m), 1.74 (2H, m), 1.06 (6H, s). LCMS (ES⁺) 560.2 (M+H)⁺.

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EXAMPLE 347 (METHOD AY)

3-[2-(3-{[(3*R*)-3-Aminopyrrolidin-1-yl]carbonyl}phenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one, trifluoroacetic acid salt

A mixture of *Example 318* (37 mg, 0.064 mmol), EDC (26 mg, 0.136 mmol), Et₃N (30 μ L, 0.215 mmol), 3*R*-(+)-(tert-butoxycarbonylamino)pyrrolidine (26 mg, 0.140 mmol) and 1-hydroxybenzotriazole (*ca* 1 mg) in DCM (4.0 mL) was stirred at room temperature for 18 h. Further EDC (13 mg, 0.064 mmol), Et₃N (10 μ L, 0.072 mmol), 3*R*-(+)-(tert-butoxycarbonylamino)pyrrolidine (13 mg, 0.070 mmol) and HOBT (*ca* 1mg) were added and stirring was continued for 48 h. The reaction mixture was diluted with

DCM (10 mL), then washed with water (15 mL) and saturated aqueous sodium hydrogencarbonate solution (15 mL). The organic phase was dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-5% MeOH/DCM) to give a pale yellow solid, which was dissolved in DCM (5.0 mL) and treated with trifluoroacetic acid (1.0 mL). The reaction mixture was stirred at room temperature for 75 minutes, the solvent was then removed *in vacuo* and the residue was treated with toluene (5 mL) and concentrated *in vacuo*. The residue was triturated with Et₂O and dried *in vacuo* to give the *title compound* (27 mg, 56%) as a yellow solid. δ_{H} (DMSO-d₆) 8.77-8.74 (1H, m), 8.30 (1H, s), 8.23-8.19 (1H, m), 8.00 (1H, s), 7.64-7.59 (2H, m), 7.42-7.40 (1H, m), 3.94-3.87 (1H, m), 3.87-3.80 (1H, m), 3.80-3.70 (1H, m), 3.63-3.57 (6H, m), 2.98-2.92 (4H, m), 2.70 (2H, s), 2.36-2.25 (1H, m), 2.09-1.98 (1H, m), 1.25 (6H, s). LCMS (ES⁺) 532.3 (M+H)⁺.

EXAMPLE 348

3-[2-(3-{[(3*S*)-3-Aminopyrrolidin-1-yl]carbonyl}phenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one, trifluoroacetic acid salt

The *title compound* was prepared from *Example 318* and 3*S*-(-)-(tert-butoxycarbonylamino)pyrrolidine according to *Method AY* and was obtained as a yellow solid (39%). δ_{H} (DMSO-d₆) 8.74 (1H, d, *J* 5.3 Hz), 8.36-8.30 (1H, m), 8.26-8.22 (1H, m), 8.09 (1H, s), 8.07-8.03 (1H, m), 7.98-7.90 (1H, m), 7.66-7.56 (3H, m), 7.48 (1H, dd, *J* 4.9, 1.1 Hz), 3.97-3.87 (1H, m), 3.87-3.61 (2H, m), 3.60-3.50 (6H, m), 3.01-2.88 (4H, m), 2.71 (2H, s), 2.33-2.17 (1H, m), 2.09-1.93 (1H, m), 1.19 (6H, s), LCMS (ES⁺) 532.3 (M+H)⁺.

EXAMPLE 349

tert-Butyl [(3*S*)-1-{3-[4-(2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzoyl}pyrrolidin-3-yl]carbamate

The *title compound* was prepared from *Intermediate 2*, 2-chloropyridine-4-boronic acid and *Intermediate 59* according to *Method AI* and was obtained as a clear glass (84%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_{H} (CDCl₃) 8.79-8.72 (1H, m), 8.24-8.17 (1H, m), 8.13-8.06 (1H, m), 7.83-7.76 (1H, m),

7.63-7.49 (2H, m), 7.32 (1H, dd, J 4.9, 1.3 Hz), 4.76-4.55 (1H, m), 4.40-4.12 (1H, m), 3.99-3.74 (2H, m), 3.72-3.65 (4H, m), 3.64-3.32 (1H, m), 3.09-2.98 (4H, m), 2.71-2.64 (2H, m), 2.64-2.58 (2H, m), 2.35-2.06 (3H, m), 1.99-1.82 (1H, m), 1.47 (4H, s), 1.39 (5H, s). LCMS (ES+) 603.2 (M+H)⁺.

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EXAMPLE 350

tert-Butyl [(3R)-1-{3-[4-(2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzoyl}pyrrolidin-3-yl]carbamate

10 The *title compound* was prepared from *Intermediate 2*, 2-chloropyridine-4-boronic acid and *Intermediate 60* according to *Method AI* and was obtained as a white solid (81%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_{H} (CDCl₃) 8.75 (1H, d, J 5.1 Hz), 8.23-8.17 (1H, m), 8.09 (1H, dt, J 7.3, 1.7 Hz), 7.79 (1H, s), 7.63-7.50 (2H, m), 7.32 (1H, dd, J 4.9, 1.3 Hz), 4.75-4.57 (1H, m), 4.40-4.13 (1H, m),
15 3.98-3.73 (2H, m), 3.72-3.64 (4H, m), 3.63-3.32 (2H, m), 3.08-2.98 (4H, m), 2.67 (2H, t, J 5.8 Hz), 2.64-2.58 (2H, m), 2.35-2.19 (1H, m), 2.19-2.06 (2H, m), 1.98-1.83 (1H, m), 1.47 (4H, s), 1.39 (5H, s). LCMS (ES+) 603.2 (M+H)⁺.

EXAMPLE 351

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3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]-N,N-dimethyl-5-nitrobenzamide

25 The *title compound* was prepared from *Example 73* and 5-(N,N-dimethylamino-carbonyl)-3-nitrophenylboronic acid according to *Method L* and was obtained as a yellow solid (83%) after purification by column chromatography (SiO₂, 10-100% EtOAc/heptane, then 15% MeOH/EtOAc). δ_{H} (DMSO-d₆) 9.03 (1H, t, J 1.7 Hz), 8.83 (1H, d, J 4.9 Hz), 8.67-8.62 (1H, m), 8.33 (1H, s), 8.30-8.27 (1H, m), 7.53 (1H, dd, J 4.9, 1.1 Hz), 3.58 (4H, m), 3.05 (3H, s), 3.02-2.95 (7H, m), 2.59 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES+) 535.3 (M+H)⁺.

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EXAMPLE 352

5,5-Dimethyl-3-[2-(2-methylphenyl)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 73* and 2-methylphenylboronic acid according to *Method L* and was obtained as a white solid (94%) after purification by column chromatography (SiO₂, 10-90% EtOAc/heptane). δ_{H} (DMSO-d₆) 8.77-8.71 (1H, m), 7.50 (1H, s), 7.44 (2H, dd, *J* 5.1, 1.5 Hz), 7.37-7.28 (3H, m), 3.55-3.64 (4H, m), 2.91-3.02 (4H, m), 2.58 (2H, s), 2.47-2.55 (2H, m), 2.38 (3H, s), 0.98 (6H, s). LCMS (ES+) 433.3 (M+H)⁺.

EXAMPLE 353

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(morpholin-4-ylacetyl)phenyl]pyridin-4-yl}-5,6-dihydrothieno[2,3-*c*]pyridin-7(4H)-one, formic acid salt

Morpholine (30 μ L, 0.344 mmol), potassium carbonate (16 mg, 0.116 mmol) and potassium iodide (20 mg, 0.120 mmol) were added to a solution of *Intermediate 56* (56 mg, 0.113 mmol) in DME (3.0 mL) and the reaction mixture was stirred at reflux for 18 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 2.5) and triturated with Et₂O to give the *title compound* (9 mg, 13%) as a yellow solid. δ_{H} (DMSO-d₆) 8.77 (1H, d, *J* 5.0 Hz), 8.68 (1H, s), 8.39 (1H, d, *J* 8.0 Hz), 8.17 (1H, s), 8.14 (1H, s), 8.07 (1H, d, *J* 7.5 Hz), 7.68 (1H, t, *J* 7.5 Hz), 7.58 (1H, s), 7.50-7.46 (1H, m), 3.98 (2H, s), 3.67-3.57 (8H, m), 2.96-2.87 (4H, m), 2.73 (2H, s), 2.55 (4H, s), 1.20 (6H, s). LCMS (ES+) 547.3 (M+H)⁺.

EXAMPLE 354

N-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-2-oxo-1,2-dihydropyridine-3-carboxamide

The *title compound* was prepared from *Example 77* and 2-hydroxynicotinic acid according to *Method AL* and was obtained as a pale yellow solid (24%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl₃) 11.81 (1H, br s), 10.58-10.43 (1H, m), 8.73 (1H, d, *J* 7.3 Hz), 7.83 (1H, d, *J* 1.7 Hz), 7.63-7.55 (1H, m), 7.44 (1H, t, *J* 7.7 Hz), 7.22-7.17 (1H, m), 7.14-7.08 (1H, m), 6.66-6.59 (1H, m), 3.74-3.65 (4H, m), 3.11-3.01 (4H, m), 2.51 (2H, s), 2.47 (2H, s), 1.06 (6H, s). LCMS (ES+) 478.3 (M+H)⁺.

EXAMPLE 355

N-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-2-oxo-1-phenylpyrrolidine-3-carboxamide

The *title compound* was prepared from *Example 77* and 1-phenyl-2-oxo-3-pyrrolidinecarboxylic acid according to *Method AL* and was obtained as an off-white solid (51%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 9.78 (1H, br s), 7.71-7.68 (1H, m), 7.64-7.58 (2H, m), 7.57-7.52 (1H, m), 7.49-7.37 (3H, m), 7.31-7.23 (1H, m), 7.13-7.07 (1H, m), 3.99-3.90 (2H, m), 3.77-3.63 (5H, m), 3.08-2.99 (4H, m), 2.80-2.52 (2H, m), 2.47 (2H, s), 2.46 (2H, s), 1.05 (6H, d, J 1.7 Hz). LCMS (ES+) 544.4 (M+H)⁺.

EXAMPLE 356

N-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-1-isopropyl-5-oxopyrrolidine-3-carboxamide

The *title compound* was prepared from *Example 77* and 1-isopropyl-5-oxo-3-pyrrolidinecarboxylic acid according to *Method AL* and was obtained as an off-white solid (46%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 7.74-7.46 (3H, m), 7.46-7.38 (1H, m), 7.17-7.11 (1H, m), 4.49-4.36 (1H, m), 3.79-3.56 (6H, m), 3.33-3.18 (1H, m), 3.05-2.96 (4H, m), 2.90-2.70 (2H, m), 2.46 (2H, s), 2.44 (2H, s), 1.20 (6H, t, J 6.4 Hz), 1.04 (6H, s). LCMS (ES+) 510.3 (M+H)⁺.

EXAMPLE 357

Ethyl 3-([3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]amino)-3-oxopropanoate

The *title compound* was prepared from *Example 77* and ethyl malonate potassium salt according to *Method AL* and was obtained as a pale yellow solid (70%) after purification by column chromatography (SiO_2 , 50-60% EtOAc/heptane). δ_{H} (CDCl_3) 9.46-9.35 (1H, br s), 7.70-7.65 (1H, m), 7.53-7.47 (1H, m), 7.41 (1H, t, J 7.7 Hz), 7.16-

7.10 (1H, m), 4.36-4.24 (2H, m), 3.73-3.63 (4H, m), 3.52 (2H, s), 3.08-2.96 (4H, m), 2.48 (2H, s), 2.45 (2H, s), 1.36 (3H, t, J 7.2 Hz), 1.05 (6H, s). LCMS (ES+) 471.3 (M+H)⁺.

EXAMPLE 358

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Methyl 4-{[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]amino}-4-oxobutanoate

The *title compound* was prepared from *Example 77* and *mono-methyl succinate* according to *Method AL*, with stirring for 90 h, and was obtained as a pale yellow solid (70%) after purification by column chromatography (SiO₂, 60-65% EtOAc/heptane). δ_{H} (CDCl₃) 7.71-7.65 (1H, m), 7.59 (1H, s), 7.51-7.44 (1H, m), 7.39 (1H, t, J 7.7 Hz), 7.13-7.07 (1H, m), 3.74 (3H, s), 3.71-3.65 (4H, m), 3.04-2.97 (4H, m), 2.85-2.76 (2H, m), 2.76-2.68 (2H, m), 2.48 (2H, s), 2.44 (2H, s), 1.05 (6H, s). LCMS (ES+) 471.4 (M+H)⁺.

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EXAMPLE 359

5,5-Dimethyl-3-[2-(2-ethylphenyl)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 73* and 2-ethylphenylboronic acid according to *Method L* and was isolated as a white solid (84%) after purification by column chromatography (SiO₂, 10-90% EtOAc/heptane). δ_{H} (DMSO-d₆) 8.73 (1H, dd, J 4.9, 0.6 Hz), 7.48-7.41 (2H, m), 7.40-7.27 (4H, m), 3.63-3.54 (4H, m), 3.01-2.93 (4H, m), 2.80-2.69 (2H, m), 2.56 (2H, s), 2.38 (2H, s), 1.08-1.01 (3H, m), 0.98 (6H, s). LCMS (ES+) 447.4 (M+H)⁺.

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EXAMPLE 360

3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl trifluoromethanesulfonate

30

N-Phenyltrifluoromethanesulfonimide (171 mg, 0.48 mmol) and Et₃N (122 μ L, 0.87 mmol) were added to a solution of *Example 103* (190 mg, 0.44 mmol) in DCM (10 mL) and the mixture was stirred at room temperature for 17 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-80%

EtOAc/heptane) to give the *title compound* (219 mg, 89%) as a white solid. δ_{H} (DMSO- d_6) 8.79 (1H, d, J 5.1 Hz), 8.33 (1H, d, J 7.9 Hz), 8.29 (1H, d, J 2.3 Hz), 8.21 (1H, s), 7.73 (1H, t, J 8.1 Hz), 7.61 (1H, dd, J 8.1, 2.3 Hz), 7.49 (1H, dd, J 5.1, 1.1 Hz), 3.63-3.54 (4H, m), 3.03-2.93 (4H, m), 2.59 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES+) 567.2 (M+H)⁺.

EXAMPLE 361

3-{3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl}-1-methyl-1-(piperidin-4-yl)urea, formic acid salt

Triphosgene (24 mg, 0.08 mmol) and triethylamine (50 μ L, 0.36 mmol) were added to a cooled solution of *Example 340* (82 mg, 0.19 mmol) in THF (10 mL) at -78°C. The mixture was then allowed to warm to 0°C and stirred at this temperature for 30 minutes. The reaction mixture was then recooled to -78°C and 1-(*tert*-butoxycarbonyl)-4-(methylamino)piperidine (45 mg, 0.21 mmol) was added, then allowed to warm to 0°C and stirred for 1 h. A further portion of 1-(*tert*-butoxycarbonyl)-4-(methylamino)-piperidine (45 mg, 0.21 mmol) was added and the mixture was stirred for a further 1 h at 0°C. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-80% EtOAc/heptane). The solid obtained was taken up in MeOH (2.0 mL) and a solution of HCl in Et₂O (2M, 2.0 mL, 4.0 mmol) was added and the reaction mixture was stirred at room temperature for 5 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 2.5) to give the *title compound* (51 mg, 43%) as an off-white solid. δ_{H} (CD₃OD) 8.71 (1H, dd, J 5.1, 0.6 Hz), 8.50 (1H, s), 8.12 (1H, d, J 0.9 Hz), 7.95 (1H, d, J 0.6 Hz), 7.73-7.66 (1H, m), 7.51-7.43 (3H, m), 4.51-4.38 (1H, m), 3.77-3.67 (4H, m), 3.59-3.48 (2H, m), 3.20-3.06 (6H, m), 3.01 (3H, s), 2.65 (2H, s), 2.48 (2H, s), 2.14-1.91 (4H, m), 1.06 (6H, s). LCMS (ES+) 574.2 (M+H)⁺.

EXAMPLE 362 (METHOD AZ)

3-[6-(3-{[(3R)-3-Aminopyrrolidin-1-yl]carbonyl}phenyl)pyridin-2-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4H)-one, acetic acid salt

A mixture of *Intermediate 19* (146 mg, 0.38 mmol), 6-chloropyridine-2-boronic acid pinacol ester (98 mg, 0.41 mmol), K₃PO₄ (238 mg, 1.12 mmol) and Pd(PPh₃)₄ (22 mg, 0.02 mmol) in DME (3 mL) and water (1 mL) was heated in a sealed tube at 120°C, under microwave irradiation, for 20 minutes. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane). The solid obtained was combined with *Intermediate 60* (72 mg, 0.22 mmol), K₃PO₄ (115 mg, 0.54 mmol) and Pd(PPh₃)₄ (10 mg, 0.009 mmol) in DME (3 mL) and water (1 mL) and the mixture was heated in a sealed tube at 140°C, under microwave irradiation, for 2h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane). The solid obtained was dissolved in MeOH (2 mL), treated with a solution of HCl in Et₂O (2M, 2.0 mL, 4.0 mmol) and the reaction mixture was stirred at room temperature for 5 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 5.8) to give the *title compound* (20 mg, 8%) as a white solid. δ_{H} (CD₃OD) 8.33-8.27 (1H, m), 8.26-8.20 (1H, m), 7.99 (1H, m), 7.91-7.87 (1H, m), 7.84-7.80 (1H, m), 7.68-7.61 (2H, m), 4.01-3.60 (9H, m), 3.04-3.00 (4H, m), 2.96 (2H, s), 2.45-2.27 (1H, m), 2.12-1.91 (10H, m), 1.33 (6H, s). LCMS (ES⁺) 532.3 (M+H)⁺.

EXAMPLE 363

3-[6-(3-[(3*S*)-3-Aminopyrrolidin-1-yl]carbonyl}phenyl)pyridin-2-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one, acetic acid salt

The *title compound* was prepared from *Intermediate 19*, 6-chloropyridine-2-boronic acid pinacol ester and *Intermediate 59* according to *Method AZ* and was isolated as a white solid (6%) after purification by preparative HPLC (pH 5.8). δ_{H} (CD₃OD) 8.34-8.27 (1H, m), 8.27-8.19 (1H, m), 7.99 (1H, m), 7.92-7.86 (1H, m), 7.85-7.80 (1H, m), 7.69-7.60 (2H, m), 4.00-3.54 (9H, m), 3.07-3.00 (4H, m), 2.96 (2H, s), 2.43-2.25 (1H, m), 2.10-1.92 (7H, m), 1.33 (6H, s). LCMS (ES⁺) 532.3 (M+H)⁺.

EXAMPLE 364 (METHOD BA)

3-{2-[3-(3-Aminopyrrolidin-1-yl)phenyl]pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, hydrochloride salt

A mixture of *Example 360* (100 mg, 0.18 mmol), 3-(*tert*-butoxycarbonylamino)-pyrrolidine (66 mg, 0.35 mmol), potassium *tert*-butoxide (28 mg, 0.25 mmol) and acetato(2'-di-*tert*-butylphosphino-1,1'-biphenyl-2-yl)palladium(II) (20 mg, 0.043 mmol) in 1,4-dioxane (2.0 mL) was heated in a sealed tube at 100°C, under microwave irradiation, for 2 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane). The obtained solid was taken up in DCM (10 mL), treated with a solution of HCl in Et₂O (2M, 1.0 mL, 2.0 mmol) and stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (0-20% MeOH/DCM) to give the *title compound* (36 mg, 38%) as an orange solid. δ_{H} (CD₃OD) 8.89-8.77 (1H, m), 8.57-8.44 (1H, m), 8.22-8.09 (1H, m), 7.62-7.51 (1H, m), 7.38-7.20 (2H, m), 7.02 (1H, d, *J* 7.7 Hz), 4.22-4.08 (1H, m), 3.93-3.48 (8H, m), 3.27-3.05 (4H, m), 2.81 (2H, s), 2.68-2.45 (3H, m), 2.38-2.21 (1H, m), 1.08 (6H, s). LCMS (ES⁺) 503.4 (M+H)⁺.

