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(71) Applicants (for all designated States except US): **KUDOS PHARMACEUTICALS LIMITED** [GB/GB]; 15 Stanhope Gate, London W1K 1LN (GB). **CANCER RESEARCH TECHNOLOGY LIMITED** [GB/GB]; Sardinia House, Sardinia Street, London WC2A 3NL (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **FRIGERIO Mark** [GB/GB]; KuDos Pharmaceuticals Limited, 410 Cambridge Science Park, Milton Road, Cambridge CB4 0PE (GB). **HUMMERSON, Marc, Geoffrey** [GB/GB]; KuDos Pharmaceuticals Limited, 410 Cambridge Science Park, Milton Road, Cambridge CB4 0PE (GB). **MENEAR, Keith, Allan** [GB/GB]; KuDos Pharmaceuticals Limited, 410 Cambridge Science Park, Milton Road, Cambridge CB4 0PE (GB). **FINLAY, Maurice, Raymond, Verschoye** [GB/GB]; AstraZeneca PLC, Mereside, Alderley Park, Macclesfield SK10 4TG (GB). **GRIFFIN, Edward, Jolyon** [GB/GB]; AstraZeneca PLC, Mereside, Alderley Park, Macclesfield SK10 4TG (GB). **RUSTON,**

Linette, Lys [GB/GB]; AstraZeneca PLC, Mereside, Alderley Park, Macclesfield SK10 4TG (GB). **MORRIS, Jeffrey, James** [GB/GB]; AstraZeneca PLC, Mereside, Alderley Park, Macclesfield SK10 4TG (GB). **TING, Attila, Kuan, Tsuei** [BE/GB]; AstraZeneca PLC, Mereside, Alderley Park, Macclesfield SK10 4TG (GB). **GOLDING, Bernard, Thomas** [GB/GB]; NICR School of Natural Sciences-Chemistry, Bedson Building, University of Newcastle Upon Tyne, Newcastle Upon Tyne NE1 7RU (GB). **GRIFFIN, Roger, John** [GB/GB]; NICR School of Natural Sciences-Chemistry, Bedson Building, University of Newcastle Upon Tyne, Newcastle Upon Tyne NE1 7RU (GB). **HARDCASTLE, Ian, Robert** [GB/GB]; NICR School of Natural Sciences-Chemistry, Bedson Building, University of Newcastle Upon Tyne, Newcastle Upon Tyne NE1 7RU (GB). **RODRIGUEZ-ARISTEGUI, Sonsoles** [ES/GB]; NICR School of Natural Sciences-Chemistry, Bedson Building, University of Newcastle Upon Tyne, Newcastle Upon Tyne NE1 7RU (GB).

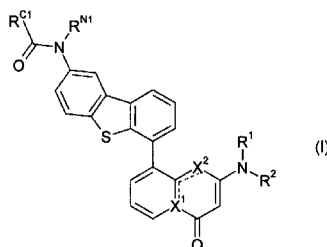
(74) Agents: **WATSON, Robert, James** et al.; MEWBURN ELLIS LLP, 33 Gutter Lane, London EC2V 8AS (GB).

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(54) Title: DIBENZOTHIOPHENE DERIVATIVES AS DNA- PK INHIBITORS



(57) Abstract: Compound formula I: wherein: X¹ and X² may be either (a) C and O, (b) N and N, or (c) C and NH, where the dotted bonds represents a double bond in the appropriate location; R¹ and R² are independently selected from hydrogen, an optionally substituted C₁₋₇ alkyl group, an optionally substituted C₃₋₂₀ heterocyclyl group, or an optionally substituted C₅₋₂₀ aryl group, or may together form, along with the nitrogen atom to which they are attached, an optionally substituted heterocyclic ring having from 4 to 8 ring atoms; R^{N1} is selected from hydrogen and an optionally substituted C₁₋₄ alkyl group; R^{C1} is selected from an optionally substituted C₁₋₇ alkyl group, an optionally substituted C₃₋₂₀ heterocyclyl group, or an optionally substituted C₅₋₂₀ aryl group; or R^{C1} and R^{C1} may together form an optionally substituted C₂₋₄ alkylene group.



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DIBENZOTHIOPHENE DERIVATIVES AS DNA- PK INHIBITORS

The present invention relates to compounds which act as DNA-PK inhibitors, their use and synthesis.

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The DNA-dependent protein kinase (DNA-PK) is a nuclear serine/threonine protein kinase that is activated upon association with DNA. Biochemical and genetic data have revealed this kinase to be composed of a large catalytic subunit, termed DNA-PKcs, and a regulatory component termed Ku. DNA-PK has been shown to be a crucial component of both the DNA double-strand break (DSB) repair machinery and the V(D)J recombination apparatus. In addition, recent work has implicated DNA-PK components in a variety of other processes, including the modulation of chromatin structure and telomere maintenance (Smith, G. C. M. and Jackson, S.P., *Genes and Dev.*, **13**, 916-934 (1999)).

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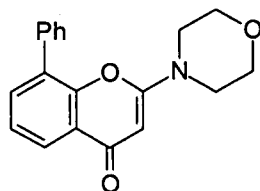
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DNA DSBs are regarded as the most lethal lesion a cell can encounter. To combat the serious threats posed by DNA DSBs, eukaryotic cells have evolved several mechanisms to mediate their repair. In higher eukaryotes, the predominant of these mechanisms is DNA non-homologous end-joining (NHEJ), also known as illegitimate recombination. DNA-PK plays a key role in this pathway. Increased DNA-PK activity has been demonstrated both *in vitro* and *in vivo* and correlates with the resistance of tumour cells to IR and bifunctional alkylating agents (Muller C., *et al.*, *Blood*, **92**, 2213-2219 (1998), Sirzen F., *et al.*, *Eur. J. Cancer*, **35**, 111-116 (1999)). Therefore, increased DNA-PK activity has been proposed as a cellular and tumour resistance mechanism. Hence, inhibition of DNA-PK with a small molecule inhibitor may prove efficacious in tumours where over-expression is regarded as a resistance mechanism.

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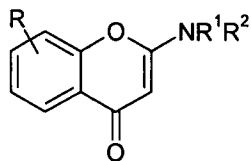
It also has been previously found that the PI 3-kinase inhibitor LY294002:



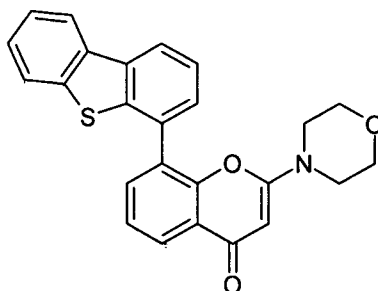
is able to inhibit DNA-PK function *in vitro* (Izzard, R.A., *et al.*, *Cancer Res.*, **59**, 2581-2586 (1999)). The IC₅₀ (concentration at which 50% of enzyme activity is lost) for LY294002 towards DNA-PK is, at ~1μM, the same as that for PI 3-kinase. Furthermore it has been shown that LY294002 is also able to weakly sensitise cells to the effects of IR (Rosenzweig, K.E., *et al.*, *Clin. Cancer Res.*, **3**, 1149-1156 (1999)).

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WO 03/024949 describes a number of classes of compounds useful as DNA-PK inhibitors, including 2-amino-chromen-4-ones of the general structure:

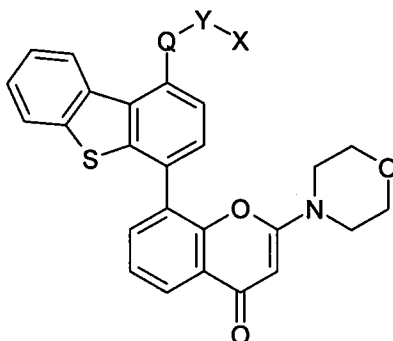


5 of which:



was one example. This compound exhibited an IC₅₀ of 10-12 nM and an DMR of 1.3 (see below for methods).

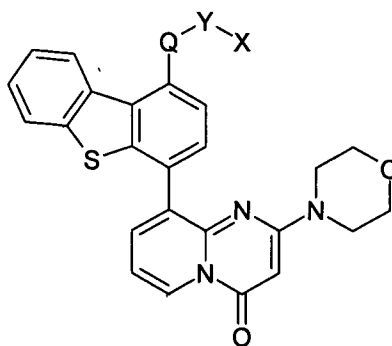
10 WO 2006/032869 describes compounds useful as DNA-PK inhibitors, including 2-amino-chromen-4-ones of the general structure:



wherein:

15 Q represents -NH-C(=O)- or -O-, Y is an optionally substituted C₁₋₅ alkylene group and X is selected from H, or a thioether or amino group.

WO 2006/109081 describes compounds useful as DNA-PK inhibitors, including 2-amino-pyridopyrimidines of the general structure:



wherein:

Q represents -NH-C(=O)- or -O-, Y is an optionally substituted C₁₋₅ alkylene group and X is selected from H, or a thioether or amino group.

5

Given the involvement of DNA-PK in DNA repair processes, and that small molecule inhibitors have been shown to radio- and chemo-sensitise mammalian cells in culture, an application of specific DNA-PK inhibitory drugs would be to act as agents that will enhance the efficacy of both cancer chemotherapy and radiotherapy. DNA-PK inhibitors may also prove useful in the treatment of retroviral mediated diseases. For example it has been demonstrated that loss of DNA-PK activity severely represses the process of retroviral integration (Daniel R, *et al.*, *Science*, **284**, 644-7 (1999)).

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However, compounds that inhibit DNA-PK may also inhibit PI 3-kinase, which in some circumstances is undesirable. Selectivity is an important issue as inhibition of other PI 3-kinase family members may lead to unwanted side-effects associated with the loss of function of those enzymes.