EXAMPLE 365

3-Amino-5-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]-*N,N*-dimethylbenzamide

A mixture of *Example 351* (203 mg, 0.38 mmol) and 20% palladium on carbon (10 mg) in EtOAc (20 mL) and MeOH (5 mL) was stirred at room temperature under an atmosphere of hydrogen for 12 days. The reaction mixture was filtered and the solvent was removed *in vacuo* to give the *title compound* (177 mg, 92%) as a pale yellow glass. δ_{H} (DMSO-*d*₆) 8.71 (1H, d, *J* 5.1 Hz), 7.90 (1H, s), 7.43 (1H, s), 7.40-7.36 (1H, m), 7.23 (1H, s), 6.63 (1H, s), 5.48-5.41 (2H, m), 3.63-3.54 (4H, m), 2.97 (10H, s), 2.56 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES⁺) 505.3 (M+H)⁺.

EXAMPLE 366

5,5-Dimethyl-2-(morpholin-4-yl)-3-[3-(piperazin-1-yl)phenyl]-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one, acetic acid salt

A mixture of *Intermediate 19* (106 mg, 0.28 mmol), 3-[4-(*tert*-butoxycarbonyl)-piperazin-1-yl]phenylboronic acid pinacol ester (109 mg, 0.28 mmol), K₃PO₄ (179 mg, 0.84 mmol) and Pd(PPh₃)₄ (16 mg, 0.014 mmol) in DME (3 mL) and water (1 mL) was

heated in a sealed tube at 140°C, under microwave irradiation, for 2 h. The solvent was removed *in vacuo* and the residue taken up in MeOH. A solution of HCl in Et₂O (2M, 2.0 mL, 4.0 mmol) was added and the reaction mixture was stirred at room temperature for 20 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 5.8) to give the *title compound* (34 mg, 22%) as an off-white solid (34 mg). δ_{H} (DMSO-d₆) 7.43 (1H, s), 7.27 (1H, t, *J* 7.9 Hz), 6.95 (1H, s), 6.92-6.86 (1H, m), 6.76 (1H, d, *J* 7.5 Hz), 3.60-3.53 (4H, m), 3.13-3.04 (4H, m), 2.90-2.79 (8H, m), 2.58 (2H, s), 1.18 (6H, s), 1.90 (6H, s). LCMS (ES⁺) 427.4 (M+H)⁺.

EXAMPLE 367

5,5-Dimethyl-2-(morpholin-4-yl)-3-{6-[3-(piperazin-1-yl)phenyl]pyridin-2-yl}-5,6-dihydro-1-benzothiophen-7(4H)-one, acetic acid salt

The *title compound* was prepared from *Example 17*, 6-chloropyridine-2-boronic acid pinacol ester and 3-[4-(*tert*-butoxycarbonyl)piperazin-1-yl]phenylboronic acid pinacol ester according to *Method AZ* and was isolated as a white solid (11%) after purification by preparative HPLC (pH 5.8). δ_{H} (CD₃OD) 8.56 (1H, s), 7.97 (1H, t, *J* 7.7 Hz), 7.84 (1H, dd, *J* 7.9, 0.8 Hz), 7.76-7.72 (1H, m), 7.63 (1H, dd, *J* 7.5, 0.8 Hz), 7.60-7.55 (1H, m), 7.44 (1H, t, *J* 8.1 Hz), 7.18-7.12 (1H, m), 3.75-3.67 (4H, m), 3.50-3.41 (4H, m), 3.38-3.28 (4H, m), 3.12-3.04 (4H, m), 2.75 (2H, s), 2.48 (2H, s), 1.94 (3H, s), 1.08 (6H, s). LCMS (ES⁺) 503.4 (M+H)⁺.

EXAMPLE 368 (METHOD BB)

tert-Butyl 3-({3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl}amino)pyrrolidine-1-carboxylate

A mixture of *Example 360* (115 mg, 0.20 mmol), 3-amino-1-(*tert*-butoxycarbonyl)pyrrolidine (76 mg, 0.41 mmol), potassium *tert*-butoxide (32 mg, 0.28 mmol) and acetato(2'-di-*tert*-butylphosphino-1,1'-biphenyl-2-yl)palladium(II) (20 mg, 0.043 mmol) in 1,4-dioxane (2.0 mL) was heated in a sealed tube at 100°C, under microwave irradiation, for 2 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane) to give the *title compound* (79 mg, 65%) as an off-white solid. δ_{H} (CDCl₃) 8.73 (1H, d, *J* 5.1 Hz), 7.75 (1H, s), 7.38

(1H, s), 7.35-7.23 (3H, m), 6.74-6.68 (1H, m), 4.25-4.12 (1H, m), 4.00-3.88 (1H, m), 3.84-3.73 (1H, m), 3.72-3.64 (4H, m), 3.58-3.43 (2H, m), 3.37-3.20 (1H, m), 3.07-2.99 (4H, m), 2.53 (2H, s), 2.45 (2H, s), 2.31-2.17 (1H, m), 2.01-1.89 (1H, m), 1.47 (9H, s), 1.05 (6H, s). LCMS (ES⁺) 603.2 (M+H)⁺.

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EXAMPLE 369

tert-Butyl [(3R)-1-(3-{4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)-6-[(4-methoxybenzyl)amino]pyridin-2-yl}benzoyl)pyrrolidin-3-yl]carbamate

10

The *title compound* was prepared from *Example 269*, 4-methoxybenzylamine and *Intermediate 60* according to *Method AW* and was isolated as a clear oil (38%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_H (CDCl₃) 8.22-8.16 (1H, m), 8.10-8.03 (1H, m), 7.58-7.45 (2H, m), 7.36 (1H, s), 7.33 (1H, s), 7.14-7.10 (1H, m), 6.92 (1H, s), 6.89 (1H, s), 6.26 (1H, s), 5.22-5.13 (1H, m), 4.78-4.60 (1H, m), 4.58-4.51 (2H, m), 4.39-4.11 (1H, m), 3.99-3.67 (5H, m), 3.64-3.58 (4H, m), 3.57-3.27 (2H, m), 3.07-2.99 (4H, m), 2.40 (2H, s), 2.37 (2H, s), 2.33-2.09 (1H, m), 1.96-1.81 (1H, m), 1.47 (4H, s), 1.39 (5H, s), 1.00 (6H, s). LCMS (ES⁺) 766.3 (M+H)⁺.

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EXAMPLE 370

tert-Butyl [(3S)-1-(3-{4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)-6-[(4-methoxybenzyl)amino]pyridin-2-yl}benzoyl)pyrrolidin-3-yl]carbamate

25

The *title compound* was prepared from *Example 269*, 4-methoxybenzylamine and *Intermediate 59* according to *Method AW* and was isolated as a clear oil (40%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_H (CDCl₃) 8.23-8.15 (1H, m), 8.11-8.02 (1H, m), 7.59-7.44 (2H, m), 7.36 (1H, s), 7.33 (1H, s), 7.15-7.10 (1H, m), 6.92 (1H, s), 6.89 (1H, s), 6.27 (1H, d, *J* 0.6 Hz), 5.26-5.14 (1H, m), 4.83-4.62 (1H, m), 4.54 (2H, d, *J* 5.7 Hz), 4.39-4.10 (1H, m), 4.00-3.68 (5H, m), 3.67-3.25 (6H, m), 3.10-2.97 (4H, m), 2.47-2.33 (4H, m), 1.75-2.32 (2H, m), 1.47 (4H, s), 1.39 (5H, s), 1.00 (6H, s). LCMS (ES⁺) 766.3 (M+H)⁺.

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EXAMPLE 371 (METHOD BC)

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(pyrrolidin-3-ylamino)phenyl]pyridin-4-yl}-5,6-dihydro-1-benzothiophen-7(4H)-one, acetic acid salt

- 5 A solution of HCl in Et₂O (2M, 1.0 mL, 2.0 mmol) was added to a solution of *Example 368* (70 mg, 0.12 mmol) in DCM (10 mL) and the mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 5.8) to give the *title compound* (36 mg, 44%) as a yellow solid. δ_{H} (CD₃OD) 8.69 (1H, dd, *J* 5.1, 0.6 Hz), 7.89 (1H, d, *J* 0.6 Hz), 7.45 (1H, dd, *J* 5.1, 1.5 Hz),
10 7.38-7.25 (3H, m), 6.85-6.78 (1H, m), 4.39-4.28 (1H, m), 3.75-3.64 (4H, m), 3.59-3.29 (4H, m), 3.13-3.04 (4H, m), 2.63 (2H, s), 2.48 (2H, s), 2.45-2.34 (1H, m), 2.19-2.05 (1H, m), 1.94 (9H, s), 1.06 (6H, s). LCMS (ES⁺) 503.3 (M+H)⁺.

EXAMPLE 372

- 15 3-[2-Amino-6-(3-{[(3*S*)-3-aminopyrrolidin-1-yl]carbonyl}phenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, acetic acid salt

- The *title compound* was prepared from *Example 370* according to *Method AV* and was isolated as a white solid (44%) after purification by preparative HPLC (pH 5.8). δ_{H}
20 (CD₃OD) 8.20-8.13 (1H, m), 8.12-8.05 (1H, m), 7.65-7.56 (2H, m), 7.15 (1H, s), 6.59 (1H, d, *J* 1.1 Hz), 3.99-3.42 (9H, m), 3.18-3.09 (4H, m), 2.62 (2H, s), 2.46 (2H, s), 2.42-2.24 (1H, m), 2.08-1.98 (1H, m), 1.96 (4.5H, s), 1.06 (6H, s). LCMS (ES⁺) 546.3 (M+H)⁺.

- 25 **EXAMPLE 373**

3-[2-Amino-6-(3-{[(3*R*)-3-aminopyrrolidin-1-yl]carbonyl}phenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, acetic acid salt

- The *title compound* was prepared from *Example 369* according to *Method AV* and
30 was isolated as a white solid (28%) after purification by preparative HPLC (pH 5.8). δ_{H} (CD₃OD) 7.42-7.36 (1H, m), 7.35-7.27 (1H, m), 6.87-6.81 (2H, m), 6.38 (1H, s), 5.81 (1H, d, *J* 0.9 Hz), 2.22-3.64 (9H, m), 2.40-2.32 (4H, m), 1.85 (2H, s), 1.68 (2H, s), 1.64-1.20 (2H, m), 1.18 (3H, s), 0.29 (6H, s). LCMS (ES⁺) 546.3 (M+H)⁺.

EXAMPLE 374

1-[2-(Dimethylamino)ethyl]-3-[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]urea, formic acid salt

The *title compound* was prepared from *Example 77* and *N,N*-dimethylethylenediamine according to *Method AP* and was isolated as a pale yellow solid (36%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 8.43 (1H, s), 7.85-7.67 (2H, m), 7.46 (1H, d, *J* 1.7 Hz), 7.44-7.39 (1H, m), 7.36-7.29 (1H, m), 6.99-6.93 (1H, m), 3.75-3.64 (6H, m), 3.23-3.18 (2H, m), 3.05-2.99 (4H, m), 2.87 (6H, s), 2.48 (2H, s), 2.43 (2H, s), 1.04 (6H, s). LCMS (ES⁺) 471.2 (M+H)⁺.

EXAMPLE 375

1-[2-(Dimethylamino)ethyl]-3-[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-1-methylurea, formic acid salt

The *title compound* was prepared from *Example 77* and *N,N,N'*-trimethylethylenediamine according to *Method AP* and was isolated as a pale yellow solid (28%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 8.50-8.37 (1H, m), 8.30 (1H, s), 7.44 (1H, s), 7.41-7.31 (2H, m), 7.04-6.98 (1H, m), 3.75 (2H, t, *J* 6.0 Hz), 3.68 (4H, m), 3.12 (3H, s), 3.08-3.00 (6H, m), 2.73 (6H, s), 2.50 (2H, s), 2.43 (2H, s), 1.04 (6H, s). LCMS (ES⁺) 485.2 (M+H)⁺.

EXAMPLE 376

1-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-3-[2-(morpholin-4-yl)ethyl]urea, formic acid salt

The *title compound* was prepared from *Example 77* and 4-(2-aminoethyl)morpholine according to *Method AP* and was isolated as a pale yellow solid (29%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 8.40 (1H, s), 7.54-7.48 (1H, m), 7.46-7.43 (1H, m), 7.42-7.31 (2H, m), 7.01-6.89 (2H, m), 4.05-3.97 (4H, m), 3.74-3.61 (6H, m), 3.09-2.97 (10H, m), 2.48 (2H, s), 2.43 (2H, s), 1.04 (6H, s). LCMS (ES⁺) 513.2 (M+H)⁺.

EXAMPLE 377

5 1-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-3-(1-methylazetidin-3-yl)urea

The *title compound* was prepared from *Example 77* and 1-methyl-3-aminoazetidine hydrochloride according to *Method AP* and was isolated as a pale yellow solid (27%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 8.37-8.28 (1H, m) 7.98-7.90 (1H, m), 7.49-7.45 (1H, m), 7.43-7.30 (2H, m), 7.01-6.97 (1H, m), 4.99-4.83
10 (1H, m), 4.59-4.43 (2H, m), 4.28-4.08 (2H, m), 3.72-3.64 (4H, m), 3.03-2.98 (4H, m), 2.96 (3H, s), 2.48 (2H, s), 2.43 (2H, s), 1.04 (6H, s). LCMS (ES+) 469.3 (M+H)⁺.

EXAMPLE 378

15 1-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-3-[(1-methyl-1H-imidazol-4-yl)methyl]urea, formic acid salt

The *title compound* was prepared from *Example 77* and (1-methyl-1H-imidazol-4-yl)methylamine according to *Method AP* and was isolated as a pale yellow solid (52%) after purification by preparative HPLC (pH 2.5). δ_{H} (CDCl_3) 8.31 (1H, s), 8.00-7.89 (1H,
20 m), 7.76 (1H, s), 7.46 (1H, s), 7.40-7.35 (1H, m), 7.27-7.03 (1H, m), 7.17-7.02 (1H, m), 6.96-6.90 (2H, m), 4.41 (2H, s), 3.70-3.55 (4H, m), 3.05-2.96 (4H, m), 2.48 (2H, s), 2.43 (2H, s), 1.04 (6H, s). LCMS (ES+) 494.2 (M+H)⁺.

EXAMPLE 379

25 3-(2-{3-[(Dimethylamino)acetyl]phenyl}pyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-c]pyridin-7(4H)-one, formic acid salt

A suspension of *Intermediate 56* (71 mg, 0.143 mmol) in MeOH (5.0 mL) was added dropwise to a methanolic solution of dimethylamine (2M, 2.5 mL, 5.0 mmol) and
30 the reaction mixture was stirred at 40°C for 10 minutes. A further portion of methanolic dimethylamine (2M, 2.5 mL, 5.0 mmol) was added and stirring was continued at 40°C for 20 minutes. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 2.5) to give the *title compound* (7 mg, 9%) as an off-white solid.

δ_H (DMSO- d_6) 8.81-8.72 (1H, m), 8.67 (1H, d, J 0.8 Hz), 8.45-8.33 (1H, m), 8.16 (1H, s), 8.11-8.01 (1H, m), 7.72-7.62 (1H, m), 7.58 (1H, s), 7.53-7.43 (1H, m), 3.88 (2H, s), 3.65-3.56 (4H, m), 2.97-2.87 (4H, m), 2.73 (2H, s), 2.50 (3H, s), 2.28 (3H, s), 1.20 (6H, s).
LCMS (ES+) 505.3 (M+H)⁺.

5

EXAMPLE 380 (METHOD BD)

3-[2-(3-{[(3R)-3-Aminopyrrolidin-1-yl]methyl}phenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

10 *Example 262* (400 mg, 0.76 mmol) was combined with (3R)-(+)-3-(*tert*-butoxycarbonylamino)pyrrolidine (150 mg, 0.81 mmol) and THF (5.0 mL) in a sealed tube and the mixture was heated at 120°C, under microwave irradiation, for 1 h. Further (3R)-(+)-3-(*tert*-butoxycarbonylamino)pyrrolidine (100 mg, 0.54 mmol) and triethylamine (0.5 mL, 3.6 mmol) were added and heating was continued at 120°C for a further 1 h. The
15 solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-20% MeOH/DCM). The obtained solid was taken up in MeOH (5 mL) and was treated with a solution of HCl in Et₂O (2M, 2 mL, 4 mmol). The reaction mixture was stirred at room temperature for 20 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-20% MeOH/DCM containing 1%
20 NH₄OH) to give the *title compound* (56 mg, 14%) as a yellow glass. δ_H (DMSO- d_6) 8.74 (1H, d, J 5.1 Hz), 8.09 (1H, s), 8.05-7.99 (2H, m), 8.05-7.99 (2H, m), 7.46 (1H, t, J 7.5 Hz), 7.42-7.36 (2H, m), 3.64 (2H, d, J 4.7 Hz), 3.62-3.57 (4H, m), 3.41-3.27 (1H, m), 3.03-2.94 (4H, m), 2.76-2.67 (1H, m), 2.59 (2H, s), 2.57-2.43 (1H, m), 2.39 (2H, s), 2.19-2.12 (1H, m), 2.09-1.83 (2H, m), 1.43-1.30 (1H, m), 0.97 (6H, s). LCMS (ES+) 517.3
25 (M+H)⁺.

EXAMPLE 381

3-[2-(3-{[(3R)-3-Aminopyrrolidin-1-yl]methyl}phenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, acetic acid salt

30 The *title compound* was prepared from *Example 262* and (3R)-(+)-3-(*tert*-butoxycarbonylamino)pyrrolidine according to *Method BD* and was isolated as an off-white solid (27%) after purification by preparative HPLC (pH 5.8). δ_H (DMSO- d_6) 8.74 (1H, d,

J 5.1 Hz), 8.09 (1H, s), 7.46 (1H, t, *J* 7.5 Hz), 7.43-7.37 (2H, m), 3.65 (2H, d, *J* 3.8 Hz), 3.63-3.57 (4H, m), 3.44-3.33 (1H, m), 3.04-2.94 (4H, m), 2.77-2.67 (1H, m), 2.59 (2H, s), 2.54-2.43 (2H, m), 2.39 (2H, s), 2.25-2.17 (1H, m), 2.11-1.98 (1H, m), 1.87 (6H, s), 1.49-1.35 (1H, m), 0.97 (6H, s). LCMS (ES+) 517.3 (M+H)⁺.

5

EXAMPLE 382

3-[2-(3-{{(3*S*)-3-Aminopyrrolidin-1-yl}methyl}phenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, acetic acid salt

10 The *title compound* was prepared from *Example 262* and (3*S*)-(-)-3-(*tert*-butoxy-carbonylamino)pyrrolidine according to *Method BD* and was isolated as an off-white solid (27%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO-*d*₆) 8.74 (1H, d, *J* 5.1 Hz), 8.09 (1H, s), 8.04 (1H, s), 8.03-7.98 (2H, m), 7.46 (1H, t, *J* 7.5 Hz), 7.42-7.36 (2H, m), 3.65 (2H, d, *J* 4.1 Hz), 3.63-3.56 (4H, m), 3.51-3.19 (1H, m), 3.03-2.94 (4H, m),
15 2.76-2.67 (1H, m), 2.59 (2H, s), 2.54-2.45 (2H, m), 2.39 (2H, s), 2.24-2.16 (1H, m), 2.11-1.97 (1H, m), 1.88 (3H, s), 1.47-1.35 (1H, m), 0.97 (6H, s). LCMS (ES+) 517.3 (M+H)⁺.

EXAMPLE 383

20 5,5-Dimethyl-3-[2-(3-{{[4-(methylamino)piperidin-1-yl]methyl}phenyl}pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, acetic acid salt

 The *title compound* was prepared from *Example 262* and 4-[*N*-(*tert*-butoxy-carbonyl)-*N*-methylamino]piperidine according to *Method BD* and was isolated as a beige glass (55%) after purification by preparative HPLC (pH 5.8). δ_{H} (DMSO-*d*₆) 8.75 (1H, d, *J* 5.1 Hz), 8.10-7.98 (3H, m), 7.46 (1H, t, *J* 7.7 Hz), 7.42-7.34 (2H, m), 3.64-3.56 (4H, m), 3.53 (2H, s), 3.02-2.94 (4H, m), 2.84-2.71 (2H, m), 2.59 (2H, s), 2.39 (2H, s), 2.26 (3H, s), 2.05-1.94 (2H, m), 1.86 (6H, s), 1.82-1.73 (2H, m), 1.33-1.17 (2H, m), 0.97 (6H, s). LCMS (ES+) 545.5 (M+H)⁺.