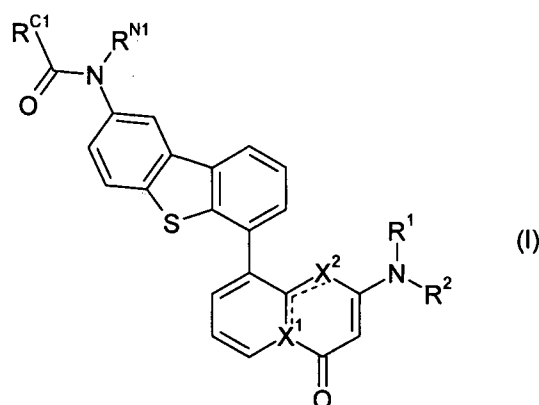
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The present inventors have now discovered further compounds which exhibit similar or improved levels of DNA-PK inhibition to existing compounds, whilst generally exhibiting lower levels of PI 3-kinase inhibition. The compounds may also possess other useful properties for use as active pharmaceuticals, in particular improved solubility and cellular efficacy. Some of the compounds of the present invention also show good solubility in both aqueous media and phosphate buffer solution – enhanced solubility may be of use in formulation the compounds for administration by an IV route, or for oral formulations (e.g. liquid and small tablet forms) for paediatric use. The oral bioavailability of the compounds of the present invention may be enhanced.

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Accordingly, the first aspect of the invention provides a compound of formula I:



wherein:

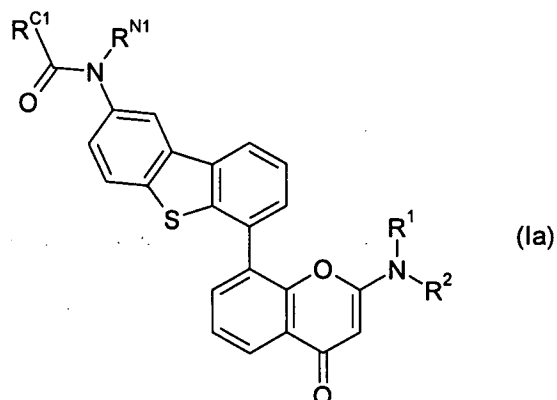
X^1 and X^2 may be either (a) C and O, (b) N and N, or (c) C and NH, where the dotted bonds represents a double bond in the appropriate location;

- 5 R^1 and R^2 are independently selected from hydrogen, an optionally substituted C_{1-7} alkyl group, an optionally substituted C_{3-20} heterocyclyl group, or an optionally substituted C_{5-20} aryl group, or may together form, along with the nitrogen atom to which they are attached, an optionally substituted heterocyclic ring having from 4 to 8 ring atoms;

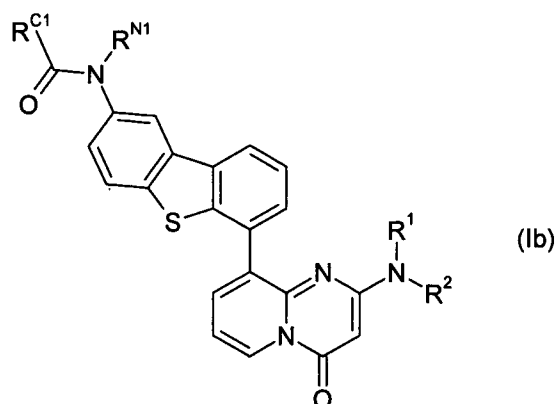
R^{N1} is selected from hydrogen and an optionally substituted C_{1-4} alkyl group;

- 10 R^{C1} is selected from an optionally substituted C_{1-7} alkyl group, an optionally substituted C_{3-20} heterocyclyl group, or an optionally substituted C_{5-20} aryl group;
or R^{N1} and R^{C1} may together form an optionally substituted C_{2-4} alkylene group.

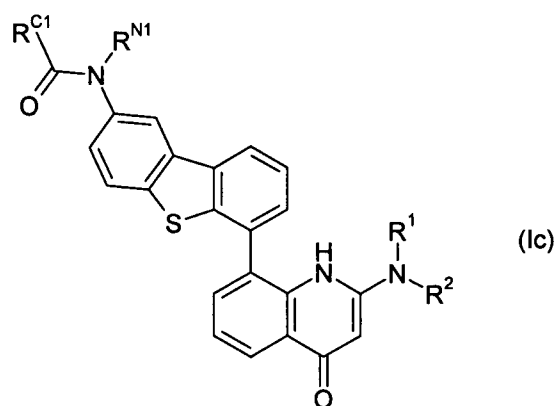
Thus, when X^1 and X^2 are C and O, the compound is of formula (Ia):



When X^1 and X^2 are both N, the compound is of formula (Ib):



When X^1 is C and X^2 is NH, the compound is of formula (Ic):



A second aspect of the invention provides a composition comprising a compound of the first aspect and a pharmaceutically acceptable carrier or diluent.

A third aspect of the invention provides a compound of the first aspect for use in a method of therapy.

A fourth aspect of the invention provides for the use of a compound of the first aspect in the preparation of a medicament for treating a disease ameliorated by the inhibition of DNA-PK. The fourth aspect of the invention also provides a compound of the first aspect for use in the method of treatment of a disease ameliorated by the inhibition of DNA-PK.

It is preferred that in the fourth aspect the compounds of the first aspect selectively inhibit the activity of DNA-PK compared to PI 3-kinase.

In particular in the fourth aspect of the invention, the compounds may be:

(a) used as, or in the preparation of a medicament for use as an adjunct in cancer therapy or for potentiating tumour cells for treatment with ionising radiation or chemotherapeutic agents; or

(b) used to treat, or in the preparation of a medicament for the treatment of, retroviral mediated diseases.

A further aspect of the invention provides an active compound as described herein for use in a method of treatment of the human or animal body, preferably in the form of a pharmaceutical composition.