30

EXAMPLE 384

N-{3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl}piperazine-1-carboxamide, acetic acid salt

Triphosgene (24 mg, 0.07 mmol) and triethylamine (50 μ L, 0.38 mmol) were added to a cooled solution of *Example 340* (83 mg, 0.19 mmol) in THF (10 mL) at -78°C . The mixture was then allowed to warm to 0°C and stirred at this temperature for 30 minutes. The reaction mixture was then recooled to -78°C , *tert*-butyl 1-piperazine-carboxylate (39 mg, 0.21 mmol) was added, and then it was allowed to warm to 0°C and stirred for 1 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2 , 0-100% EtOAc/heptane). The obtained solid was taken up in MeOH (2.0 mL) and a solution of HCl in Et_2O (2m, 2.0 mL, 4.0 mmol) was added. The reaction mixture was stirred at room temperature for 3.5 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 5.8) to give the *title compound* (44 mg, 35%) as a yellow solid. δ_{H} (CD_3OD) 8.71 (1H, d, J 5.1 Hz), 8.17-8.10 (1H, m), 7.98-7.93 (1H, m), 7.74-7.65 (1H, m), 7.51-7.43 (3H, m) 3.78-3.66 (8H, m), 3.20-3.03 (8H, m), 2.65 (2H, s), 2.48 (2H, s), 1.97 (6H, s), 1.06 (6H, s). LCMS (ES+) 546.2 ($\text{M}+\text{H}$) $^{+}$.

EXAMPLE 385

3-(2-{3-[(4-Aminopiperidin-1-yl)methyl]phenyl}pyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, acetic acid salt

The *title compound* was prepared from *Example 262* and 4-[*N*-(*tert*-butoxycarbonyl)amino]piperidine according to *Method BD* and was isolated as a beige gum (24%) after purification by preparative HPLC (pH 5.8). δ_{H} ($\text{DMSO}-d_6$) 8.75 (1H, d, J 4.9 Hz), 8.15-7.95 (3H, m), 7.46 (1H, t, J 7.5 Hz), 7.43-7.32 (2H, m), 3.66-3.57 (4H, m), 3.53 (2H, s), 3.03-2.94 (4H, m), 2.91-2.71 (2H, m), 2.59 (2H, s), 2.39 (2H, s), 2.06-1.94 (2H, m), 1.88 (6H, s), 1.81-1.66 (2H, m), 1.43-1.22 (2H, m), 0.97 (6H, s). LCMS (ES+) 531.3 ($\text{M}+\text{H}$) $^{+}$.

EXAMPLE 386 (METHOD BE)

5,5-Dimethyl-3-[2-(3-{[4-(methylamino)piperidin-1-yl]carbonyl}phenyl)pyrimidin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, acetic acid salt

Sodium hydride (60% dispersion in oil, 66 mg, 1.68 mmol) was slowly added to a solution of 3-methoxycarbonylbenzamidine (180 mg, 0.84 mmol) in DMF (6.0 mL) at

30°C. Stirring was continued for 5 minutes, then *Example 344* (152 mg, 0.42 mmol) was added. The reaction mixture was heated to 100°C for 7 days, then cooled to room temperature and the solvent was removed *in vacuo*. The residue was partitioned between EtOAc (100 mL) and water (60 mL), and the aqueous phase was extracted with further EtOAc (2 x 100 mL). The combined organic phases were washed with water (100 mL), dried (magnesium sulfate) and the solvent was removed *in vacuo*. The obtained solid was taken up in a mixture of MeOH (4.0 mL), THF (6.0 mL) and water (2.0 mL) and lithium hydroxide monohydrate (70 mg, 1.62 mmol) was added. The reaction mixture was stirred at room temperature for 22 h then concentrated *in vacuo*. The residue was diluted with water (7 mL) and acidified with concentrated HCl. The precipitate was filtered off, washed with a little ice water and dried *in vacuo*. The obtained solid was combined with HBTU (64 mg, 0.16 mmol), DIPEA (0.08 mL, 0.48 mmol) and 4-[*N*-(*tert*-butoxycarbonyl)-*N*-methylamino]piperidine (51 mg, 0.24 mmol) in DMF (2.0 mL) and the reaction mixture was stirred at room temperature for 4 h. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc (100 mL) and water (40 mL). The organic layer was washed with water (3 x 40 mL), dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane). The obtained solid was taken up in DCM (5.0 mL) and treated with a solution of HCl in Et₂O (2M, 2.0 mL, 4.0 mmol). The reaction mixture was stirred at room temperature for 72 h. A further portion of HCl in Et₂O (2M, 1.0 mL, 2.0 mmol) was added and stirring was continued for a further 5 h. The solvent was removed *in vacuo* and purified by preparative HPLC (pH 5.8) to give the *title compound* (29 mg, 10%) as a yellow solid. δ_{H} (CDCl₃) 8.85 (1H, d, *J* 5.1 Hz), 8.61-8.50 (2H, m), 7.65 (1H, d, *J* 5.1 Hz), 7.61-7.52 (2H, m), 4.93-4.68 (1H, m), 4.01-3.84 (1H, m), 3.83-3.72 (4H, m), 3.17-3.07 (4H, m), 3.05-2.90 (2H, m), 2.86 (2H, s), 2.56 (3H, s), 2.50 (2H, s), 2.24-1.87 (10H, m), 1.74-1.47 (2H, m), 1.09 (6H, s). LCMS (ES⁺) 560.3 (M+H)⁺.

EXAMPLE 387

5,5-Dimethyl-3-[2-(3-{[4-(methylamino)piperidin-1-yl]carbonyl}phenyl)pyrimidin-4-yl]-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one, acetic acid salt

The *title compound* was prepared from *Intermediate 55*, 3-methoxycarbonylbenzamidine and 4-[*N*-(*tert*-butoxycarbonyl)-*N*-methylamino]piperidine according to

Method BE and was obtained as a yellow solid (13%) after purification by preparative HPLC (pH 5.8). δ_{H} (CDCl_3) 8.84 (1H, d, J 5.3 Hz), 8.54 (1H, s), 8.52-8.49 (1H, m), 7.82 (1H, d, J 5.3 Hz), 7.60-7.53 (2H, m), 5.87 (1H, s), 4.79-4.61 (1H, m), 3.76-3.87 (4H, m), 3.38-3.17 (4H, m), 3.11 (2H, s), 3.10-3.03 (4H, m), 2.88-2.75 (1H, m), 2.51 (3H, s), 2.09 (6H, s), 1.60-1.42 (2H, m), 1.37 (6H, s). LCMS (ES+) 561.3 ($\text{M}+\text{H}$)⁺.

EXAMPLE 388

10 Methyl [3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]acetate

A mixture of *Example 17* (1.0 g, 2.56 mmol), [3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]acetic acid methyl ester (0.85 g, 3.08 mmol), K_3PO_4 (0.55 g, 2.59 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.35 g, 0.30 mmol) in DME (0.3 mL) and water (10 mL) was heated at 90°C for 17 h. A further portion of [3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]acetic acid methyl ester (0.40 g, 1.45 mmol) was added and heating was continued for a further 24 h. A saturated solution of sodium hydrogencarbonate (50 mL) was added and the mixture was extracted into EtOAc (3 x 100 mL). The combined organic phases were dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by column chromatography (SiO_2 , 0-80% EtOAc/heptane) to give the *title compound* (0.44 g, 42%) as a pale brown foam. δ_{H} ($\text{DMSO}-d_6$) 7.42 (1H, t, J 7.7 Hz), 7.33 (1H, s), 7.29-7.21 (2H, m), 3.74 (2H, s), 3.64 (3H, s), 3.60-3.52 (4H, m), 2.96-2.84 (4H, m), 2.47 (2H, s), 2.36 (2H, s), 0.96 (6H, s). LCMS (ES+) 414.3 ($\text{M}+\text{H}$)⁺.

EXAMPLE 389

25

3-(2-{3-[(3*S*)-3-Aminopyrrolidin-1-yl]phenyl}pyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, acetic acid salt

The *title compound* was prepared from *Example 360* and (3*S*)-(-)-3-(*tert*-butoxycarbonylamino)pyrrolidine according to *Method BA* and was obtained as a clear glass (18%) after purification by column chromatography (SiO_2 , 0-20% MeOH/DCM). δ_{H} (CD_3OD) 8.73-8.68 (1H, m), 7.93 (1H, d, J 0.8 Hz), 7.45 (1H, dd, J 5.1, 1.5 Hz), 7.43-7.36 (1H, m), 7.32-7.26 (2H, m), 6.80 (1H, dd, J 7.3, 1.5 Hz), 4.12-4.01 (1H, m), 3.79-

3.63 (6H, m), 3.58-3.43 (2H, m), 3.15-3.04 (4H, m), 2.64 (2H, s), 2.59-2.42 (3H, m), 2.28-2.13 (1H, m), 1.95 (6H, s), 1.06 (6H, s). LCMS (ES⁺) 503.4 (M+H)⁺.

EXAMPLE 390

5

3-(2-{3-[(3R)-3-Aminopyrrolidin-1-yl]phenyl}pyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 360* and (3R)-(+)-3-(*tert*-butoxy-carbonylamino)pyrrolidine according to *Method BA* and was obtained as a white solid
10 (17%) after partitioning between saturated sodium hydrogencarbonate solution and DCM, and subsequent purification by column chromatography (SiO₂, 0-20% MeOH/DCM). δ_{H} (CD₃OD) 8.68 (1H, dd, *J* 5.1, 0.6 Hz), 7.90 (1H, d, *J* 0.6 Hz), 7.43 (1H, dd, *J* 5.3, 1.5 Hz), 7.35 (1H, t, *J* 7.9 Hz), 7.28-7.18 (2H, m), 6.77-6.69 (1H, m), 3.87-3.76 (1H, m), 3.75-3.66 (4H, m), 3.64-3.54 (2H, m), 3.50-3.38 (1H, m), 3.30-3.22 (1H, m), 3.13-3.01 (4H, m),
15 2.63 (2H, s), 2.46 (2H, s), 2.43-2.28 (1H, m), 2.08-1.90 (1H, m), 1.05 (6H, s). LCMS (ES⁺) 503.4 (M+H)⁺.

EXAMPLE 391

20 3-(2-{3-[(3R)-3-Aminopyrrolidin-1-yl]phenyl}pyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, acetic acid salt

The *title compound* was prepared from *Example 360* and (3R)-(+)-3-(*tert*-butoxy-carbonylamino)pyrrolidine according to *Method BA* and was obtained as a clear glass
(15%) after purification by column chromatography (SiO₂, 0-20% MeOH/DCM). δ_{H}
25 (CD₃OD) 8.70 (1H, d, *J* 5.1 Hz), 7.98-7.89 (1H, m), 7.45 (1H, dd, *J* 5.1, 1.5 Hz), 7.39 (1H, t, *J* 8.1 Hz), 7.33-7.26 (2H, m), 6.85-6.75 (1H, m), 4.14-4.00 (1H, m), 3.80-3.63 (6H, m), 3.60-3.42 (2H, m), 3.14-3.02 (4H, m), 2.63 (2H, s), 2.59-2.44 (3H, m), 2.30-2.13 (1H, m), 1.95 (9H, s), 1.05 (6H, s). LCMS (ES⁺) 503.4 (M+H)⁺.

30

EXAMPLE 392

tert-Butyl (3R)-3-({3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl}amino)pyrrolidine-1-carboxylate

The *title compound* was prepared from *Example 360* and (*R*)-(+)-3-amino-1-(*tert*-butoxycarbonyl)pyrrolidine according to *Method BB* and was obtained as a clear glass (60%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_{H} (CDCl₃) 8.73 (1H, d, *J* 5.1 Hz), 7.80-7.71 (1H, m), 7.41-7.36 (1H, m), 7.34-7.22 (3H, m), 6.74-6.66 (1H, m), 4.28-4.04 (1H, m), 3.97-3.84 (1H, m), 3.83-3.62 (5H, m), 3.59-3.39 (2H, m), 3.38-3.17 (1H, m), 3.08-2.96 (4H, m), 2.53 (2H, s), 2.46 (2H, s), 2.33-2.15 (1H, m), 2.02-1.87 (1H, m), 1.47 (9H, s), 1.05 (6H, s). LCMS (ES⁺) 603.6 (M+H)⁺.

EXAMPLE 393

tert-Butyl (3*S*)-3-({3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl}amino)pyrrolidine-1-carboxylate

The *title compound* was prepared from *Example 360* and (*S*)-(-)-3-amino-1-(*tert*-butoxycarbonyl)pyrrolidine according to *Method BB* and was obtained as a clear glass (44%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_{H} (CDCl₃) 8.73 (1H, d, *J* 4.9 Hz), 7.76-7.71 (1H, m), 7.40-7.35 (1H, m), 7.33-7.28 (2H, m), 7.27-7.21 (1H, m), 6.74-6.66 (1H, m), 4.24-4.11 (1H, m), 3.93-3.84 (1H, m), 3.84-3.63 (5H, m), 3.58-3.40 (2H, m), 3.36-3.19 (1H, m), 3.07-2.98 (4H, m), 2.54 (2H, s), 2.45 (2H, s), 2.32-2.14 (1H, m), 2.04-1.84 (1H, m), 1.46 (9H, s), 1.04 (6H, s). LCMS (ES⁺) 603.6 (M+H)⁺.

EXAMPLE 394

5,5-Dimethyl-2-(morpholin-4-yl)-3-(2-{3-[(3*S*)-pyrrolidin-3-ylamino]phenyl}pyridin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from *Example 393* according to *Method AM* and was obtained as a clear glass (42%) after purification by column chromatography (SiO₂, 0-20% MeOH/DCM, 1% NH₄OH). δ_{H} (CDCl₃) 8.72 (1H, t, *J* 7.7 Hz), 7.75 (1H, s), 7.40-7.32 (1H, m), 7.32-7.21 (3H, m), 6.77-6.64 (1H, m), 6.39-5.72 (1H, br m), 4.93-4.07 (2H, m), 3.72-3.62 (4H, m), 3.53-3.27 (2H, m), 3.06-2.98 (4H, m), 2.97-2.55 (2H, m), 2.52 (2H, s), 2.45 (2H, s), 2.39-1.68 (2H, m), 1.04 (6H, s). LCMS (ES⁺) 503.4 (M+H)⁺.

EXAMPLE 395

5,5-Dimethyl-2-(morpholin-4-yl)-3-(2-{3-[(3R)-pyrrolidin-3-ylamino]phenyl}pyridin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 392* according to *Method AM* and was obtained as a clear glass (63%). δ_{H} (CDCl_3) 8.74-8.69 (1H, m), 7.78-7.72 (1H, m), 7.42-7.20 (4H, m), 6.77-6.64 (1H, m), 4.90-4.75 (1H, m), 4.37-4.28 (1H, m), 3.74-3.62 (4H, m), 3.54-3.25 (2H, m), 3.07-2.96 (4H, m), 2.96-2.88 (1H, m), 2.80-2.72 (1H, m), 2.52 (2H, s), 2.45 (2H, s), 2.39-1.70 (2H, m), 1.04 (6H, s). LCMS (ES+) 503.4 (M+H)⁺.

10

EXAMPLE 396

3-[2-(3-{[4-(Dimethylamino)piperidin-1-yl]carbonyl}phenyl)pyrimidin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-c]pyridin-7(4H)-one, formic acid solvate

15

The *title compound* was prepared from *Intermediate 55*, 3-methoxycarbonyl-benzamidine and 4-(dimethylamino)piperidine according to *Method BE*, omitting the final acidic deprotection step, and was obtained as a beige solid (14%). δ_{H} (CDCl_3) 8.84 (1H, d, *J* 5.3 Hz), 8.57-8.50 (2H, m), 8.39 (0.5H, s), 7.82 (1H, d, *J* 5.3 Hz), 7.61-7.55 (2H, m), 5.39 (1H, br s), 4.99-4.75 (1H, m), 4.00-3.89 (1H, m), 3.83-3.76 (4H, m), 3.11 (2H, s), 3.10-3.04 (4H, m), 2.89-2.75 (3H, m), 2.48 (6H, s), 2.09-1.43 (1H, m), 1.37 (6H, s). LCMS (ES+) 575.3 (M+H)⁺.

20

EXAMPLE 397

25

tert-Butyl (1-{[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]acetyl}piperidin-4-yl)carbamate

30

The *title compound* was prepared from *Example 71* and 4-(*tert*-butoxycarbonylamino)piperidine according to *Method I* and was obtained as an off-white solid (100%). δ_{H} (DMSO-d_6) 7.40 (1H, t, *J* 7.5 Hz), 7.28-7.17 (3H, m), 6.88-6.81 (1H, m), 4.28-4.18 (1H, m), 3.94-3.84 (1H, m), 3.77-3.72 (2H, m), 3.59-3.52 (4H, m), 3.49-3.42 (1H, m), 3.12-2.99 (1H, m), 2.94-2.86 (4H, m), 2.77-2.63 (1H, m), 2.44 (2H, s), 2.35 (2H, s), 1.75-1.61 (2H, m), 1.36 (9H, s), 1.26-1.13 (2H, m), 0.95 (6H, s). LCMS (ES+) 582.2 (M+H)⁺.

EXAMPLE 398

2-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-N-(pyridin-4-ylmethyl)acetamide

5 The *title compound* was prepared from *Example 71* and 4-(aminomethyl)pyridine according to *Method I* and was obtained as an off-white solid (100%). δ_{H} (DMSO- d_6) 8.74-8.66 (1H, m), 8.47-8.40 (2H, m), 7.45-7.33 (2H, m), 7.30-7.21 (2H, m), 7.20 (2H, d, J 5.8 Hz), 4.31 (2H, d, J 5.8 Hz), 3.56 (2H, s), 3.55-3.49 (4H, m), 2.92-2.84 (4H, m), 2.46 (2H, s), 2.35 (2H, s), 0.93 (6H, s). LCMS (ES+) 490.3 (M+H)⁺.

10

EXAMPLE 399

tert-Butyl [(3S)-1-{[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]acetyl}pyrrolidin-3-yl]carbamate

15 The *title compound* was prepared from *Example 71* and (3S)-(-)-3-(tert-butoxycarbonylamino)pyrrolidine according to *Method I* and was obtained as an off-white solid (100%). δ_{H} (DMSO- d_6) 7.44-7.34 (1H, m), 7.31-7.13 (4H, m), 4.08-3.90 (1H, m), 3.74-3.29 (8H, m), 2.94-2.85 (4H, m), 2.46 (2H, s), 2.35 (2H, s), 2.12-1.63 (4H, m), 1.38 (9H, d, J 2.5 Hz), 0.95 (6H, s). LCMS (ES+) 568.2 (M+H)⁺.

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EXAMPLE 400

tert-Butyl 3-({[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]acetyl}amino)azetidine-1-carboxylate

25 The *title compound* was prepared from *Example 71* and 3-amino-1-(tert-butoxycarbonyl)azetidine according to *Method I* and was obtained as an off-white solid (96%). δ_{H} (DMSO- d_6) 8.74 (1H, br d, J 7.2 Hz), 7.40 (1H, t, J 7.2 Hz), 7.33-7.31 (1H, m), 7.25-7.19 (2H, m), 4.44-4.31 (1H, m), 4.13-4.00 (2H, m), 3.71-3.61 (2H, m), 3.57-3.51 (4H, m), 3.45 (2H, s), 2.93-2.82 (4H, m), 2.46 (2H, s), 2.36 (2H, s), 1.36 (9H, s), 0.95 (6H, s).
30 (LCMS (ES+) 554.1 (M+H)⁺).

EXAMPLE 401

2-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-N,N-dimethylacetamide

The *title compound* was prepared from *Example 71* and dimethylamine hydrochloride according to *Method I* and was obtained as a white solid (92%). δ_{H} (DMSO- d_6) 7.40 (1H, t, J 7.5 Hz), 7.27-7.17 (3H, m), 3.73 (2H, s), 3.60-3.51 (4H, m), 3.02 (3H, s), 2.92-2.87 (4H, m), 2.84 (3H, s), 2.45 (2H, s), 2.35 (2H, s), 0.95 (6H, s). LCMS (ES+) 427.3 (M+H)⁺.

EXAMPLE 402

2-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-N-(pyridin-4-yl)acetamide

The *title compound* was prepared from *Example 71* and 4-aminopyridine according to *Method I* and was obtained as a yellow solid (42%) after trituration with Et₂O. δ_{H} (DMSO- d_6) 10.60 (1H, br s), 8.44-8.40 (2H, m), 7.60-7.55 (2H, m), 7.47-7.39 (2H, m), 7.32-7.19 (2H, m), 3.74 (2H, s), 3.59-3.47 (4H, m), 2.94-2.82 (4H, m), 2.46 (2H, s), 2.34 (2H, s), 0.92 (6H, s). LCMS (ES+) 476.3 (M+H)⁺.

EXAMPLE 403

N-[2-(Diethylamino)ethyl]-2-[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-N-methylacetamide

The *title compound* was prepared from *Example 71* and *N,N*-diethyl-*N'*-methyl-ethylenediamine according to *Method I* and was obtained as a white foam (93%). δ_{H} (DMSO- d_6) 7.40 (1H, t, J 7.5 Hz), 7.28-7.16 (3H, m), 3.78 (1H, s), 3.72 (1H, s), 3.60-3.51 (4H, m), 3.41-3.30 (4H, m), 3.03 (1.5H, s), 2.93-2.87 (4H, m), 2.85 (1.5H, s), 2.50-2.45 (4H, m), 2.42 (2H, s), 2.35 (2H, s), 0.98-0.85 (12H, m). LCMS (ES+) 512.2 (M+H)⁺.

EXAMPLE 404

tert-Butyl 3-[(3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]acetyl} amino)methyl]pyrrolidine-1-carboxylate

The *title compound* was prepared from *Example 71* and 3-(aminomethyl)-1-(*tert*-butoxycarbonyl)pyrrolidine according to *Method I* and was obtained as an off-white solid (86%). δ_{H} (DMSO- d_6) 8.25-8.16 (1H, m), 7.39 (1H, t, J 7.7 Hz), 7.35-7.32 (1H, m), 7.26-7.19 (2H, m), 3.59-3.52 (4H, m), 3.45 (2H, s), 3.42-3.23 (3H, m), 3.21-2.97 (3H, m),
5 2.94-2.83 (4H, m), 2.46 (2H, s), 2.35 (2H, m), 2.30-2.18 (1H, m), 1.92-1.75 (1H, m), 1.55-1.44 (1H, m), 1.37 (9H, s), 0.95 (6H, s). LCMS (ES+) 582.1 (M+H)⁺.

EXAMPLE 405

10 *tert*-Butyl (1-{3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzoyl}azetidin-3-yl)carbamate

The *title compound* was prepared from *Example 254* and azetidin-3-ylcarbamic acid *tert*-butyl ester according to *Method AL* and was obtained as a yellow solid (42%) after purification by column chromatography (SiO₂, 75-100% EtOAc/heptane). δ_{H}
15 (CDCl₃) 8.85-8.79 (1H, m), 8.39-8.35 (1H, m), 8.23-8.17 (1H, m), 7.95-7.90 (1H, m), 7.77-7.71 (1H, m), 7.61 (1H, t, J 7.7 Hz), 7.44-7.38 (1H, m), 5.17-5.05 (1H, m), 4.69-4.50 (3H, m), 4.34-4.23 (1H, m), 4.12-4.00 (1H, m), 3.77-3.65 (4H, m), 3.10-3.00 (4H, m), 2.56 (2H, s), 2.48 (2H, s), 1.46 (9H, s), 1.07 (6H, s). LCMS (ES+) 617.2 (M+H)⁺.

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EXAMPLE 406

tert-Butyl 3-({3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzoyl}amino)azetidine-1-carboxylate

The *title compound* was prepared from *Example 254* and 3-amino-1-(*tert*-butoxycarbonyl)azetidine according to *Method AL* and was obtained as a cream solid (66%) after purification by column chromatography (SiO₂, 75-100% EtOAc/heptane). δ_{H}
25 (CDCl₃) 8.82-8.78 (1H, m), 8.67-8.59 (1H, m), 8.23-8.15 (1H, m), 8.04-7.97 (1H, m), 7.95-7.90 (1H, m), 7.65 (1H, t, J 7.7 Hz), 7.44-7.37 (1H, m), 4.95-4.82 (1H, m), 4.41-4.32 (2H, m), 3.99-3.90 (2H, m), 3.73-3.66 (4H, m), 3.09-3.00 (4H, m), 2.54 (2H, s), 2.42 (2H,
30 s), 1.46 (9H, s), 1.06 (6H, s). LCMS (ES+) 617.1 (M+H)⁺.

EXAMPLE 407

tert-Butyl N-(1-{[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl]phenyl}acetyl)piperidin-4-yl)-N-methylcarbamate

The *title compound* was prepared from *Example 71* and 4-[*N*-(*tert*-butoxycarbonyl)-*N*-methylamino]piperidine according to *Method I* and was obtained as a white solid (56%) after purification by column chromatography (SiO₂, 0-100% EtOAc/heptane). δ_{H} (DMSO-*d*₆) 7.41 (1H, t, *J* 7.5 Hz), 7.31-7.28 (1H, m), 7.26-7.19 (2H, m), 4.56-4.45 (1H, m), 4.09-3.97 (2H, m), 3.77 (2H, s), 3.59-3.51 (4H, m), 3.07-2.95 (1H, m), 2.93-2.86 (4H, m), 2.56 (3H, s), 2.44 (2H, s), 2.36 (2H, s), 1.56-1.44 (4H, m), 1.38 (9H, s), 0.95 (6H, s). LCMS (ES⁺) 596.2 (M+H)⁺.

EXAMPLE 408

3-{3-[2-(4-Aminopiperidin-1-yl)-2-oxoethyl]phenyl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, trifluoroacetic acid salt

The *title compound* was prepared from *Example 397* according to *Method AT* and was obtained as a white solid (100%) after trituration with Et₂O. δ_{H} (DMSO-*d*₆) 7.93-7.76 (3H, br m), 7.41 (1H, t, *J* 7.7 Hz), 7.29-7.17 (3H, m), 4.48-4.34 (1H, m), 4.11-3.98 (1H, m), 3.88-3.68 (2H, m), 3.57-3.54 (4H, m), 3.31-3.17 (1H, m), 3.12-2.96 (1H, m), 2.95-2.86 (4H, m), 2.70-2.58 (1H, m), 2.45 (2H, s), 2.36 (2H, s), 1.97-1.77 (2H, m), 1.39-1.21 (2H, m), 0.96 (6H, s). LCMS (ES⁺) 482.3 (M+H)⁺.

EXAMPLE 409

3-(3-{2-[(3*S*)-3-Aminopyrrolidin-1-yl]-2-oxoethyl}phenyl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, trifluoroacetic acid salt

The *title compound* was prepared from *Example 399* according to *Method AT* and was obtained as a white solid (96%) after trituration with Et₂O. δ_{H} (DMSO-*d*₆) 8.14-7.91 (3H, m), 7.41 (1H, t, *J* 7.7 Hz), 7.34-7.17 (3H, m), 3.98-3.51 (8H, m), 2.97-2.86 (4H, m), 2.46 (2H, s), 2.36 (2H, s), 0.96 (6H, s). LCMS (ES⁺) 468.3 (M+H)⁺.

EXAMPLE 410

N-(Azetidin-3-yl)-2-[3-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]acetamide, trifluoroacetic acid salt

The *title compound* was prepared from *Example 400* according to *Method AT* and was obtained as a grey-brown solid (56%) after trituration with Et₂O. δ_{H} (DMSO-d₆) 8.91-8.80 (1H, m), 8.74-8.54 (2H, m), 7.41 (1H, t, *J* 7.5 Hz), 7.33 (1H, s), 7.29-7.18 (2H, m), 4.69-4.53 (1H, m), 4.20-4.01 (4H, m), 3.99-3.84 (2H, m), 3.60-3.52 (4H, m), 2.97-2.83 (4H, m), 2.46 (2H, s), 2.36 (2H, s), 0.95 (6H, s). LCMS (ES⁺) 454.3 (M+H)⁺.

EXAMPLE 411

2-[3-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)phenyl]-N-(pyrrolidin-3-ylmethyl)acetamide, trifluoroacetic acid salt

The *title compound* was prepared from *Example 404* according to *Method AT* and was obtained as a grey-brown solid (68%) after trituration with Et₂O. δ_{H} (DMSO-d₆) 8.74-8.49 (2H, m), 8.33-8.21 (1H, m), 7.40 (1H, t, *J* 7.5 Hz), 7.35-7.31 (1H, m), 7.25-7.19 (2H, m), 3.61-3.52 (4H, m), 3.47 (2H, s), 3.26-3.00 (3H, m), 2.94-2.86 (4H, m), 2.85-2.71 (2H, m), 2.46 (2H, s), 2.43-2.32 (4H, m), 2.01-1.88 (1H, m), 1.64-1.50 (1H, m), 0.95 (6H, s). LCMS (ES⁺) 482.4 (M+H)⁺.

EXAMPLE 412

5,5-Dimethyl-3-(3-{2-[4-(methylamino)piperidin-1-yl]-2-oxoethyl}phenyl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one, trifluoroacetic acid salt

The *title compound* was prepared from *Example 407* according to *Method AT* and was obtained as a yellow solid (94%) after trituration with Et₂O. δ_{H} (DMSO-d₆) 8.62-8.44 (2H, m), 4.71 (1H, t, *J* 7.9 Hz), 7.30-7.16 (3H, m), 4.52-4.41 (1H, m), 4.16-4.02 (1H, m), 3.91-3.66 (2H, m), 3.63-3.53 (4H, m), 3.28-3.12 (1H, m), 3.09-2.95 (1H, m), 2.94-2.86 (4H, m), 2.62-2.53 (4H, m), 2.45 (2H, s), 2.36 (2H, s), 2.09-1.88 (2H, m), 1.47-1.42 (2H, m), 0.96 (6H, s). LCMS (ES⁺) 496.3 (M+H)⁺.

EXAMPLE 413

N-(Azetidin-3-yl)-3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzamide

The *title compound* was prepared from *Example 406* according to *Method AM* and was obtained as a yellow solid (46%) after trituration with Et₂O. δ_{H} (CD₃OD) 8.76 (1H, d, *J* 5.5 Hz), 8.56-8.48 (1H, m), 8.29-8.18 (1H, m), 8.04 (1H, s), 7.99-7.93 (1H, m), 7.66 (1H, t, *J* 7.7 Hz), 7.49 (1H, dd, *J* 5.1, 1.3 Hz), 5.01-4.84 (1H, m), 4.06-3.75 (4H, m), 3.72-3.64 (4H, m), 3.13-3.03 (4H, m), 2.64 (2H, s), 2.48 (2H, s), 1.05 (6H, s). LCMS (ES+) 517.3 (M+H)⁺.

EXAMPLE 414

3-{2-[3-(3-Aminoazetidin-1-yl)phenyl]pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 360* and azetidin-3-ylcarbamic acid *tert*-butyl ester according to *Method BA* and was obtained as a white solid (13%) after washing with saturated aqueous sodium hydrogencarbonate solution and purification by column chromatography (SiO₂, 0-20% MeOH/DCM, 1% NH₄OH). δ_{H} (CD₃OD) 8.56 (1H, dd, *J* 5.1, 0.8 Hz), 7.79 (1H, d, *J* 0.8 Hz), 7.34-7.30 (1H, m), 7.27-7.13 (2H, m), 7.02-6.97 (1H, m), 6.54-6.48 (1H, m), 4.17-4.07 (2H, m), 3.90-3.77 (1H, m), 3.64-3.44 (6H, m), 3.01-2.89 (4H, m), 2.56 (2H, s), 2.36 (2H, s), 0.94 (6H, s). LCMS (ES+) 489.3 (M+H)⁺.

EXAMPLE 415

3-{2-[3-(Azetidin-3-ylamino)phenyl]pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 360* and 3-amino-1-(*tert*-butoxycarbonyl)azetidine according to *Method BA* and was obtained as a yellow solid (24%) after washing with saturated aqueous sodium hydrogencarbonate solution and purification by column chromatography (SiO₂, 0-20% MeOH/DCM, 1% NH₄OH). δ_{H} (CD₃OD) 8.70 (1H, d, *J* 5.1 Hz), 7.89 (1H, s), 7.49-7.42 (1H, m), 7.38-7.28 (2H, m), 7.25-7.20 (1H, m), 6.79-6.70 (1H, m), 4.71-4.58 (1H, m), 4.53-4.40 (2H, m), 4.12-3.98 (2H, m), 3.77-3.59

(4H, m), 3.15-2.98 (4H, m), 2.62 (2H, s), 2.47 (2H, s), 1.05 (6H, s). LCMS (ES+) 489.2 (M+H)⁺.

EXAMPLE 416 (METHOD BF)

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3-{2-[3-(1,4-Diazepan-1-ylmethyl)phenyl]pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

A mixture of 3-(bromomethyl)phenylboronic acid (246 mg, 1.14 mmol), 1-(*tert*-butoxycarbonyl)homopiperazine (229 mg, 1.14 mmol) and triethylamine (280 μ L, 2.0 mmol) in DCM (20 mL) was stirred at room temperature for 21 h. The solvent was removed *in vacuo* and the resulting boronic acid was combined with *Example 73* (177 mg, 0.47 mmol), K₃PO₄ (80 mg, 0.38 mmol) and Pd(PPh₃)₄ (10 mg, 0.01 mmol) in DME (4.0 mL) and water (1.0 mL) and the reaction mixture was heated in a sealed tube at 140°C, under microwave irradiation, for 3 h. The reaction mixture was partitioned between EtOAc (25 mL) and aqueous sodium hydroxide solution (2*N*, 25 mL). The organic phase was concentrated *in vacuo* and purified by column chromatography (SiO₂, 0-20% MeOH/DCM, 1% NH₄OH). The obtained solid was taken up in MeOH (5.0 mL) and was treated with a solution of HCl in Et₂O (2*N*, 2.0 mL, 4.0 mmol). The reaction mixture was stirred at room temperature for 3 h and the solvent was removed *in vacuo*. The residue was partitioned between EtOAc (25 mL) and aqueous sodium hydroxide solution (2*N*, 25 mL). The organic phase was concentrated *in vacuo* and purified by column chromatography (SiO₂, 0-20% MeOH/DCM, 1% NH₄OH) to give the *title compound* (68 mg, 27%) as a clear glass. δ_{H} (DMSO-*d*₆) 8.75 (1H, d, *J* 5.1 Hz), 8.10 (1H, s), 8.04-7.97 (2H, m), 7.51-7.36 (3H, m), 3.71 (2H, s), 3.63-3.54 (4H, m), 3.40-3.27 (2H, m), 3.02-2.93 (4H, m), 2.83 (2H, t, *J* 6.2 Hz), 2.78-2.73 (2H, m), 2.69-2.63 (2H, m), 2.59 (2H, s), 2.39 (2H, s), 1.73-1.61 (2H, m), 0.97 (6H, s). LCMS (ES+) 531.3 (M+H)⁺.

EXAMPLE 417

tert-Butyl 4-{3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-3-yl)pyridin-2-yl]phenyl}piperazine-1-carboxylate

A mixture of *Intermediate 19* (2.00 g, 5.10 mmol), 2-chloropyridine-4-boronic acid (0.81 g, 5.16 mmol), K₃PO₄ (1.1 g, 5.19 mmol) and Pd(PPh₃)₄ (0.59 g, 0.51 mmol) in

DME (65 mL) and water (18 mL) was heated at 90°C for 22 h. The reaction mixture was quenched with saturated aqueous sodium hydrogencarbonate solution (100 mL) and extracted into EtOAc (3 x 150 mL). The combined organic phases were washed with brine (100 mL) and dried (magnesium sulfate). The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane). A sample of the solid obtained (100 mg) was combined with 3-[4-(*tert*-butoxycarbonyl)-piperazin-1-yl]phenylboronic acid pinacol ester (120 mg, 0.31 mmol), K₃PO₄ (85 mg, 0.40 mmol) and Pd(PPh₃)₄ (15 mg, 0.013 mmol) in DME (4 mL) and water (1 mL) and the mixture was heated in a sealed tube at 130°C, under microwave irradiation, for 1.5 h.

The reaction mixture was partitioned between saturated aqueous sodium hydrogencarbonate solution (30 mL) and EtOAc (30 mL) and the aqueous phase was extracted with further EtOAc (30 mL). The combined organic phases were dried (magnesium sulfate); the solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-4% MeOH/DCM) to give the *title compound* (127 mg, 41%) as a white solid. δ_{H} (DMSO-*d*₆) 8.70 (1H, d, *J* 5.9 Hz), 8.07-8.03 (1H, m), 7.71-7.66 (1H, m), 7.60-7.52 (2H, m), 7.42 (1H, dd, *J* 4.9, 1.1 Hz), 7.37 (1H, t, *J* 8.1 Hz), 7.06 (1H, dd, *J* 7.9, 1.9 Hz), 3.64-3.55 (4H, m), 3.55-3.44 (4H, m), 3.24-3.16 (4H, m), 2.94-2.86 (4H, m), 2.71 (2H, s), 1.42 (9H, s), 1.07 (6H, s). LCMS (ES⁺) 604.2 (M+H)⁺.

EXAMPLE 418

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(piperazin-1-yl)phenyl]pyridin-4-yl}-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one, trifluoroacetic acid salt

The *title compound* was prepared from *Example 417* according to *Method AT* and was obtained as a yellow solid (88%) after trituration with Et₂O. δ_{H} (DMSO-*d*₆) 8.81-8.68 (3H, m), 8.08 (1H, s), 7.75-7.70 (1H, m), 7.66-7.61 (1H, m), 7.57 (1H, s), 7.48-7.37 (2H, m), 7.14-7.08 (1H, m), 3.65-3.56 (4H, m), 3.48-3.40 (4H, m), 3.35-3.21 (4H, m), 2.94-2.86 (4H, m), 2.71 (2H, s), 1.19 (6H, s). LCMS (ES⁺) 504.4 (M+H)⁺.

EXAMPLE 419 (METHOD BG)

5,5-Dimethyl-2-(morpholin-4-yl)-3-{6-[3-(piperazin-1-ylmethyl)phenyl]pyridin-2-yl}-5,6-dihydro-1-benzothiophen-7(4*H*)-one

A mixture of *Example 17* (1.00 g, 2.56 mmol), 6-chloropyridine-2-boronic acid pinacol ester (613 mg, 2.56 mmol), K₃PO₄ (1.63 g, 7.67 mmol) and Pd(PPh₃)₄ (148 mg, 0.128 mmol) in DME (6 mL) and water (2 mL) was heated in a sealed tube at 120°C, under microwave irradiation, for 20 minutes. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane). A sample of this intermediate (100 mg, 0.27 mmol), K₃PO₄ (85 mg, 0.40 mmol) and Pd(PPh₃)₄ (15 mg, 0.013 mmol) in DME (3 mL) and water (1 mL) was combined with the boronic acid (200 mg, 0.92 mmol) [formed from the reaction between 3-(bromomethyl)-phenylboronic acid (300 mg, 1.40 mmol), 1-(*tert*-butoxycarbonyl)piperazine (373 mg, 2.00 mmol) and triethylamine (280 µL, 2.00 mmol) in DCM (20 mL) and stirred at room temperature for 2 h before removal of the solvent *in vacuo*]. The mixture was heated in a sealed tube at 140°C, under microwave irradiation, for 2 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-20% MeOH/EtOAc). The obtained solid was taken up in DCM (2.0 mL), MeOH (2.0 mL) and treated with a solution of HCl in Et₂O (2*N*, 4.0 mL, 8.0 mmol) and stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-20% MeOH/DCM, 1% NH₄OH) to give the *title compound* (69 mg, 16%) as a yellow solid. δ_H (CD₃OD) 8.29-8.22 (1H, m), 8.17-8.04 (2H, m), 8.01-7.95 (1H, m), 7.68 (1H, dd, *J* 7.5, 0.8 Hz), 7.65-7.61 (2H, m), 4.30-4.16 (2H, m), 3.77-3.65 (4H, m), 3.35-3.42 (4H, m), 3.29-3.16 (4H, m), 3.14-3.04 (4H, m), 2.71 (2H, s), 2.48 (2H, s), 1.07 (6H, s). LCMS (ES⁺) 517.3 (M+H)⁺.