Another aspect of the invention provides a method of inhibiting DNA-PK *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of an active compound as described herein.

Definitions

C₁₋₇ alkyl: The term "C₁₋₇ alkyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a C₁₋₇ hydrocarbon compound having from 1 to 7 carbon atoms, which may be aliphatic or alicyclic, or a combination thereof, and which may be saturated, partially unsaturated, or fully unsaturated.

Examples of saturated linear C₁₋₇ alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, and n-pentyl (amyl).

Examples of saturated branched C₁₋₇ alkyl groups include, but are not limited to, iso-propyl, iso-butyl, sec-butyl, tert-butyl, and neo-pentyl.

Examples of saturated alicyclic C₁₋₇ alkyl groups (also referred to as "C₃₋₇ cycloalkyl" groups) include, but are not limited to, groups such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, as well as substituted groups (e.g., groups which comprise such groups), such as methylcyclopropyl, dimethylcyclopropyl, methylcyclobutyl, dimethylcyclobutyl, methylcyclopentyl, dimethylcyclopentyl, methylcyclohexyl, dimethylcyclohexyl, cyclopropylmethyl and cyclohexylmethyl.

Examples of unsaturated C₁₋₇ alkyl groups which have one or more carbon-carbon double bonds (also referred to as "C₂₋₇ alkenyl" groups) include, but are not limited to, ethenyl (vinyl, -CH=CH₂), 2-propenyl (allyl, -CH=CH-CH₂), isopropenyl (-C(CH₃)=CH₂), butenyl, pentenyl, and hexenyl.

Examples of unsaturated C_{1-7} alkyl groups which have one or more carbon-carbon triple bonds (also referred to as " C_{2-7} alkynyl" groups) include, but are not limited to, ethynyl (ethynyl) and 2-propynyl (propargyl).

- 5 Examples of unsaturated alicyclic (carbocyclic) C_{1-7} alkyl groups which have one or more carbon-carbon double bonds (also referred to as " C_{3-7} cycloalkenyl" groups) include, but are not limited to, unsubstituted groups such as cyclopropenyl, cyclobutenyl, cyclopentenyl, and cyclohexenyl, as well as substituted groups (e.g., groups which comprise such groups) such as cyclopropenylmethyl and cyclohexenylmethyl.

10

C_{3-20} heterocyclyl: The term " C_{3-20} heterocyclyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a C_{3-20} heterocyclic compound, said compound having one ring, or two or more rings (e.g., spiro, fused, bridged), and having from 3 to 20 ring atoms, atoms, of which from 1 to 10 are ring
15 heteroatoms, and wherein at least one of said ring(s) is a heterocyclic ring. Preferably, each ring has from 3 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms. Ring heteroatoms may preferably be selected from the group consisting of O, N, S and P. " C_{3-20} " denotes ring atoms, whether carbon atoms or heteroatoms.

- 20 Examples of C_{3-20} heterocyclyl groups having one nitrogen ring atom include, but are not limited to, those derived from aziridine, azetidine, pyrrolidines (tetrahydropyrrole), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole), piperidine, dihydropyridine, tetrahydropyridine, and azepine.

- 25 Examples of C_{3-20} heterocyclyl groups having one oxygen ring atom include, but are not limited to, those derived from oxirane, oxetane, oxolane (tetrahydrofuran), oxole (dihydrofuran), oxane (tetrahydropyran), dihydropyran, pyran (C_6), and oxepin. Examples of substituted C_{3-20} heterocyclyl groups include sugars, in cyclic form, for example, furanoses and pyranoses, including, for example, ribose, lyxose, xylose, galactose, sucrose, fructose,
30 and arabinose.

Examples of C_{3-20} heterocyclyl groups having one sulphur ring atom include, but are not limited to, those derived from thiirane, thietane, thiolane (tetrahydrothiophene), thiane (tetrahydrothiopyran), and thiepane.

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Examples of C₃₋₂₀ heterocyclyl groups having two oxygen ring atoms include, but are not limited to, those derived from dioxolane, dioxane, and dioxepane.

5 Examples of C₃₋₂₀ heterocyclyl groups having two nitrogen ring atoms include, but are not limited to, those derived from imidazolidine, pyrazolidine (diazolidine), imidazoline, pyrazoline (dihydropyrazole), and piperazine.

10 Examples of C₃₋₂₀ heterocyclyl groups having one nitrogen ring atom and one oxygen ring atom include, but are not limited to, those derived from tetrahydrooxazole, dihydrooxazole, tetrahydroisoxazole, dihydroisoxazole, morpholine, tetrahydrooxazine, dihydrooxazine, and oxazine.

15 Examples of C₃₋₂₀ heterocyclyl groups having one oxygen ring atom and one sulphur ring atom include, but are not limited to, those derived from oxathiolane and oxathiane (thioxane).

20 Examples of C₃₋₂₀ heterocyclyl groups having one nitrogen ring atom and one sulphur ring atom include, but are not limited to, those derived from thiazoline, thiazolidine, and thiomorpholine.

Other examples of C₃₋₂₀ heterocyclyl groups include, but are not limited to, oxadiazine and oxathiazine.