EXAMPLE 420

1-{3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzyl}pyrrolidine-2,5-dione

A mixture of *Example 155* (100 mg, 0.22 mmol), diethyl azodicarboxylate (40 µL, 0.22 mmol), triphenylphosphine (59 mg, 0.22 mmol) and succinimide (22 mg, 0.22 mmol) in THF (5.0 mL) was stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane) to give the *title compound* (51 mg, 44%) as a white solid. δ_H (DMSO-d₆) 8.75 (1H, d, *J* 5.1 Hz), 8.08-7.96 (3H, m), 7.47 (1H, t, *J* 7.7 Hz), 7.42 (1H, dd, *J* 5.1, 1.3

Hz), 7.37-7.32 (1H, m), 4.64 (2H, s), 3.66-3.55 (4H, m), 3.02-2.93 (4H, m), 2.70 (2H, s), 2.58 (2H, s), 2.38 (4H, s), 0.97 (6H, s). LCMS (ES⁺) 530.3 (M+H)⁺.

EXAMPLE 421

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3-(3-Bromophenyl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one

The *title compound* was prepared from *Intermediate 19* and 3-bromophenylboronic acid according to *Method J* and was obtained as a white solid (40%) after
10 purification by column chromatography (SiO₂, 0-80% EtOAc/heptane). δ_{H} (DMSO-*d*₆) 7.66 (1H, s), 7.56-7.47 (2H, m), 7.46-7.40 (2H, m), 3.62-3.53 (4H, m), 2.90-2.78 (4H, m), 2.60 (2H, s), 1.18 (6H, s). LCMS (ES⁺) 421.2, 423.2 (M+H)⁺.

EXAMPLE 422

15

tert-Butyl (1-{3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-3-yl)pyridin-2-yl]benzoyl}piperidin-4-yl)carbamate

The *title compound* was prepared from *Example 318* and 4-(*tert*-butoxycarbonylamino)piperidine according to *Method I* and was obtained as a white solid (88%) after
20 trituration with Et₂O. δ_{H} (DMSO-*d*₆) 8.74 (1H, d, *J* 4.9 Hz), 8.23-8.18 (1H, m), 8.15-8.12 (1H, m), 8.10-8.07 (1H, m), 7.62-7.53 (2H, m), 7.49-7.39 (2H, m), 6.94-6.84 (1H, m), 4.45-4.27 (1H, m), 3.64-3.54 (4H, m), 3.54-3.43 (1H, m), 3.26-3.06 (1H, m), 2.93-2.86 (4H, m), 2.71 (2H, s), 1.91-1.64 (4H, m), 1.38 (9H, s), 1.18 (6H, s). LCMS (ES⁺) 646.2 (M+H)⁺.

25

EXAMPLE 423

tert-Butyl *N*-(1-{3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-3-yl)pyridin-2-yl]benzoyl}piperidin-4-yl)-*N*-methylcarbamate

30

The *title compound* was prepared from *Example 318* and 4-[*N*-(*tert*-butoxycarbonyl)-*N*-methylamino]piperidine according to *Method I* and was obtained as a white solid (87%) after trituration with Et₂O. δ_{H} (DMSO-*d*₆) 8.74 (1H, d, *J* 4.7 Hz), 8.26-8.20 (1H, m), 8.19-8.16 (1H, m), 8.12-8.10 (1H, m), 7.62-7.54 (2H, m), 7.50-7.44 (2H, m),

4.70-4.52 (1H, m), 4.16-3.85 (1H, m), 3.76-3.53 (5H, m), 3.31 (3H, s), 3.23-3.06 (1H, m), 2.94-2.86 (4H, m), 2.74-2.70 (1H, m), 2.69 (2H, s), 1.78-1.54 (4H, m), 1.40 (9H, s), 1.18 (6H, s). LCMS (ES+) 660.2 (M+H)⁺.

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EXAMPLE 424

3-[2-(3-{[4-(Dimethylamino)piperidin-1-yl]carbonyl}phenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-c]pyridin-7(4H)-one

The *title compound* was prepared from *Example 318* and 4-(dimethylamino)-
10 piperidine according to *Method I* and was obtained as an off-white solid (92%) after
trituration with Et₂O. δ_H (DMSO-d₆) 8.74 (1H, d, *J* 5.3 Hz), 8.24-8.19 (1H, m), 8.16-8.14
(1H, m), 8.12-8.08 (1H, m), 7.62-7.54 (2H, m), 7.48-7.43 (2H, m), 4.56-4.38 (1H, m),
3.76-3.53 (5H, m), 3.18-2.98 (1H, m), 2.94-2.80 (4H, m), 2.71 (2H, s), 2.44-2.30 (1H, m),
2.23-2.13 (6H, s), 1.91-1.77 (1H, m), 1.77-1.63 (1H, m), 1.46-1.28 (2H, m), 1.19 (6H, s).
15 LCMS (ES+) 574.3 (M+H)⁺.

EXAMPLE 425

5,5-Dimethyl-3-(2-{3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyridin-4-yl)-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-c]pyridin-7(4H)-one

The *title compound* was prepared from *Example 318* and *N*-methylpiperazine
according to *Method I* and was obtained as a pale yellow solid (90%) after trituration with
Et₂O. δ_H (DMSO-d₆) 8.74 (1H, d, *J* 5.1 Hz), 8.25-8.19 (1H, m), 8.15-8.08 (2H, m), 7.62-
7.53 (2H, m), 7.49-7.42 (2H, m), 3.75-3.54 (6H, m), 3.43-3.26 (2H, m), 2.95-2.85 (4H,
25 m), 2.71 (2H, s), 2.43-2.23 (4H, m), 2.19 (3H, s), 1.19 (6H, s). LCMS (ES+) 546.3
(M+H)⁺.

EXAMPLE 426

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(pyrrolidin-1-ylcarbonyl)phenyl]pyridin-4-yl}-5,6-dihydrothieno[2,3-c]pyridin-7(4H)-one

The *title compound* was prepared from *Example 318* and pyrrolidine according to
Method I and was obtained as a pale yellow solid (85%) after trituration with Et₂O. δ_H

(DMSO-d₆) 8.74 (1H, d, *J* 5.1 Hz), 8.27 (1H, s), 8.24-8.19 (1H, m), 8.10 (1H, s), 7.63-7.54 (3H, m), 7.47 (1H, dd, *J* 5.1, 1.3 Hz), 3.62-3.56 (4H, m), 3.53-3.37 (4H, m), 2.93-2.84 (4H, m), 2.71 (2H, s), 1.95-1.76 (4H, m), 1.19 (6H, s). LCMS (ES+) 517.3 (M+H)⁺.

5

EXAMPLE 427

3-(2-{3-[(4-Aminopiperidin-1-yl)carbonyl]phenyl}pyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one, trifluoroacetic acid salt

The *title compound* was prepared from *Example 422* according to *Method AT* and was obtained as a yellow solid (100%) after trituration with Et₂O. δ_H (DMSO-d₆) 8.74 (1H, d, *J* 5.1 Hz), 8.25-8.19 (1H, m), 8.17 (1H, s), 8.10 (1H, s), 7.93-7.84 (3H, m), 7.62 (1H, t, *J* 7.7 Hz), 7.57 (1H, s), 7.50-7.42 (2H, m), 4.60-4.40 (1H, m), 4.27-3.78 (1H, m), 3.68-3.64 (1H, m), 3.64-3.55 (4H, m), 3.34-3.24 (1H, m), 3.23-3.07 (1H, m), 2.93-2.87 (4H, m), 2.71 (2H, s), 2.06-1.77 (2H, m), 1.59-1.31 (2H, m), 1.19 (6H, s). LCMS (ES+) 546.3 (M+H)⁺.

15

EXAMPLE 428

5,5-Dimethyl-3-[2-(3-{[4-(methylamino)piperidin-1-yl]carbonyl}phenyl)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one, trifluoroacetic acid salt

The *title compound* was prepared from *Example 423* according to *Method AT* and was obtained as a yellow solid (100%) after trituration with Et₂O. δ_H (DMSO-d₆) 8.74 (1H, d, *J* 5.1 Hz), 8.57-8.46 (2H, m), 8.25-8.20 (1H, m), 8.17 (1H, s), 8.11 (1H, s), 7.62 (1H, t, *J* 7.7 Hz), 7.57 (1H, s), 7.50-7.43 (2H, m), 4.97-4.00 (2H, m), 3.79-3.64 (1H, m), 3.63-3.55 (4H, m), 3.33-3.19 (1H, m), 3.19-3.08 (1H, m), 2.94-2.83 (4H, m), 2.71 (2H, s), 2.62-2.55 (3H, m), 2.18-1.86 (2H, m), 1.58-1.32 (2H, m), 1.19 (6H, s). LCMS (ES+) 560.3 (M+H)⁺.

25

EXAMPLE 429 (METHOD BH)

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tert-Butyl 3-[*N*-(3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzoyl)-*N*-(ethyl)amino]azetidine-1-carboxylate

Sodium hydride (60% dispersion in oil, 20 mg, 0.49 mmol) was added to a solution of *Example 406* (120 mg, 0.33 mmol) in DMF (7.0 mL) and the reaction mixture was stirred at room temperature for 30 minutes. Bromoethane (40 μ L, 0.49 mmol) was added and stirring was continued at room temperature for 1.5 h. Water (20 mL) was added and the mixture was extracted with EtOAc (75 mL). The organic phase was washed with water (7 x 20 mL), then with brine (20 mL), and was then dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by column chromatography (SiO₂, 75-100% EtOAc/heptane) to give the *title compound* (60 mg, 48%) as a yellow solid. δ_{H} (CD₃OD) 8.75 (1H, d, *J* 5.1 Hz), 8.20-8.14 (1H, m), 8.11-8.06 (1H, m), 8.04-8.01 (1H, m), 7.66 (1H, t, *J* 7.7 Hz), 7.56-7.46 (2H, m), 4.80-4.60 (1H, m), 4.27-4.15 (4H, m), 3.74-3.62 (6H, m), 3.14-3.04 (4H, m), 2.64 (2H, s), 2.48 (2H, s), 1.46 (9H, s), 1.35-1.15 (3H, m), 1.05 (6H, s). LCMS (ES⁺) 645.1 (M+H)⁺.

EXAMPLE 430

Methyl {3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl}acetate

The *title compound* was prepared from *Example 73* and [3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]acetic acid methyl ester according to *Method J* and was obtained as a white solid (50%) after purification by column chromatography (SiO₂, 0-3% MeOH/DCM and subsequently 0-100% EtOAc/heptane). δ_{H} (DMSO-*d*₆) 8.75 (1H, d, *J* 4.9 Hz), 8.10-8.00 (3H, m), 7.47 (1H, t, *J* 7.7 Hz), 7.41 (1H, dd, *J* 4.9, 1.3 Hz), 7.38-7.33 (1H, m), 3.80 (2H, s), 3.63 (3H, s), 3.61-3.56 (4H, m), 3.01-2.92 (4H, m), 2.58 (2H, s), 2.38 (2H, s), 0.97 (6H, s). LCMS (ES⁺) 491.3 (M+H)⁺.

EXAMPLE 431

tert-Butyl 4-[3'-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-3-yl)biphenyl-3-yl]piperazine-1-carboxylate

The *title compound* was prepared from *Example 421* and 3-[4-(*tert*-butoxy-carbonyl)piperazin-1-yl]phenylboronic acid pinacol ester according to *Method L*, stirring at 130°C under microwave irradiation for 1.5 h, and was obtained as a white solid (43%) after purification by column chromatography (SiO₂, 0-80% EtOAc/heptane and

subsequently 0-3% MeOH/DCM). δ_H (DMSO- d_6) 7.71 (1H, s), 7.65-7.58 (1H, m), 7.52 (1H, t, J 7.7 Hz), 7.49 (1H, s), 7.44-7.42 (1H, m), 7.41-7.39 (1H, m), 7.36-7.30 (1H, m), 7.22-7.19 (1H, m), 7.16-7.11 (1H, m), 7.01-6.95 (1H, m), 3.62-3.53 (4H, m), 3.53-3.44 (4H, m), 3.24-3.15 (4H, m), 2.92-2.83 (4H, m), 2.65 (2H, s), 1.42 (9H, s), 1.19 (6H, s).

5 LCMS (ES+) 603.1 (M+H)⁺.

EXAMPLE 432 (METHOD BD)

5,5-Dimethyl-3-(2-{3-[3-(methylamino)azetidin-1-yl]phenyl}pyridin-4-yl)-2-(morpholin-
10 4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

A mixture of *Example 360* (200 mg, 0.35 mmol), azetidin-3-ylcarbamic acid *tert*-butyl ester (125 mg, 0.71 mmol), potassium *tert*-butoxide (60 mg, 0.49 mmol) and acetato(2'-di-*tert*-butylphosphino-1,1'-biphenyl-2-yl)palladium(II) (10 mg, 0.02 mmol) in 1,4-dioxane (3.0 mL) was heated in a sealed tube at 100°C, under microwave irradiation,
15 for 30 minutes. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane). To a solution of the obtained solid in DMF (10 mL) was added sodium hydride (60% dispersion in oil, 10 mg, 0.24 mmol) and the reaction was stirred at room temperature for 30 minutes. Methyl iodide (18 μ L, 0.29 mmol) was added and stirring was continued at room temperature for 18 h.
20 Further sodium hydride (60% dispersion in oil, 10 mg, 0.24 mmol) was added and stirring was continued for 2 h at room temperature. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane). To a solution of the obtained solid in DCM (8 mL) was added TFA (2 mL) and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and
25 the residue was partitioned between DCM (20 mL) and saturated aqueous sodium hydrogencarbonate solution (20 mL). The organic phase was concentrated *in vacuo* and was purified by column chromatography (SiO₂, 0-20% MeOH/DCM) to give the *title compound* (5 mg, 31%) as a clear glass. δ_H (CD₃OD) 8.68 (1H, d, J 5.1 Hz), 7.91 (1H, s), 7.44 (1H, dd, J 5.3, 1.7 Hz), 7.39-7.29 (2H, m), 7.14-7.08 (1H, m), 6.68-6.60 (1H, m),
30 4.29-4.17 (2H, m), 4.02-3.91 (1H, m), 3.74-3.56 (6H, m), 3.15-3.01 (4H, m), 2.64 (2H, s), 2.47 (2H, m), 1.05 (6H, s). LCMS (ES+) 503.3 (M+H)⁺.

EXAMPLE 433

5,5-Dimethyl-2-(morpholin-4-yl)-3-[3'-(piperazin-1-yl)biphenyl-3-yl]-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one, trifluoroacetic acid salt

The *title compound* was prepared from *Example 431* according to *Method AT* and was obtained as a white solid (98%) after trituration with Et₂O. δ_{H} (DMSO-*d*₆) 8.79-8.68 (2H, m), 7.73 (1H, s), 7.68-7.62 (1H, m), 7.58-7.48 (2H, m), 7.47-7.34 (2H, m), 7.26 (1H, d, *J* 0.6 Hz), 7.23-7.18 (1H, m), 7.07-7.00 (1H, m), 3.61-3.54 (4H, m), 3.52-3.30 (4H, m), 3.31-3.23 (4H, m), 2.91-2.84 (4H, m), 2.65 (2H, s), 1.19 (6H, s). LCMS (ES+) 503.3 (M+H)⁺.

EXAMPLE 434

3-[2-(3-{[(3*R*)-3-Aminopyrrolidin-1-yl]carbonyl}phenyl)pyridin-4-yl]-2-(morpholin-4-yl)-5,5,6-trimethyl-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one

Sodium hydride (60% dispersion in oil, 32 mg, 0.80 mmol) was slowly added to a mixture of 3-(2-chloropyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one (300 mg, 0.79 mmol) and methyl iodide (107 mg, 0.75 mmol) in DMF (7.0 mL) and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane). A sample of the obtained solid (100 mg) was combined with *Intermediate 60* (105 mg, 0.31 mmol), K₃PO₄ (43 mg, 0.20 mmol), tetrabutylammonium bromide (80 mg, 0.25 mmol) and Pd(PPh₃)₄ (240 mg, 0.208 mmol) in DME (2.0 mL) and water (0.5 mL) and the mixture was heated in a sealed tube at 140°C, under microwave irradiation, for 3 h. The reaction mixture was partitioned between aqueous sodium hydroxide solution (2*M*, 15 mL) and EtOAc (15 mL). The organic phase was concentrated *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-10% MeOH/DCM). The obtained solid was taken up in MeOH (5.0 mL) and a solution of HCl in Et₂O (2*N*, 2.0 mL, 4.0 mmol) was added. The reaction mixture was stirred at room temperature for 3 h and the solvent was removed *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-15% MeOH/DCM, 0.75% NH₄OH) to give the *title compound* (68 mg, 33%) as a clear oil. δ_{H} (CD₃OD) 8.73 (1H, d, *J* 5.1 Hz), 8.31-8.24 (1H, m), 8.20-8.14 (1H, m), 8.05 (1H, s), 7.73-7.60 (2H, m), 7.53-

7.47 (1H, m), 4.07-3.56 (9H, m), 3.04 (3H, s), 3.00-2.94 (4H, m), 2.86 (2H, s), 2.49-2.31 (1H, m), 2.19-2.04 (1H, m), 1.32 (6H, s). LCMS (ES+) 546.1 (M+H)⁺.

EXAMPLE 435 (METHOD BJ)

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4-{3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzyl}piperazin-2-one, acetic acid salt

A mixture of 3-(bromomethyl)phenylboronic acid (246 mg, 1.14 mmol),
piperazinone (114 mg, 1.14 mmol) and triethylamine (280 µL, 2.0 mmol) in DCM (20
10 mL) was stirred at room temperature for 21 h. The solvent was removed *in vacuo* and the
resulting boronic acid was combined with *Example 73* (285 mg, 0.76 mmol), K₃PO₄ (80
mg, 0.38 mmol) and Pd(PPh₃)₄ (10 mg, 0.01 mmol) in DME (5.0 mL) and water (1.0 mL)
and the reaction mixture was heated in a sealed tube at 140°C, under microwave
irradiation, for 3 h. The organic phase was concentrated *in vacuo* and purified by
15 preparative HPLC (pH 5.8) to give the *title compound* (70 mg, 16%) as an off-white solid.
δ_H (DMSO-d₆) 8.75 (1H, d, *J* 4.9 Hz), 8.13 (1H, s), 8.08-8.02 (2H, m), 7.76 (1H, s), 7.49
(1H, t, *J* 7.7 Hz), 7.44-7.38 (2H, m), 3.67 (2H, s), 3.63-3.56 (4H, m), 3.21-3.13 (2H, m),
3.03-2.96 (4H, m), 2.94 (2H, s), 2.65-2.56 (4H, m), 2.39 (2H, s), 1.88 (3H, s), 0.97 (6H,
s). LCMS (ES+) 531.3 (M+H)⁺.

20

EXAMPLE 436

5,5-Dimethyl-2-(morpholin-4-yl)-3-(6-{3-[(3*S*)-pyrrolidin-3-ylamino]phenyl}pyridin-2-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

A mixture of *Example 17* (8.16 g, 20.9 mmol), 6-chloropyridine-2-boronic acid
pinacol ester (5.0 mg, 20.9 mmol), K₃PO₄ (6.64 g, 31.3 mmol) and Pd(PPh₃)₄ (1.20 g,
1.04 mmol) in DME (350 mL) and water (35 mL) was heated at reflux for 50 h. The
solvent was removed *in vacuo* and the residue was purified by column chromatography
(SiO₂, 20-60% EtOAc/heptane). A sample of the intermediate so obtained (400 mg) was
25 combined with 3-hydroxyphenylboronic acid (148 mg, 1.07 mmol), K₃PO₄ (340 mg, 1.60
mmol) and Pd(PPh₃)₄ (60 mg, 0.052 mmol) in DME (9 mL) and water (3 mL) and the
mixture was heated in a sealed tube at 120°C, under microwave irradiation, for 2 h. The
solvent was removed *in vacuo* and the residue was purified by column chromatography.

(SiO₂, 0-100% EtOAc/heptane). The obtained solid was combined with *N*-phenyl-trifluoromethanesulfonimide (228 mg, 0.61 mmol), and triethylamine (0.15 mL, 1.11 mmol) in DCM (10 mL) and the reaction mixture was stirred at room temperature for 1.5 h. The solvent was removed *in vacuo* and the residue was purified by column

5 chromatography (SiO₂, 0-100% EtOAc/heptane). A sample of the obtained solid (100 mg) was combined with (*S*)-3-amino-1-(*tert*-butoxycarbonyl)pyrrolidine (0.06 mL, 0.35 mmol), potassium *tert*-butoxide (28 mg, 0.25 mmol) and acetato(2'-di-*tert*-butylphosphino-1,1'-biphenyl-2-yl)palladium(II) (42 mg, 0.09 mmol) in 1,4-dioxane (2.0 mL) and the mixture was heated in a sealed tube at 100°C, under microwave irradiation, for 1
10 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane). A sample of the obtained solid (20 mg) was taken up in DCM (1.0 mL) and MeOH (1.0 mL) and was treated with a solution of HCl in Et₂O (2M, 0.5 mL, 1.0 mmol). The reaction mixture was stirred at room
15 temperature for 18 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (0-20% MeOH/DCM, 1% NH₄OH) to give the *title compound* (11 mg, 4%) as a yellow solid. δ_{H} (CD₃OD) 7.98-7.91 (1H, m), 7.78 (1H, dd, *J* 7.7, 0.6 Hz), 7.56 (1H, dd, *J* 7.7, 0.8 Hz), 7.36-7.23 (3H, m), 6.77 (1H, dt, *J* 7.3, 1.9 Hz), 4.19-4.08 (1H, m), 3.74-3.64 (4H, m), 3.31-3.15 (2H, m), 3.12-2.94 (6H, m), 2.70 (2H, s), 2.47 (2H, s), 2.33-2.17 (1H, m), 1.94-1.80 (1H, m), 1.06 (6H, s). LCMS (ES⁺) 503.4 (M+H)⁺.

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EXAMPLE 437

3-[2-(3-Bromophenyl)pyrimidin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

25 A mixture of *Example 344* (1.60 g, 4.42 mmol), 3-bromobenzamidinium hydrochloride (1.04 g, 4.42 mmol) and sodium methoxide solution (25% w/w in MeOH, 3 mL, 15 mmol) in MeOH was heated at reflux for 21h. The reaction mixture was evaporated *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane) to give the *title compound* (477 mg, 22%) as a pale yellow solid.
30 δ_{H} (CDCl₃) 8.83 (1H, d, *J* 5.3 Hz), 8.66 (1H, d, *J* 1.5 Hz), 8.41 (1H, dd, *J* 7.7, 0.9 Hz), 7.69-7.62 (2H, m), 7.40 (1H, t, *J* 7.7 Hz), 3.82-3.73 (4H, m), 3.13-3.05 (4H, m), 2.90 (2H, s), 2.49 (2H, s), 1.10 (6H, s). LCMS (ES⁺) 500.2 (M+H)⁺.

EXAMPLE 438 (METHOD BK)**5,5-Dimethyl-3-[2-(4-methylphenyl)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one**

- 5 A mixture of *Example 73* (100 mg, 0.27 mmol), 4-methylphenylboronic acid (37 mg, 0.27 mmol), K₃PO₄ (65 mg, 0.31 mmol) and Pd(PPh₃)₄ (11 mg, 0.01 mmol) in DME (4 mL) and water (1 mL) was heated in a sealed tube at 150°C, under microwave irradiation, for 10 minutes. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC (pH 2.5) to give the *title compound* (12 mg, 10%) as a yellow solid.
- 10 δ_{H} (CDCl₃) 8.76 (1H, d, *J* 5.3 Hz), 7.98-7.92 (2H, m), 7.78 (1H, s), 7.36-7.31 (2H, m), 7.24 (1H, dd, *J* 5.1, 1.5 Hz), 3.74-3.65 (4H, m), 3.09-3.00 (4H, m), 2.55 (2H, s), 2.47 (2H, s), 2.45 (3H, s), 1.06 (6H, s). LCMS (ES⁺) 433.3 (M+H)⁺.

EXAMPLE 439

15

5,5-Dimethyl-3-[2-(4-fluorophenyl)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

- The *title compound* was prepared from *Example 73* and 4-fluorophenylboronic acid according to *Method BK* and was obtained as a beige solid (21%) after purification
- 20 by preparative HPLC (pH 2.5). δ_{H} (CDCl₃) 8.76 (1H, d, *J* 4.1 Hz), 8.08-8.00 (2H, m), 7.76 (1H, s), 7.31-7.16 (3H, m), 3.74-3.65 (4H, m), 3.08-2.99 (4H, m), 2.55 (2H, s), 2.48 (2H, s), 1.07 (6H, s). LCMS (ES⁺) 437.0 (M+H)⁺.

EXAMPLE 440

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3-[2-(4-Chlorophenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

- The *title compound* was prepared from *Example 73* and 4-chlorophenylboronic acid according to *Method BK* and was obtained as a yellow solid (21%) after purification
- 30 by preparative HPLC (pH 2.5). δ_{H} (CDCl₃) 8.77 (1H, d, *J* 5.1 Hz), 8.03-7.97 (2H, m), 7.79 (1H, s), 7.53-7.46 (2H, m), 7.30-7.26 (1H, m), 3.73-3.64 (4H, m), 3.09-2.99 (4H, m), 2.54 (2H, s), 2.47 (2H, s), 1.07 (6H, s). LCMS (ES⁺) 453.3, 455.3 (M+H)⁺.

EXAMPLE 441 (METHOD BL)

2-{3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl}-N,N-dimethylacetamide

- 5 A solution of lithium hydroxide monohydrate (58 mg, 1.38 mmol) in water (7.5 mL) was added to a solution of *Example 430* (340 mg, 0.69 mmol) in THF (30 mL) and the reaction mixture was stirred at room temperature for 23 h. Dilute aqueous HCl (1*N*) was added dropwise until a yellow coloration just persisted and the mixture was extracted into EtOAc (2 x 50 mL). The combined organic extracts were washed with brine (40 mL), dried (magnesium sulfate) and evaporated *in vacuo*. A sample of the obtained solid (40 mg) was combined with dimethylamine hydrochloride (8.0 mg, 0.1 mmol), triethylamine (38 μ L, 0.27 mmol), EDC (17 mg, 0.09 mmol) and 1-hydroxybenzotriazole (catalytic amount) in DCM (3.0 mL) and the reaction mixture was stirred at room temperature for 72 h. The reaction mixture was diluted with DCM (5 mL), then washed with water (10 mL) and saturated aqueous sodium hydrogencarbonate solution (10 mL). The organic phase was dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was triturated with Et₂O to give the *title compound* (25 mg, 64%) as a white powder. δ_{H} (DMSO-*d*₆) 8.74 (1H, d, *J* 4.9 Hz), 8.05-7.97 (3H, m), 7.45 (1H, t, *J* 7.7 Hz), 7.39 (1H, dd, *J* 4.9, 1.1 Hz), 7.34-7.29 (1H, m), 3.79 (2H, s), 3.64-3.55 (4H, m), 3.04 (3H, s), 3.00-2.94 (4H, m), 2.84 (3H, s), 2.57 (2H, s), 2.38 (2H, s), 0.97 (6H, s). LCMS (ES⁺) 504.3 (M+H)⁺.
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- 15
- 20

EXAMPLE 442

- 25 5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)phenyl]pyridin-4-yl}-5,6-dihydro-1-benzothiophen-7(4*H*)-one

- The *title compound* was prepared from *Example 430* and pyrrolidine according to *Method BL* and was obtained as an off-white solid (97%). δ_{H} (DMSO-*d*₆) 8.74 (1H, d, *J* 4.9 Hz), 8.06-7.94 (3H, m), 7.45 (1H, t, *J* 7.7 Hz), 7.40 (1H, dd, *J* 4.9, 1.1 Hz), 7.35-7.29 (1H, m), 3.72 (2H, s), 3.63-3.55 (4H, m), 3.56-3.47 (2H, m), 3.37-3.26 (2H, m), 3.01-2.92 (4H, m), 2.56 (2H, s), 2.38 (2H, s), 1.93-1.82 (2H, m), 1.82-1.70 (2H, m), 0.97 (6H, s). LCMS (ES⁺) 530.3 (M+H)⁺.
- 30

EXAMPLE 443

5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(piperazin-1-ylmethyl)phenyl]pyridin-4-yl}-5,6-dihydrothieno[2,3-c]pyridin-7(4H)-one

- 5 A mixture of *Intermediate 19* (700 mg, 1.79 mmol), 2-chloropyridine-4-boronic acid (284 mg, 1.81 mmol), K₃PO₄ (456 mg, 2.15 mmol) and Pd(PPh₃)₄ (240 mg, 0.208 mmol) in DME (22 mL) and water (6.8 mL) was heated in a sealed tube at 120°C, under microwave irradiation, for 40 minutes. The reaction was quenched with saturated aqueous NaHCO₃ solution and extracted into EtOAc (4 x 85 mL). The combined organic
- 10 phases were dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane) to give a pale orange solid (235 mg). A portion of this intermediate (100 mg) was combined with the boronic acid (105 mg, 0.48 mmol) [formed from the reaction between 3-(bromo-
- 15 methyl)phenylboronic acid (300 mg, 1.40 mmol), 1-(*tert*-butoxycarbonyl)piperazine (373 mg, 2.00 mmol) and triethylamine (280 µL, 2.00 mmol) in DCM (20 mL) and stirred at room temperature for 2 h before removal of the solvent *in vacuo*], K₃PO₄ (43 mg, 0.20 mmol), tetrabutylammonium bromide (80 mg, 0.25 mmol) and Pd(PPh₃)₄ (5 mg, 0.004 mmol) in DME (2.0 mL) and water (0.5 mL) and was heated in a sealed tube at 140°C, under microwave irradiation, for 3 h. The reaction mixture was partitioned between
- 20 aqueous sodium hydroxide solution (2M, 15 mL) and EtOAc (15 mL). The organic phase was concentrated *in vacuo* and the residue was taken up in MeOH (4.0 mL) and a solution of HCl in Et₂O (2N, 4.0 mL, 8.0 mmol) was added. The reaction mixture was stirred at room temperature for 4 h and the solvent was removed *in vacuo*. The residue was
- 25 *title compound* (16 mg, 4%) as a yellow solid. δ_H (CD₃OD) 8.75 (1H, d, *J* 4.9 Hz), 8.13 (1H, s), 8.07-8.01 (2H, m), 7.79-7.74 (1H, m), 7.49 (1H, t, *J* 7.7 Hz), 7.43-7.38 (2H, m), 3.64 (2H, s), 3.62-3.56 (4H, m), 3.00-2.95 (4H, m), 2.93 (2H, s), 2.59 (2H, s), 2.39 (2H, s), 1.88 (3H, s), 0.97 (6H, s). LCMS (ES⁺) 518.1 (M+H)⁺.

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EXAMPLE 444

5,5-Dimethyl-3-(2-{3-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]phenyl}pyridin-4-yl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 430* and 1-methylpiperazine according to *Method BL* and was obtained as a white solid (62%). δ_{H} (DMSO- d_6) 8.74 (1H, d, J 5.1 Hz), 8.05-7.97 (3H, m), 7.45 (1H, t, J 7.5 Hz), 7.39 (1H, dd, J 5.1, 1.3 Hz), 7.34-7.29 (1H, m), 3.81 (2H, s), 3.62-3.55 (4H, m), 3.53-3.44 (4H, m), 3.02-2.91 (4H, m), 2.57 (2H, s), 2.38 (2H, s), 2.27-2.17 (4H, m), 2.12 (3H, s), 0.97 (6H, s). LCMS (ES+) 559.3 (M+H)⁺.

EXAMPLE 445

10 *N*-[2-(Diethylamino)ethyl]-2-{3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl}-*N*-methylacetamide

The *title compound* was prepared from *Example 430* and *N,N*-diethyl-*N'*-methylethylenediamine according to *Method BL* and was obtained as a white solid (89%). δ_{H} (DMSO- d_6) 8.74 (1H, d, J 4.9 Hz), 8.04-7.96 (3H, m), 7.49-7.36 (2H, m), 7.35-7.27 (1H, m), 3.83 (1H, s), 3.77 (1H, s), 3.64-3.56 (4H, m), 3.44-3.36 (2H, m), 3.01-2.94 (4H, m), 2.85 (3H, s), 2.57 (2H, s), 2.48-2.36 (14H, m), 0.96 (6H, s), 0.93-0.84 (6H, m). LCMS (ES+) 589.2 (M+H)⁺.

EXAMPLE 446

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tert-Butyl 3-[(3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl)acetyl]amino]azetidine-1-carboxylate

The *title compound* was prepared from *Example 430* and 3-amino-1-(*tert*-butoxycarbonyl)azetidine according to *Method BL* and was obtained as a white solid (100%). δ_{H} (DMSO- d_6) 8.78-8.72 (2H, m), 8.09-8.05 (1H, m), 8.02-7.96 (2H, m), 7.45 (1H, t, J 7.7 Hz), 7.40 (1H, dd, J 4.9, 1.3 Hz), 7.36-7.31 (1H, m), 4.43-4.31 (1H, m), 4.10-4.00 (2H, m), 3.71-3.63 (2H, m), 3.62-3.55 (4H, m), 3.01-2.92 (4H, m), 2.57 (2H, m), 2.38 (2H, m), 1.37 (9H, s), 0.97 (6H, s). LCMS (ES+) 631.1 (M+H)⁺.

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EXAMPLE 447 (METHOD BM)

3-(2-{3-[(3-Aminoazetidin-1-yl)carbonyl]phenyl}pyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

Trifluoroacetic acid (1.0 mL) was added to a solution of *Example 405* (75 mg, 0.122 mmol) in DCM (5.0 mL) and the reaction mixture was stirred at room temperature for 30 minutes. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (pH 5.8). The obtained product was partitioned between saturated sodium hydrogencarbonate solution (50 mL) and DCM (75 mL) and the aqueous phase was extracted with further DCM (75 mL). The combined organic phases were dried (magnesium sulfate) and the solvent was removed *in vacuo* to give the *title compound* as an off-white solid (26 mg, 41%). δ_{H} (CD_3OD) 8.75 (1H, dd, J 5.1, 0.6 Hz), 8.35-8.31 (1H, m), 8.22-8.16 (1H, m), 8.00 (1H, s), 7.80-7.82 (1H, m), 7.65 (1H, t, J 7.9 Hz), 7.51-7.45 (1H, m), 4.65-4.56 (1H, m), 4.50-4.38 (1H, m), 4.19-4.09 (1H, m), 3.99-3.84 (2H, m), 3.73-3.64 (4H, m), 3.12-3.04 (4H, m), 2.65 (2H, m), 2.48 (2H, m), 1.05 (6H, s). LCMS (ES⁺) 517.3 (M+H)⁺.

EXAMPLE 448

tert-Butyl [1-({3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl}acetyl)azetidin-3-yl]carbamate

The *title compound* was prepared from *Example 430* and azetidin-3-ylcarbamic acid *tert*-butyl ester according to *Method BL* and was obtained as a white solid (47%) after purification by column chromatography (SiO_2 , 0-100% EtOAc/heptane). δ_{H} ($\text{DMSO}-d_6$) 8.74 (1H, d J 5.1 Hz), 8.04-7.94 (3H, m), 7.60-7.52 (1H, m), 7.60-7.52 (1H, m), 7.47-7.36 (2H, m), 7.34-7.30 (1H, m), 4.47-4.36 (1H, m), 4.31-4.21 (1H, m), 4.12-3.95 (2H, m), 3.72-3.63 (1H, m), 3.62-3.56 (4H, m), 3.51 (2H, s), 3.03-2.92 (4H, m), 2.58 (2H, s), 2.38 (1H, s), 1.37 (9H, s), 0.97 (6H, s). LCMS (ES⁺) 631.2 (M+H)⁺.

EXAMPLE 449

tert-Butyl [(3*S*)-1-({3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl}acetyl)pyrrolidin-3-yl]carbamate

The *title compound* was prepared from *Example 430* and (3*S*)-(-)-3-(*tert*-butoxycarbonylamino)pyrrolidine according to *Method BL* and was obtained as a white solid (78%) after purification by column chromatography (SiO_2 , 0-100% EtOAc/heptane). δ_{H} ($\text{DMSO}-d_6$) 8.74 (1H, d, J 4.9 Hz), 8.04 (1H, s), 8.02-7.96 (2H, m), 7.48-7.37 (2H, m),

7.34-7.29 (1H, m), 7.21-7.11 (1H, m), 4.09-3.89 (1H, m), 3.77-3.09 (10H, m), 3.01-2.94 (4H, m), 2.57 (2H, s), 2.38 (2H, s), 2.11-1.65 (2H, m), 1.37 (9H, d, J 4.5 Hz), 0.97 (6H, s). LCMS (ES⁺) 645.2 (M+H)⁺.

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EXAMPLE 450

tert-Butyl *N*-[1-({3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl}acetyl)piperidin-4-yl]-*N*-methylcarbamate

The *title compound* was prepared from *Example 430* and 4-[*N*-(*tert*-butoxy-carbonyl)-*N*-methylamino]piperidine according to *Method BL* and was obtained as a white solid (100%). δ_{H} (DMSO- d_6) 8.74 (1H, d, J 5.1 Hz), 8.04 (1H, s), 8.02-7.97 (2H, m), 7.46 (1H, t, J 7.7 Hz), 7.39 (1H, dd, J 4.9, 1.3 Hz), 7.36-7.31 (1H, m), 4.58-4.47 (1H, m), 4.09-3.96 (2H, m), 3.86-3.81 (2H, m), 3.63-3.55 (4H, m), 3.08-2.92 (6H, m), 2.57 (2H, s), 2.53-2.46 (3H, m), 2.38 (2H, s), 1.63-1.43 (4H, m), 0.97 (6H, s). LCMS (ES⁺) 673.2 (M+H)⁺.

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EXAMPLE 451

N-(Azetidin-3-yl)-2-{3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]phenyl}acetamide, trifluoroacetic acid salt

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The *title compound* was prepared from *Example 446* according to *Method AT* and was obtained as a yellow solid (83%). δ_{H} (DMSO- d_6) 8.85 (1H, d, J 7.0 Hz), 8.75 (1H, d, J 5.1 Hz), 8.68-8.58 (2H, br m), 8.45-8.30 (1H, br m), 8.07 (1H, s), 8.02-7.97 (2H, m), 7.50-7.30 (3H, m), 4.64-4.46 (1H, m), 4.28-3.83 (6H, m), 3.64-3.50 (4H, m), 3.03-2.90 (4H, m), 2.57 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES⁺) 531.3 (M+H)⁺.

25

EXAMPLE 452

3-(2-{3-[2-(3-Aminoazetidin-1-yl)-2-oxoethyl]phenyl}pyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, trifluoroacetic acid salt

30

The *title compound* was prepared from *Example 448* according to *Method AT* and was obtained as a yellow solid (100%). δ_{H} (DMSO- d_6) 8.75 (1H, d, J 7.9 Hz), 8.32-8.20 (3H, m), 8.05 (1H, s), 8.02-7.97 (2H, m), 7.47 (1H, t, J 7.7 Hz), 7.42 (1H, dd, J 4.9, 1.3

Hz), 7.37-7.32 (1H, m), 4.53-4.43 (1H, m), 4.22-3.78 (4H, m), 3.63-3.53 (6H, m), 3.03-2.92 (4H, m), 2.57 (2H, s), 2.39 (2H, s), 0.97 (6H, s). LCMS (ES+) 531.3 (M+H)⁺.