25 Examples of heterocyclyl groups which additionally bear one or more oxo (=O) groups, include, but are not limited to, those derived from:

C₅ heterocyclics, such as furanone, pyrone, pyrrolidone (pyrrolidinone), pyrazolone (pyrazolinone), imidazolidone, thiazolone, and isothiazolone;

30 C₆ heterocyclics, such as piperidinone (piperidone), piperidinedione, piperazinone, piperazinedione, pyridazinone, and pyrimidinone (e.g., cytosine, thymine, uracil), and barbituric acid;

fused heterocyclics, such as oxindole, purinone (e.g., guanine), benzoxazolinone, benzopyrone (e.g., coumarin);

cyclic anhydrides (-C(=O)-O-C(=O)- in a ring), including but not limited to maleic anhydride, succinic anhydride, and glutaric anhydride;

cyclic carbonates (-O-C(=O)-O- in a ring), such as ethylene carbonate and 1,2-propylene carbonate;

imides (-C(=O)-NR-C(=O)- in a ring), including but not limited to, succinimide, maleimide, phthalimide, and glutarimide;

5 lactones (cyclic esters, -O-C(=O)- in a ring), including, but not limited to, β -propiolactone, γ -butyrolactone, δ -valerolactone (2-piperidone), and ϵ -caprolactone;

lactams (cyclic amides, -NR-C(=O)- in a ring), including, but not limited to, β -propiolactam, γ -butyrolactam (2-pyrrolidone), δ -valerolactam, and ϵ -caprolactam;

cyclic carbamates (-O-C(=O)-NR- in a ring), such as 2-oxazolidone;

10 cyclic ureas (-NR-C(=O)-NR- in a ring), such as 2-imidazolidone and pyrimidine-2,4-dione (e.g., thymine, uracil).

C₅₋₂₀ aryl: The term "C₅₋₂₀ aryl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of a C₅₋₂₀ aromatic compound, said
15 compound having one ring, or two or more rings (e.g., fused), and having from 5 to 20 ring atoms, and wherein at least one of said ring(s) is an aromatic ring. Preferably, each ring has from 5 to 7 ring atoms.

The ring atoms may be all carbon atoms, as in "carboaryl groups", in which case the group
20 may conveniently be referred to as a "C₅₋₂₀ carboaryl" group.

Examples of C₅₋₂₀ aryl groups which do not have ring heteroatoms (i.e. C₅₋₂₀ carboaryl groups) include, but are not limited to, those derived from benzene (i.e. phenyl) (C₆), naphthalene (C₁₀), anthracene (C₁₄), phenanthrene (C₁₄), naphthacene (C₁₈), and pyrene
25 (C₁₆).

Examples of aryl groups which comprise fused rings, one of which is not an aromatic ring, include, but are not limited to, groups derived from indene and fluorene.

30 Alternatively, the ring atoms may include one or more heteroatoms, including but not limited to oxygen, nitrogen, and sulphur, as in "heteroaryl groups". In this case, the group may conveniently be referred to as a "C₅₋₂₀ heteroaryl" group, wherein "C₅₋₂₀" denotes ring atoms, whether carbon atoms or heteroatoms. Preferably, each ring has from 5 to 7 ring atoms, of which from 0 to 4 are ring heteroatoms.

Examples of C₅₋₂₀ heteroaryl groups include, but are not limited to, C₅ heteroaryl groups derived from furan (oxole), thiophene (thiole), pyrrole (azole), imidazole (1,3-diazole), pyrazole (1,2-diazole), triazole, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, tetrazole, oxadiazole (furazan) and oxatriazole; and C₆ heteroaryl groups derived from isoxazine, pyridine (azine), pyridazine (1,2-diazine), pyrimidine (1,3-diazine; e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) and triazine.

Examples of C₅₋₂₀ heterocyclic groups (some of which are C₅₋₂₀ heteroaryl groups) which comprise fused rings, include, but are not limited to, C₉ heterocyclic groups derived from benzofuran, isobenzofuran, indole, isoindole, purine (e.g., adenine, guanine), benzothiophene, benzimidazole; C₁₀ heterocyclic groups derived from quinoline, isoquinoline, benzodiazine, pyridopyridine, quinoxaline; C₁₃ heterocyclic groups derived from carbazole, dibenzothiophene, dibenzofuran; C₁₄ heterocyclic groups derived from acridine, xanthene, phenoxathiin, phenazine, phenoxazine, phenothiazine.

The above C₁₋₇ alkyl, C₃₋₂₀ heterocyclyl and C₅₋₂₀ aryl groups whether alone or part of another substituent, may themselves optionally be substituted with one or more groups selected from themselves and the additional substituents listed below.

Halo: -F, -Cl, -Br, and -I.

Hydroxy: -OH.

Ether: -OR, wherein R is an ether substituent, for example, a C₁₋₇ alkyl group (also referred to as a C₁₋₇ alkoxy group, discussed below), a C₃₋₂₀ heterocyclyl group (also referred to as a C₃₋₂₀ heterocyclyloxy group), or a C₅₋₂₀ aryl group (also referred to as a C₅₋₂₀ aryloxy group), preferably a C₁₋₇ alkyl group.

C₁₋₇ alkoxy: -OR, wherein R is a C₁₋₇ alkyl group. Examples of C₁₋₇ alkoxy groups include, but are not limited to, -OCH₃ (methoxy), -OCH₂CH₃ (ethoxy) and -OC(CH₃)₃ (tert-butoxy).