EXAMPLE 453

5

3-[2-(3-{2-[(3*S*)-3-Aminopyrrolidin-1-yl]-2-oxoethyl}phenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, trifluoroacetic acid salt

The *title compound* was prepared from *Example 449* according to *Method AT* and was obtained as a yellow solid (95%). δ_{H} (DMSO- d_6) 8.74 (1H, d, *J* 4.9 Hz), 8.11-7.92 (6H, m), 7.50-7.38 (2H, m), 7.37-7.29 (1H, m), 4.02-3.32 (9H, m), 3.04-2.91 (4H, m), 2.57 (2H, s), 2.38 (2H, s), 2.32-1.86 (2H, m), 0.96 (6H, s). LCMS (ES+) 545.3 (M+H)⁺.

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EXAMPLE 454

15 5,5-Dimethyl-3-[2-(3-{2-[4-(methylamino)piperidin-1-yl]-2-oxoethyl}phenyl)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, trifluoroacetic acid salt

The *title compound* was prepared from *Example 450* according to *Method AT* and was obtained as a yellow solid (86%). δ_{H} (DMSO- d_6) 8.75 (1H, d, *J* 4.9 Hz), 8.56-8.41 (2H, br m), 8.08-7.96 (3H, m), 7.46 (1H, t, *J* 7.5 Hz), 7.41 (1H, dd, *J* 4.9, 1.1 Hz), 7.33 (1H, m), 4.52-4.40 (1H, m), 4.18-4.08 (1H, m), 4.00-3.65 (2H, m), 3.65-3.54 (2H, m), 3.28-3.14 (1H, m), 3.09-2.90 (5H, m), 2.65-2.52 (6H, m), 2.39 (2H, s), 2.05-1.91 (2H, m), 1.37-1.20 (2H, m), 0.97 (6H, s). LCMS (ES+) 573.3 (M+H)⁺.

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EXAMPLE 455

25

3-{2-[3-(3,8-Diazabicyclo[3.2.1]oct-3-ylmethyl)phenyl]pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

The *title compound* was prepared from 3-(bromomethyl)phenylboronic acid, 8-(*tert*-butoxycarbonyl)-3,8-diazabicyclo[3.2.1]octane and *Example 73* according to *Method BF* and was obtained as an off-white solid (50%) after purification by column chromatography (SiO₂, 0-20% MeOH/DCM, 1% NH₄OH). δ_{H} (DMSO- d_6) 8.75 (1H, d, *J* 4.9 Hz), 8.10-7.93 (3H, m), 7.46 (1H, t, *J* 7.5 Hz), 7.42-7.33 (2H, m), 3.66-3.55 (4H, m),

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3.52 (2H, s), 3.04-2.90 (4H, m), 2.59-2.48 (6H, m), 2.17 (2H, d, J 10.2 Hz), 2.39 (2H, s), 1.79 (2H, d, J 6.4 Hz), 1.64-1.55 (2H, m), 0.97 (6H, s). LCMS (ES+) 543.3 (M+H)⁺.

EXAMPLE 456

5

3-[6-(3-{[(3R)-3-Aminopyrrolidin-1-yl]methyl}phenyl)pyridin-2-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 17*, 6-chloropyridine-2-boronic acid pinacol ester, 3-(bromomethyl)phenylboronic acid and (3*S*)-(-)-3-(*tert*-butoxycarbonylamino)pyrrolidine according to *Method BG* and was obtained as a yellow solid (8%) after purification by column chromatography (SiO₂, 0-20% MeOH/DCM, 1% NH₄OH). δ_{H} (DMSO-*d*₆) 8.13 (1H, s), 8.01-7.88 (3H, m), 7.62 (1H, dd, J 7.4, 7.2 Hz), 7.40-7.36 (2H, m), 3.70-3.56 (6H, m), 3.40-3.24 (1H, m), 3.01-2.92 (4H, m), 2.73 (3H, s), 2.70-2.66 (1H, m), 2.62-2.53 (1H, m), 2.53-2.47 (1H, m), 2.40 (2H, s), 2.21-2.15 (1H, m), 2.09-1.96 (1H, m), 1.46-1.31 (1H, m), 1.00 (6H, s). LCMS (ES+) 517.3 (M+H)⁺.

10

15

EXAMPLE 457

tert-Butyl *N*-(1-{3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzoyl}azetidin-3-yl)-*N*-methylcarbamate

20

The *title compound* was prepared from *Example 405* and iodomethane according to *Method BH* and was obtained as an off-white solid (55%) after purification by column chromatography (SiO₂, 75-100% EtOAc/heptane). δ_{H} (CD₃OD) 8.75 (1H, d, J 4.5 Hz), 8.36-8.33 (1H, m), 8.23-8.18 (1H, m), 8.02 (1H, s), 7.81-7.76 (1H, m), 7.66 (1H, t, J 7.7 Hz), 7.49 (1H, dd, J 5.1, 1.5 Hz), 4.88-4.87 (1H, m), 4.64-4.55 (2H, m), 4.47-4.28 (2H, m), 3.72-3.63 (4H, m), 3.10-3.05 (4H, m), 2.98 (3H, s), 2.65 (2H, s), 2.48 (2H, s), 1.48 (9H, s), 1.05 (6H, s). LCMS (ES+) 631.2 (M+H)⁺.

25

EXAMPLE 458

30

5,5-Dimethyl-3-[2-(3-{[3-(methylamino)azetidin-1-yl]carbonyl}phenyl)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 457* according to *Method BM* and was obtained as an off-white solid (59%). δ_{H} (CD_3OD) 8.75 (1H, d, J 5.1 Hz), 8.35-8.32 (1H, m), 8.22-8.17 (1H, m), 8.01 (1H, s), 7.78-7.73 (1H, m), 7.65 (1H, t, J 7.7 Hz), 7.48 (1H, dd, J 5.1, 1.5 Hz), 4.65-4.54 (1H, m), 4.44-4.33 (1H, m), 4.22-4.12 (1H, m), 4.01-3.92 (1H, m), 3.75-3.63 (5H, m), 3.13-3.04 (4H, m), 2.64 (2H, s), 2.48 (2H, s), 2.36 (3H, s), 1.05 (6H, s). LCMS (ES+) 531.2 ($\text{M}+\text{H}$)⁺.

EXAMPLE 459

10 5,5-Dimethyl-2-(morpholin-4-yl)-3-{2-[3-(piperazin-1-yl)phenyl]pyrimidin-4-yl}-5,6-dihydro-1-benzothiophen-7(4H)-one

The *title compound* was prepared from *Example 437* and 1-*tert*-butoxycarbonyl-piperazine according to *Method BA* and was obtained as a brown solid (16%) after purification by column chromatography (SiO_2 , 0-20% MeOH/DCM, 1% NH_4OH). δ_{H} (DMSO- d_6) 8.92 (1H, d, J 5.1 Hz), 8.06-8.02 (1H, m), 7.95 (1H, d, J 7.9 Hz), 7.70 (1H, d, J 5.3 Hz), 7.45 (1H, t, J 8.1 Hz), 7.21 (1H, dd, J 7.9, 2.3 Hz), 3.74-3.62 (4H, m), 3.46-3.38 (4H, m), 3.26-3.19 (4H, m), 3.07-2.99 (4H, m), 2.91-2.85 (2H, m), 2.46-2.41 (2H, m), 1.00 (6H, s). LCMS (ES+) 504.1 ($\text{M}+\text{H}$)⁺.

EXAMPLE 460

20 5,5-Dimethyl-3-[2-(3-{[(3R)-3-(methylamino)pyrrolidin-1-yl]carbonyl}phenyl)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

To a solution of *Example 254* (300 mg, 0.44 mmol) in DCM (20 mL) was added triethylamine (0.6 mL, 4.35 mmol), EDC (334 mg, 1.74 mmol) and 1-hydroxybenzotriazole (10 mg, 0.09 mmol) and the reaction mixture was stirred at room temperature for 2 h. (3R)-(+)-3-(*tert*-Butoxycarbonylamino)pyrrolidine (323 mg, 1.74 mmol) was then added and stirring was continued at room temperature for 18 h. Water (30 mL) was added and the mixture was extracted into DCM (100 mL). The organic phase was washed with saturated aqueous sodium hydrogencarbonate solution (30 mL) and dried (magnesium sulfate). The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2 , 75-100% EtOAc/heptane). The obtained solid was taken up in DMF (5.0 mL) and sodium hydride (60% dispersion in oil, 14 mg, 0.36 mmol) was

added. The reaction mixture was stirred at room temperature for 30 minutes, then iodomethane (20 μ L, 0.36 mmol) was added and stirring was continued for 1 h. Water (20 mL) was added and the reaction mixture was extracted with EtOAc (80 mL). The organic phase was washed with water (6 x 20 mL) and brine (20 mL), then dried (magnesium sulfate). The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 75-100% EtOAc/heptane). The obtained solid was taken up in DCM (5.0 mL) and trifluoroacetic acid (1.0 mL) was added. The reaction mixture was stirred at room temperature for 30 minutes and the solvent was removed *in vacuo*. The residue was purified by preparative HPLC (pH 5.8) and the obtained product was partitioned between sodium hydrogencarbonate solution (20 mL) and DCM (2 x 75 mL). The combined organic phases were dried (magnesium sulfate) and the solvent was removed *in vacuo* to give the *title compound* (25 mg, 8%) as an off-white solid. δ_{H} (CD₃OD) 8.75 (1H, d, *J* 5.1 Hz), 8.28-8.13 (2H, m), 8.01 (1H, s), 7.69-7.60 (2H, m), 7.51-7.45 (1H, m), 3.88-3.50 (7H, m), 3.41-3.22 (2H, m), 3.14-3.02 (4H, m), 2.64 (2H, s), 2.46 (3H, 2 x s), 2.33 (2H, s), 2.30-2.06 (1H, m), 1.98-1.80 (1H, m), 1.05 (6H, s). LCMS (ES⁺) 545.3 (M+H)⁺.

EXAMPLE 461

3-{2-[3-(3,8-Diazabicyclo[3.2.1]oct-8-ylmethyl)phenyl]pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, acetic acid salt

A mixture of 3-(bromomethyl)phenylboronic acid (208 mg, 0.97 mmol), *Intermediate 62* (238 mg, 0.97 mmol) and triethylamine (280 μ L, 2.0 mmol) in DCM (20 mL) was stirred at room temperature for 19 h. The solvent was removed *in vacuo* and the resulting boronic acid (150 mg) was combined with *Example 73* (125 mg, 0.33 mmol), K₃PO₄ (40 mg, 0.19 mmol) and Pd(PPh₃)₄ (10 mg, 0.01 mmol) in DME (5.0 mL) and water (1.0 mL) and the reaction mixture was heated in a sealed tube at 140°C, under microwave irradiation, for 3 h. The reaction mixture was partitioned between EtOAc (50 mL) and 2*N* aqueous sodium hydroxide solution (50 mL). The organic phase was concentrated *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-20% MeOH/DCM, 1% NH₄OH). The residue was taken up in MeOH (15 mL) and 10% palladium on carbon was added. The reaction mixture was stirred under an atmosphere of hydrogen at room temperature for 23 h and the solvent was removed *in vacuo*. The

residue was purified by column chromatography (SiO₂, 0-20% MeOH/DCM, 1% NH₄OH) and preparative HPLC (pH 5.8) to give the *title compound* (14 mg, 7%) as a white solid. δ_H (DMSO-d₆) 8.75 (1H, d, *J* 5.1 Hz), 8.14 (1H, s), 8.02-8.01 (1H, m), 8.01-7.97 (1H, m), 7.46 (2H, d, *J* 4.9 Hz), 7.40 (1H, d, *J* 5.1 Hz), 3.65-3.57 (4H, m), 3.49 (2H, s), 3.42-3.17 (2H, m), 3.02-2.92 (4H, m), 2.77 (2H, d, *J* 11.7 Hz), 2.59 (2H, s), 2.48-2.41 (2H, m), 2.39 (2H, s), 1.98-1.90 (2H, m), 1.89 (3H, s), 1.75-1.65 (2H, m), 0.97 (6H, s). LCMS (ES⁺) 543.3 (M+H)⁺.

EXAMPLE 462

3-{2-[3-(4-Aminopiperidin-1-yl)phenyl]pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4H)-one

A mixture of *Example 360* (150 mg, 0.27 mmol), 4-(*tert*-butoxycarbonylamino)-piperidine (105 mg, 0.52 mmol), potassium *tert*-butoxide (45 mg, 0.37 mmol) and acetato(2'-di-*tert*-butylphosphino-1,1'-biphenyl-2-yl)palladium(II) (20 mg, 0.043 mmol) in 1,4-dioxane (6.0 mL) was heated in a sealed tube at 100°C, under microwave irradiation, for 30 minutes. The solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO₂, 0-100% EtOAc/heptane). A sample of the obtained solid (43 mg) was taken up in DCM (8.0 mL), treated with trifluoroacetic acid (2.0 mL) and stirred at room temperature for 4 h. The reaction mixture was partitioned between DCM (20 mL) and saturated aqueous sodium hydrogencarbonate solution (20 mL). The organic phase was dried (magnesium sulfate), the solvent was removed *in vacuo* and the residue was purified by column chromatography (0-20% MeOH/DCM, 1% NH₄OH) to give the *title compound* (23 mg, 33%) as a clear glass. δ_H (CD₃OD) 8.68 (1H, d, *J* 5.1 Hz), 7.91 (1H, s), 7.64-7.59 (1H, m), 7.46-7.33 (3H, m), 7.15-7.06 (1H, m), 3.87-3.77 (2H, m), 3.72-3.64 (4H, m), 3.10-3.00 (4H, m), 2.92-2.75 (3H, m), 2.63 (2H, s), 2.46 (2H, s), 2.01-1.90 (2H, m), 1.63-1.47 (2H, m), 1.04 (6H, s). LCMS (ES⁺) 517.3 (M+H)⁺.

EXAMPLES 463 & 464

tert-Butyl 1-{3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzyl}-L-prolinate, formic acid salt and 1-{3-[4-(5,5-

dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzyl}-L-proline, formic acid salt

The *title compounds* were prepared from 3-(bromomethyl)phenylboronic acid, *L*-proline *tert*-butyl ester hydrochloride and *Example 73* according to *Method BJ* and were

5 obtained as yellow glasses (2% and 11% respectively) after purification by preparative HPLC (pH 2.5). *Example 463*: δ_{H} (DMSO- d_6) 8.74 (1H, d, *J* 5.1 Hz), 8.27 (2H, s), 8.10 (1H, s), 8.03-7.97 (2H, m), 7.46 (1H, t, *J* 7.5 Hz), 7.41-7.38 (2H, m), 3.98-3.54 (7H, m), 3.20-3.12 (1H, m), 3.02-2.95 (4H, m), 2.92-2.84 (1H, m), 2.58 (2H, s), 2.38 (2H, s), 2.10-1.96 (1H, m), 1.85-1.64 (3H, m), 1.36 (9H, s), 0.96 (6H, s). LCMS (ES+) 602.1 (M+H)⁺.

10 *Example 464*: δ_{H} (DMSO- d_6) 8.76 (1H, d, *J* 5.1 Hz), 8.23-8.18 (2H, m), 8.11-8.01 (2H, m), 7.50-7.44 (2H, m), 7.41 (1H, d, *J* 5.3 Hz), 4.16 (1H, d, *J* 13.0 Hz), 3.83 (1H, d, *J* 12.6 Hz), 3.65 (1H, s), 3.61-3.55 (4H, m), 3.40-3.32 (1H, m), 3.14-3.05 (1H, m), 3.01-2.94 (4H, m), 2.59 (2H, s), 2.38 (2H, s), 2.19-2.04 (1H, m), 1.95-1.67 (3H, m), 0.97 (6H, s). LCMS (ES+) 546.3 (M+H)⁺.

EXAMPLE 465

5,5-Dimethyl-3-(2-{3-[4-(methylamino)piperidin-1-yl]phenyl}pyridin-4-yl)-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, acetic acid salt

20 The *title compound* was prepared from *Example 360*, 4-(*tert*-butoxycarbonyl-amino)piperidine and iodomethane according to *Method BI* and was obtained as a clear glass (3 mg, 3%). δ_{H} (CD₃OD) 8.70 (1H, d, *J* 5.3 Hz), 7.94 (1H, s), 7.65 (1H, d, *J* 0.9 Hz), 7.50-7.38 (3H, m), 7.19-7.12 (1H, m), 4.04-3.90 (2H, m), 3.75-3.65 (4H, m), 3.29-3.16 (1H, m), 3.15-3.04 (4H, m), 3.01-2.86 (2H, m), 2.74 (3H, s), 2.65 (2H, s), 2.48 (2H, s), 2.28-2.08 (2H, m), 1.89-1.71 (2H, m), 1.06 (6H, s). LCMS (ES+) 531 (M+H)⁺.

EXAMPLE 466

tert-Butyl (3*S*)-3-({3-[4-(5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzoyl}amino)pyrrolidine-1-carboxylate

30 To a solution of (*S*)-(-)-3-amino-1-(*tert*-butoxycarbonyl)pyrrolidine (323 mg, 1.74 mmol) in DCM (20 mL) was added *Example 254* (300 mg, 0.65 mmol), triethylamine (0.6 mL, 4.35 mmol), EDC (334 mg, 1.74 mmol) and 1-hydroxybenzotriazole (12 mg,

0.09 mmol). The reaction mixture was stirred at room temperature for 18 h. Water (30 mL) was added and the mixture was extracted with DCM (100 mL). The organic phase was washed with sodium hydrogencarbonate solution (30 mL), then dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by column chromatography (SiO₂, 100% EtOAc) to give the *title compound* (106 mg, 26%) as a yellow solid. δ_{H} (CD₃OD) 8.76 (1H, d, *J* 5.1 Hz), 8.49-8.45 (1H, m), 8.24-8.18 (1H, m), 8.03 (1H, s), 7.97-7.91 (1H, m), 7.68-7.61 (1H, m), 7.45 (1H, dd, *J* 5.1, 1.5 Hz), 4.65-4.54 (1H, m), 3.79-3.25 (8H, m), 3.12-3.03 (4H, m), 2.64 (2H, s), 2.48 (2H, s), 2.34-2.20 (1H, m), 2.14-2.03 (1H, m), 1.48 (9H, s), 1.05 (6H, s). LCMS (ES⁺) 631.1 (M+H)⁺.

10

EXAMPLE 467

5,5-Dimethyl-3-[2-(3-{[*N*-isopropyl-*N*-(methyl)amino]methyl}phenyl)pyridin-4-yl]-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, formic acid salt

15 The *title compound* was prepared from 3-(bromomethyl)phenylboronic acid, *N*-methylisopropylamine and *Example 73* according to *Method BJ* and was obtained as an off-white solid (16%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-*d*₆) 8.75 (1H, d, *J* 5.1 Hz), 8.17 (0.5H, s), 8.10 (1H, s), 8.02 (1H, s), 8.00 (1H, d, *J* 7.5 Hz), 7.48-7.35 (3H, m), 3.63-3.59 (4H, m), 3.58 (2H, s), 3.02-2.93 (4H, m), 2.93-2.82 (1H, m),
20 2.59 (2H, s), 2.39 (2H, s), 2.09 (3H, s), 1.05 (3H, s), 1.03 (3H, s), 0.97 (6H, s). LCMS (ES⁺) 504.2 (M+H)⁺.

EXAMPLE 468

25 1-{3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1-benzothien-3-yl)pyridin-2-yl]benzyl}piperazin-2-one

Sodium hydride (60% dispersion in oil, 56 mg, 1.40 mmol) was added to a solution of 1-(*tert*-butoxycarbonyl)-3-oxopiperazine (280 mg, 1.40 mmol) in DMF (10 mL) and the reaction mixture was stirred at room temperature for 15 minutes. 3-(Bromo-
30 methyl)phenylboronic acid neopentyl glycol ester (396 mg, 1.40 mmol) was then added and stirring was continued at room temperature for 16 h. The solvent was removed *in vacuo* and the resulting boronic acid was combined with *Example 73* (250 mg, 0.66 mmol), K₃PO₄ (80 mg, 0.38 mmol) and Pd(PPh₃)₄ (10 mg, 0.01 mmol) in DME (5.0 mL)

and water (1.0 mL) and the reaction mixture was heated in a sealed tube at 140°C, under microwave irradiation, for 3 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO₂, 20-100% EtOAc/heptane, then 15% MeOH/DCM). The obtained solid was taken up in MeOH (5.0 mL) and was treated with a solution of HCl in Et₂O (2*N*, 2.0 mL, 4.0 mmol). The reaction mixture was stirred at room temperature for 19 h and the solvent was removed *in vacuo*. The residue was partitioned between EtOAc (25 mL) and aqueous sodium hydroxide solution (2*N*, 25 mL). The organic phase was concentrated *in vacuo* and purified by column chromatography (SiO₂, 0-20% MeOH/DCM, 1% NH₄OH) to give the *title compound* (61 mg, 17%) as a yellow glass. δ_{H} (DMSO-*d*₆) 8.74 (1H, d, *J* 5.1 Hz), 8.04 (1H, s), 8.00 (1H, s), 7.66-7.31 (4H, m), 4.63 (2H, s), 4.01-3.98 (2H, m), 3.64-3.57 (4H, m), 3.57-3.50 (2H, m), 3.30-3.27 (2H, m), 3.02-2.93 (4H, m), 2.57 (2H, s), 2.38 (2H, s), 1.38 (9H, s), 0.96 (6H, s). LCMS (ES⁺) 531.3 (M+H)⁺.