Oxo (keto, -one): =O. Examples of cyclic compounds and/or groups having, as a substituent, an oxo group (=O) include, but are not limited to, carbocyclics such as cyclopentanone and cyclohexanone; heterocyclics, such as pyrone, pyrrolidone, pyrazolone, pyrazolinone, piperidone, piperidinedione, piperazinedione, and imidazolidone; cyclic

anhydrides, including but not limited to maleic anhydride and succinic anhydride; cyclic carbonates, such as propylene carbonate; imides, including but not limited to, succinimide and maleimide; lactones (cyclic esters, $-O-C(=O)-$ in a ring), including, but not limited to, β -propiolactone, γ -butyrolactone, δ -valerolactone, and ϵ -caprolactone; and lactams (cyclic amides, $-NH-C(=O)-$ in a ring), including, but not limited to, β -propiolactam, γ -butyrolactam (2-pyrrolidone), δ -valerolactam, and ϵ -caprolactam.

Imino (imine): $=NR$, wherein R is an imino substituent, for example, hydrogen, C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably hydrogen or a C_{1-7} alkyl group. Examples of ester groups include, but are not limited to, $=NH$, $=NMe$, $=NEt$, and $=NPh$.

Formyl (carbaldehyde, carboxaldehyde): $-C(=O)H$.

Acyl (keto): $-C(=O)R$, wherein R is an acyl substituent, for example, a C_{1-7} alkyl group (also referred to as C_{1-7} alkylacyl or C_{1-7} alkanoyl), a C_{3-20} heterocyclyl group (also referred to as C_{3-20} heterocyclylacyl), or a C_{5-20} aryl group (also referred to as C_{5-20} arylacyl), preferably a C_{1-7} alkyl group. Examples of acyl groups include, but are not limited to, $-C(=O)CH_3$ (acetyl), $-C(=O)CH_2CH_3$ (propionyl), $-C(=O)C(CH_3)_3$ (butyryl), and $-C(=O)Ph$ (benzoyl, phenone).

Carboxy (carboxylic acid): $-COOH$.

Ester (carboxylate, carboxylic acid ester, oxycarbonyl): $-C(=O)OR$, wherein R is an ester substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of ester groups include, but are not limited to, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)OC(CH_3)_3$, and $-C(=O)OPh$.

Acyloxy (reverse ester): $-OC(=O)R$, wherein R is an acyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group.

Examples of acyloxy groups include, but are not limited to, $-OC(=O)CH_3$ (acetoxyl), $-OC(=O)CH_2CH_3$, $-OC(=O)C(CH_3)_3$, $-OC(=O)Ph$, and $-OC(=O)CH_2Ph$.

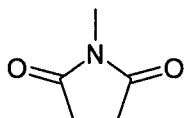
Amido (carbamoyl, carbamyl, aminocarbonyl, carboxamide): $-C(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$,

-C(=O)NHCH₂CH₃, and -C(=O)N(CH₂CH₃)₂, as well as amido groups in which R¹ and R², together with the nitrogen atom to which they are attached, form a heterocyclic structure as in, for example, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, and piperazinocarbonyl.

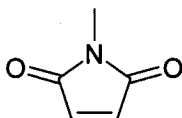
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Acylamido (acylamino): -NR¹C(=O)R², wherein R¹ is an amide substituent, for example, hydrogen, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably hydrogen or a C₁₋₇ alkyl group, and R² is an acyl substituent, for example, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably hydrogen or a C₁₋₇ alkyl group.

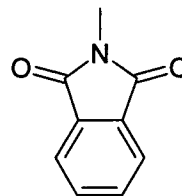
10 Examples of acylamide groups include, but are not limited to, -NHC(=O)CH₃, -NHC(=O)CH₂CH₃, and -NHC(=O)Ph. R¹ and R² may together form a cyclic structure, as in, for example, succinimidyl, maleimidyl and phthalimidyl:



succinimidyl



maleimidyl



phthalimidyl

15 Acylureido: -N(R¹)C(O)NR²C(O)R³ wherein R¹ and R² are independently ureido substituents, for example, hydrogen, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably hydrogen or a C₁₋₇ alkyl group. R³ is an acyl group as defined for acyl groups. Examples of acylureido groups include, but are not limited to, -NHCONHC(O)H, -NHCONMeC(O)H, -NHCONEtC(O)H, -NHCONMeC(O)Me, -NHCONEtC(O)Et, -NMeCONHC(O)Et, -NMeCONHC(O)Me, -NMeCONHC(O)Et, -NMeCONMeC(O)Me, -NMeCONEtC(O)Et, and -NMeCONHC(O)Ph.

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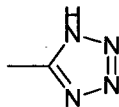
Carbamate: -NR¹-C(O)-OR² wherein R¹ is an amino substituent as defined for amino groups and R² is an ester group as defined for ester groups. Examples of carbamate groups include, but are not limited to, -NH-C(O)-O-Me, -NMe-C(O)-O-Me, -NH-C(O)-O-Et, -NMe-C(O)-O-t-butyl, and -NH-C(O)-O-Ph.

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Thioamido (thiocarbamyl): -C(=S)NR¹R², wherein R¹ and R² are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, -C(=S)NH₂, -C(=S)NHCH₃, -C(=S)N(CH₃)₂, and -C(=S)NHCH₂CH₃.

30

Tetrazolyl: a five membered aromatic ring having four nitrogen atoms and one carbon atom,



Amino: $-NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, for example,
 5 hydrogen, a C_{1-7} alkyl group (also referred to as C_{1-7} alkylamino or di- C_{1-7} alkylamino), a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably H or a C_{1-7} alkyl group, or, in the case of a "cyclic" amino group, R^1 and R^2 , taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Examples of amino groups include, but are not limited to, $-NH_2$, $-NHCH_3$, $-NHC(CH_3)_2$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, and
 10 $-NHPh$. Examples of cyclic amino groups include, but are not limited to, aziridino, azetidino, pyrrolidino, piperidino, piperazino, morpholino, and thiomorpholino.

Imino: $=NR$, wherein R is an imino substituent, for example, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably H or a C_{1-7} alkyl group.

15 Amidine: $-C(=NR)NR_2$, wherein each R is an amidine substituent, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably H or a C_{1-7} alkyl group. An example of an amidine group is $-C(=NH)NH_2$.

20 Carbazoyl (hydrazinocarbonyl): $-C(O)-NN-R^1$ wherein R^1 is an amino substituent as defined for amino groups. Examples of azino groups include, but are not limited to, $-C(O)-NN-H$, $-C(O)-NN-Me$, $-C(O)-NN-Et$, $-C(O)-NN-Ph$, and $-C(O)-NN-CH_2-Ph$.

Nitro: $-NO_2$.

25 Nitroso: $-NO$.

Azido: $-N_3$.

30 Cyano (nitrile, carbonitrile): $-CN$.

Isocyano: $-NC$.

Cyanato: $-OCN$.

Isocyanato: -NCO.

Thiocyano (thiocyanato): -SCN.

5

Isothiocyano (isothiocyanato): -NCS.

Sulfhydryl (thiol, mercapto): -SH.

10 Thioether (sulfide): -SR, wherein R is a thioether substituent, for example, a C₁₋₇ alkyl group (also referred to as a C₁₋₇ alkylthio group), a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably a C₁₋₇ alkyl group. Examples of C₁₋₇ alkylthio groups include, but are not limited to, -SCH₃ and -SCH₂CH₃.

15 Disulfide: -SS-R, wherein R is a disulfide substituent, for example, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably a C₁₋₇ alkyl group (also referred to herein as C₁₋₇ alkyl disulfide). Examples of C₁₋₇ alkyl disulfide groups include, but are not limited to, -SSCH₃ and -SSCH₂CH₃.

20 Sulfone (sulfonyl): -S(=O)₂R, wherein R is a sulfone substituent, for example, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably a C₁₋₇ alkyl group. Examples of sulfone groups include, but are not limited to, -S(=O)₂CH₃ (methanesulfonyl, mesyl), -S(=O)₂CF₃ (triflyl), -S(=O)₂CH₂CH₃, -S(=O)₂C₄F₉ (nonafllyl), -S(=O)₂CH₂CF₃ (tresyl), -S(=O)₂Ph (phenylsulfonyl), 4-methylphenylsulfonyl (tosyl), 4-bromophenylsulfonyl (brosyl),
25 and 4-nitrophenyl (nosyl).

Sulfine (sulfinyl, sulfoxide): -S(=O)R, wherein R is a sulfine substituent, for example, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably a C₁₋₇ alkyl group. Examples of sulfine groups include, but are not limited to, -S(=O)CH₃ and -S(=O)CH₂CH₃.

30 Sulfonyloxy: -OS(=O)₂R, wherein R is a sulfonyloxy substituent, for example, a C₁₋₇ alkyl group, a C₃₋₂₀ heterocyclyl group, or a C₅₋₂₀ aryl group, preferably a C₁₋₇ alkyl group. Examples of sulfonyloxy groups include, but are not limited to, -OS(=O)₂CH₃ and -OS(=O)₂CH₂CH₃.

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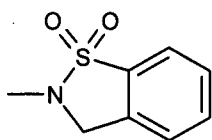
Sulfinyloxy: $-\text{OS}(=\text{O})\text{R}$, wherein R is a sulfinyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfinyloxy groups include, but are not limited to, $-\text{OS}(=\text{O})\text{CH}_3$ and $-\text{OS}(=\text{O})\text{CH}_2\text{CH}_3$.

- 5 Sulfamino: $-\text{NR}^1\text{S}(=\text{O})_2\text{OH}$, wherein R^1 is an amino substituent, as defined for amino groups. Examples of sulfamino groups include, but are not limited to, $-\text{NHS}(=\text{O})_2\text{OH}$ and $-\text{N}(\text{CH}_3)\text{S}(=\text{O})_2\text{OH}$.

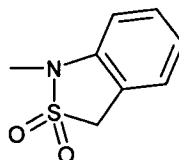
- 10 Sulfinamino: $-\text{NR}^1\text{S}(=\text{O})\text{R}$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfinamino substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfinamino groups include, but are not limited to, $-\text{NHS}(=\text{O})\text{CH}_3$ and $-\text{N}(\text{CH}_3)\text{S}(=\text{O})\text{C}_6\text{H}_5$.