EXAMPLE 469

3-[2-(3-[(3-*exo*)-3-Amino-8-azabicyclo[3.2.1]oct-8-yl)methyl]phenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one

A mixture of 3-(bromomethyl)phenylboronic acid (204 mg, 0.95 mmol), *Intermediate 63* (243 mg, 0.95 mmol) and triethylamine (280 μ L, 2.0 mmol) in DCM (20 mL) was stirred at room temperature for 17 h. The solvent was removed *in vacuo* and the resulting boronic acid was combined with *Example 73* (250 mg, 0.66 mmol), K₃PO₄ (80 mg, 0.38 mmol) and Pd(PPh₃)₄ (10 mg, 0.01 mmol) in DME (5.0 mL) and water (1.0 mL) and the reaction mixture was heated in a sealed tube at 140 °C, under microwave irradiation, for 3 h. The reaction mixture was concentrated *in vacuo* and was purified by column chromatography (SiO₂, 0-20% MeOH/DCM, 1% NH₄OH). The residue was taken up in EtOH (5.0 mL) and treated with hydrazine hydrate (105 μ L, 2.16 mmol). The reaction mixture was stirred at room temperature for 21 h and then concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-20% MeOH/DCM, 1% NH₄OH) to give the *title compound* (124 mg, 23%) as a pale yellow solid. δ_{H} (DMSO-*d*₆) 8.75 (1H, d, *J* 5.1 Hz), 8.13 (1H, s), 8.02 (2H, s), 7.48-7.39 (3H, m), 3.64-3.57 (4H, m), 3.18-3.10 (2H, m), 3.01-2.94 (4H, m), 2.91-2.78 (1H, m), 2.59 (2H, s), 2.39 (2H, s), 2.00-

1.88 (2H, m), 1.62-1.47 (4H, m), 1.43-1.31 (2H, m), 0.97 (6H, s). LCMS (ES+) 557.3 (M+H)⁺.

EXAMPLE 470

3-[2-(3-{[(2*R*,6*S*)-2,6-Dimethylmorpholin-4-yl]methyl}phenyl)pyridin-4-yl]-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydro-1-benzothiophen-7(4*H*)-one, formic acid salt

The *title compound* was prepared from 3-(bromomethyl)phenylboronic acid, *cis*-2,6-dimethylmorpholine and *Example 73* according to *Method BJ* and was obtained as a clear glass (46%) after purification by preparative HPLC (pH 2.5). δ_{H} (DMSO-*d*₆) 8.75 (1H, d, *J* 4.9 Hz), 8.14 (0.5H, s), 8.11-8.01 (3H, m), 7.47 (3H, t, *J* 7.4 Hz), 7.41-7.36 (3H, m), 3.65-3.57 (6H, m), 3.53 (2H, s), 3.02-2.94 (4H, m), 2.70 (2H, d, *J* 11.3 Hz), 2.59 (2H, s), 2.39 (2H, s), 1.68 (2H, t, *J* 10.6 Hz), 1.03 (3H, s), 1.01 (3H, s), 0.97 (6H, s). LCMS (ES+) 546.3 (M+H)⁺.

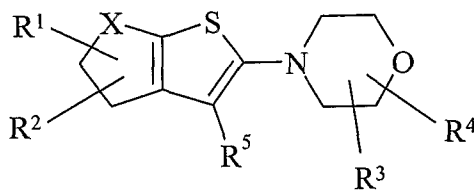
EXAMPLE 471

tert-Butyl (4-{3-[4-(5,5-Dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-3-yl)pyridin-2-yl]phenyl}piperazin-1-yl)acetate

A mixture of *Example 418* (41 mg, 0.056 mmol) and triethylamine (25 μ L, 0.179 mmol) was added dropwise to a solution of *tert*-butyl bromoacetate (10 μ L, 0.068 mmol) in THF (4.0 mL) and the reaction mixture was heated at reflux for 2 h. Further *tert*-butyl bromoacetate (4 μ L, 0.068 mmol) was added and reflux was continued for a further 0.5 h. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and partitioned between EtOAc (15 mL) and water (15 mL). The organic phase was washed with water (15 mL), dried (magnesium sulfate) and the solvent was removed *in vacuo* to give the *title compound* (35 mg, 100%) as a white powder. δ_{H} (DMSO-*d*₆) 8.70 (1H, d, *J* 5.1 Hz), 8.04 (1H, s), 7.65 (1H, br s), 7.55-7.52 (2H, m), 7.42-7.40 (1H, m), 7.34 (1H, t, *J* 8.1 Hz), 7.03 (1H, dd, *J* 8.1, 1.9 Hz), 3.65-3.56 (4H, m), 3.27-3.21 (4H, m), 2.95-2.86 (4H, m), 2.71 (1H, s), 2.69-2.62 (4H, m), 1.42 (9H, s), 1.18 (6H, s). LCMS (ES+) 618.2 (M+H)⁺.

Claims:

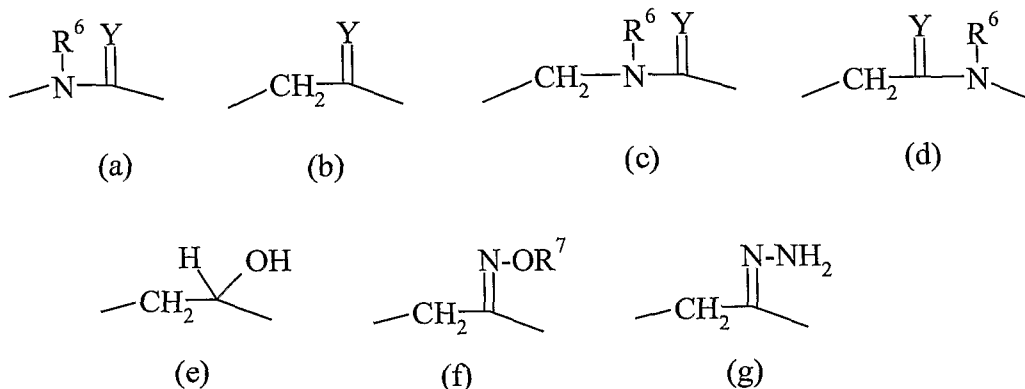
1. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof:



(I)

wherein

-X- represents a group of formula (a), (b), (c), (d), (e), (f) or (g):



Y represents oxygen or sulphur;

R^1 and R^2 independently represent hydrogen; or C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl-
15 (C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; or

R^1 and R^2 , when both are attached to the same carbon atom, represent, when taken together with the carbon atom to which they are both attached, C_{3-7} cycloalkyl or C_{3-7}
20 heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents; or

R^1 and R^2 , when attached to adjacent carbon atoms, represent, when taken together with the carbon atoms to which they are attached, C_{5-7} cycloalkyl, phenyl or heteroaryl, any of which groups may be optionally benzo-fused and/or substituted by one or more substituents;

5 R^3 and R^4 independently represent hydrogen; or C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, biaryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkylcarbonyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl-aryl(C_{1-6})alkyl or aryl-heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or
10 more substituents; or

R^3 and R^4 , when both are attached to the same carbon atom, represent, when taken together with the carbon atom to which they are both attached, C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents; or

15 R^3 and R^4 , when attached to adjacent carbon atoms, represent, when taken together with the carbon atoms to which they are attached, C_{5-7} cycloalkyl, phenyl or heteroaryl, any of which groups may be optionally benzo-fused and/or substituted by one or more substituents;

R^5 represents hydrogen, halogen, cyano, $-SR^a$, $-COR^e$, $-CO_2R^b$ or $-CONR^cR^d$; or R^5
20 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkenylcarbonyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, C_{3-7} cycloalkyl(C_{2-6})alkenyl, C_{3-7} cycloalkyl(C_{2-6})alkynyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, biaryl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl(C_{2-6})alkenyl, C_{3-7} heterocycloalkyl-
(C_{2-6})alkynyl, C_{3-7} heterocycloalkylcarbonyl(C_{2-6})alkynyl, C_{5-9} heterobicycloalkyl-
25 (C_{2-6})alkynyl, C_{3-7} heterocycloalkyl-aryl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl-aryl, C_{3-7} heterocycloalkyl-biaryl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{1-6})alkylcarbonyl, heteroaryl(C_{2-6})alkenyl, heteroaryl(C_{2-6})alkynyl, heteroarylcarbonyl, C_{3-7} heterocycloalkyl-heteroaryl, C_{3-7} heterocycloalkyl-heteroaryl(C_{2-6})alkynyl, heteroaryl-aryl, heteroaryl-aryl(C_{1-6})alkyl, aryl-heteroaryl, aryl-heteroaryl(C_{1-6})alkyl, C_{3-7}
30 heterocycloalkyl-aryl-heteroaryl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl-aryl-heteroaryl, C_{5-9} heterobicycloalkyl(C_{1-6})alkyl-aryl-heteroaryl, heteroaryl-aryl-heteroaryl, bi(heteroaryl), C_{3-7} heterocycloalkylcarbonyl-bi(heteroaryl), aryloxyaryl, aryl(C_{1-6})alkoxyaryl, heteroaryl(C_{1-6})alkoxyaryl, aryl(C_{1-6})alkylaminoaryl, heteroaryl(C_{1-6})alkylaminoaryl, C_{3-7}

cycloalkylcarbonylaminoaryl, arylcarbonylaminoaryl, aryl(C₁₋₆)alkylcarbonylaminoaryl, C₃₋₇ heterocycloalkylcarbonylaminoaryl, heteroarylcarbonylaminoaryl, aryl-(C₃₋₇)heterocycloalkylcarbonylaminoaryl, arylsulphonylaminoaryl, aryl(C₁₋₆)alkylsulphonylaminoaryl, heteroaryl(C₁₋₆)alkylsulphonylaminoaryl, C₃₋₇ cycloalkylaminocarbonylaminoaryl, arylaminocarbonylaminoaryl, C₃₋₇ heterocycloalkylaminocarbonylaminoaryl, C₃₋₇ heterocycloalkylaminocarbonylaminoaryl, heteroaryl(C₁₋₆)alkylaminocarbonylaminoaryl, C₃₋₇ heterocycloalkylcarbonylcarbonylaminoaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylaminocarbonylcarbonylaminoaryl, arylcarbonylaryl, C₃₋₇ heterocycloalkylcarbonylaryl, C₃₋₇ heterocycloalkylcarbonyl(C₁₋₆)alkylaryl, aryl(C₁₋₆)alkylaminocarbonylaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylaminocarbonylaryl, heteroarylaminocarbonylaryl, heteroaryl(C₁₋₆)alkylaminocarbonylaryl, C₃₋₇ heterocycloalkylaminocarbonyl(C₁₋₆)alkylaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylaminocarbonyl(C₁₋₆)alkylaryl, heteroarylaminocarbonyl(C₁₋₆)alkylaryl, heteroaryl(C₁₋₆)alkylaminocarbonyl(C₁₋₆)alkylaryl, arylaminoheteroaryl, C₃₋₇ heterocycloalkylamino-aryl-heteroaryl, C₃₋₇ heterocycloalkylcarbonylamino-aryl-heteroaryl, C₃₋₇ heterocycloalkylaminocarbonyl-amino-aryl-heteroaryl, C₃₋₇ heterocycloalkylcarbonyl-aryl-heteroaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylcarbonyl-aryl-heteroaryl, C₅₋₉ heterobicycloalkylcarbonyl-aryl-heteroaryl, C₃₋₇ heterocycloalkylcarbonyl(C₁₋₆)alkyl-aryl-heteroaryl, C₃₋₇ heterocycloalkylaminocarbonyl-aryl-heteroaryl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkylaminocarbonyl-aryl-heteroaryl or C₃₋₇ heterocycloalkylaminocarbonyl(C₁₋₆)alkyl-aryl-heteroaryl, any of which groups may be optionally substituted by one or more substituents;

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

R^b represents hydrogen; or optionally substituted C₁₋₆ alkyl;

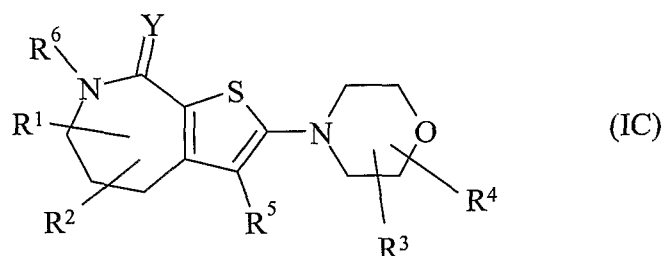
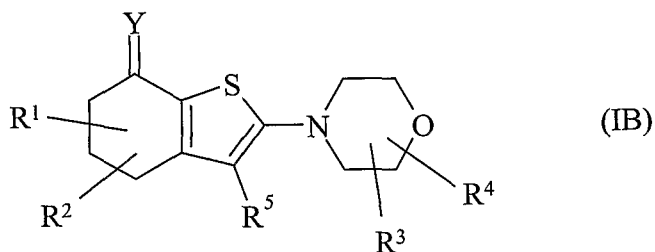
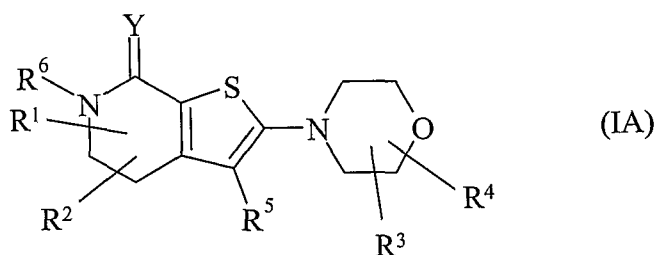
R^c represents hydrogen; or C₁₋₆ alkyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl or (aryl)(heteroaryl)(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents;

R^d represents hydrogen or C₁₋₆ alkyl;

R^e represents C₁₋₆ alkyl; and

R⁶ and R⁷ independently represent hydrogen or C₁₋₆ alkyl.

2. A compound of formula (IA), (IB) or (IC), or a pharmaceutically acceptable salt or solvate thereof:

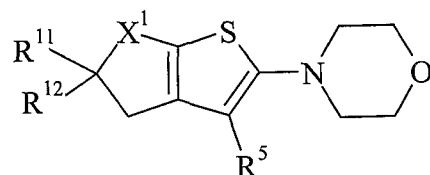


5

wherein Y, R¹, R², R³, R⁴, R⁵ and R⁶ are as defined in claim 1.

3. A compound of formula (IIA), or a pharmaceutically acceptable salt or solvate thereof:

10



(IIA)

wherein

-X¹- represents a group of formula (a), (b) or (c) as defined in claim 1;

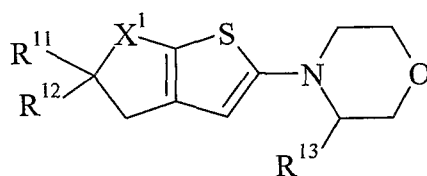
15 R⁵ is as defined in claim 1;

R¹¹ represents hydrogen or optionally substituted C₁₋₆ alkyl; and

R^{12} represents hydrogen; or C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; or

- 5 R^{11} and R^{12} , when taken together with the carbon atom to which they are both attached, represent C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents.

- 10 4. A compound of formula (IIB), or a pharmaceutically acceptable salt or solvate thereof:



(IIB)

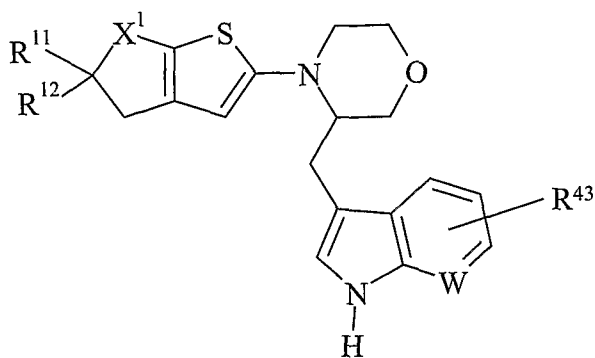
wherein

- 15 $-X^1$, R^{11} and R^{12} are as defined in claim 3; and

R^{13} represents hydrogen; or C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, biaryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkylcarbonyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl-aryl(C_{1-6})alkyl or aryl-heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

20

5. A compound as claimed in claim 4 of formula (IIC), or a pharmaceutically acceptable salt or solvate thereof:



(IIC)

wherein

$-X^1-$, R^{11} and R^{12} are as defined in claim 3;

5 W represents CH or N; and

R^{43} represents hydrogen, halogen, cyano, C_{1-6} alkyl, hydroxy(C_{1-6})alkyl, trifluoromethyl, aryl(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy, trifluoromethoxy, aryloxy, aryl(C_{1-6})alkoxy, C_{1-6} alkylthio, arylsulphonyl, C_{1-6} alkylsulphonyloxy, amino, C_{2-6} alkylcarbonylamino, C_{1-6} alkylsulphonylamino, C_{2-6} alkylcarbonyl or aminocarbonyl.

10

6. A compound as claimed in claim 1 as herein specifically disclosed in any one of the Examples.

7. A pharmaceutical composition comprising a compound of formula (I) as
15 defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, in association with a pharmaceutically acceptable carrier.

8. The use of a compound of formula (I) as defined in claim 1, or a
pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament
20 for the treatment and/or prevention of a disorder for which the administration of a selective PI3K inhibitor is indicated.

9. 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
25 a patient in need of such treatment an effective amount of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof.

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2007/002051

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D333/66 C07D333/68 C07D409/12 C07D409/14 C07D451/04
C07D453/02 C07D471/04 C07D495/04 A61K31/55 A61K31/5377
A61P3/00

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, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FICKENTSCHER K ET AL: "FARBREAKTIONEN VON 2,3-DICYAN-1,4-DITHIAANTHRACHINON. COLOR REACTIONS OF 2,3-DICYANO-1,4-DITIAANTHRAQUINONE. I. REACTION OF 2,3-DICYANO-4,9-THIOPHANTHRAQUINONE AND SECONDARY AMINES" ARCHIV DER PHARMAZIE, VCH VERLAGSGESELLSCHAFT MBH, WEINHEIM, DE, vol. 301, no. 8, 1968, pages 588-592, XP000856359 ISSN: 0365-6233 page 589; compound IV	1-9
A	US 2005/227959 A1 (YOSHIDA ICHIRO [JP] ET AL) 13 October 2005 (2005-10-13) paragraphs [0506], [0802]; claim 3	1-9
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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

18 September 2007

Date of mailing of the international search report

05/10/2007

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

MORIGGI, J

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2007/002051

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2006/046031 A1 (PIRAMED LTD [GB]; SHUTTLEWORTH STEPHEN J [GB]; FOLKES ADRIAN J [GB]; C) 4 May 2006 (2006-05-04) page 1, line 5 - line 6; claims 1,8,10,12 -----	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2007/002051

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2007/002051

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005227959	A1	13-10-2005	NONE
WO 2006046031	A1	04-05-2006	
		AU 2005298404 A1	04-05-2006
		AU 2005298408 A1	04-05-2006
		CA 2585089 A1	04-05-2006
		CA 2585112 A1	04-05-2006
		EP 1812444 A1	01-08-2007
		EP 1812445 A1	01-08-2007
		EP 1812446 A1	01-08-2007
		WO 2006046035 A1	04-05-2006
		WO 2006046040 A1	04-05-2006