- 15 Sulfamyl: $-\text{S}(=\text{O})\text{NR}^1\text{R}^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfamyl groups include, but are not limited to, $-\text{S}(=\text{O})\text{NH}_2$, $-\text{S}(=\text{O})\text{NH}(\text{CH}_3)$, $-\text{S}(=\text{O})\text{N}(\text{CH}_3)_2$, $-\text{S}(=\text{O})\text{NH}(\text{CH}_2\text{CH}_3)$, $-\text{S}(=\text{O})\text{N}(\text{CH}_2\text{CH}_3)_2$, and $-\text{S}(=\text{O})\text{NHPh}$.

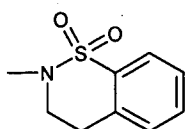
- 20 Sulfonamino: $-\text{NR}^1\text{S}(=\text{O})_2\text{R}$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfonamino substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfonamino groups include, but are not limited to, $-\text{NHS}(=\text{O})_2\text{CH}_3$ and $-\text{N}(\text{CH}_3)\text{S}(=\text{O})_2\text{C}_6\text{H}_5$. A special class of sulfonamino groups are those derived from sultams – in these groups one of R^1 and R is a C_{5-20} aryl group, preferably phenyl, whilst the other of R^1 and R is a bidentate group which links to the C_{5-20} aryl group, such as a bidentate group derived from a C_{1-7} alkyl group. Examples of such groups include, but are not limited to:
- 25



2,3-dihydro-tenzo[d]isothiazole-1,1-dioxide-2-yl



1,3-dihydro-benzo[c]isothiazole-2,2-dioxide-1-yl



3,4-dihydro-2H-benzo[e][1,2]thiazine-1,1-dioxide-2-yl

Phosphoramidite: $-\text{OP}(\text{OR}^1)-\text{NR}^2_2$, where R^1 and R^2 are phosphoramidite substituents, for example, -H, a (optionally substituted) C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably -H, a C_{1-7} alkyl group, or a C_{5-20} aryl group. Examples of phosphoramidite groups include, but are not limited to, $-\text{OP}(\text{OCH}_2\text{CH}_3)-\text{N}(\text{CH}_3)_2$,
 5 $-\text{OP}(\text{OCH}_2\text{CH}_3)-\text{N}(\text{i-Pr})_2$, and $-\text{OP}(\text{OCH}_2\text{CH}_2\text{CN})-\text{N}(\text{i-Pr})_2$.

Phosphoramidate: $-\text{OP}(=\text{O})(\text{OR}^1)-\text{NR}^2_2$, where R^1 and R^2 are phosphoramidate substituents, for example, -H, a (optionally substituted) C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably -H, a C_{1-7} alkyl group, or a C_{5-20} aryl group. Examples of
 10 phosphoramidate groups include, but are not limited to, $-\text{OP}(=\text{O})(\text{OCH}_2\text{CH}_3)-\text{N}(\text{CH}_3)_2$, $-\text{OP}(=\text{O})(\text{OCH}_2\text{CH}_3)-\text{N}(\text{i-Pr})_2$, and $-\text{OP}(=\text{O})(\text{OCH}_2\text{CH}_2\text{CN})-\text{N}(\text{i-Pr})_2$.

In many cases, substituents may themselves be substituted. For example, a C_{1-7} alkoxy group may be substituted with, for example, a C_{1-7} alkyl (also referred to as a C_{1-7} alkyl-
 15 C_{1-7} alkoxy group), for example, cyclohexylmethoxy, a C_{3-20} heterocyclyl group (also referred to as a C_{5-20} aryl- C_{1-7} alkoxy group), for example phthalimidoethoxy, or a C_{5-20} aryl group (also referred to as a C_{5-20} aryl- C_{1-7} alkoxy group), for example, benzyloxy.

Includes Other Forms

20 Included in the above are the well known ionic, salt, solvate, and protected forms of these substituents. For example, a reference to carboxylic acid ($-\text{COOH}$) also includes the anionic (carboxylate) form ($-\text{COO}^-$), a salt or solvate thereof, as well as conventional protected forms. Similarly, a reference to an amino group includes the protonated form ($-\text{N}^+\text{HR}^1\text{R}^2$), a salt or solvate of the amino group, for example, a hydrochloride salt, as well as conventional
 25 protected forms of an amino group. Similarly, a reference to a hydroxyl group also includes the anionic form ($-\text{O}^-$), a salt or solvate thereof, as well as conventional protected forms of a hydroxyl group.

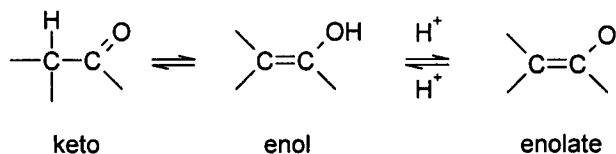
Isomers, Salts, Solvates, Protected Forms, and Prodrugs

30 Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diastereomeric, epimeric, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r- forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α - and β -

forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers", as used herein, are structural (or constitutional) isomers (i.e. isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, -OCH₃, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, -CH₂OH. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class (e.g., C₁₋₇ alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hydroxyazo, and nitro/aci-nitro.



Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ¹H, ²H (D), and ³H (T); C may be in any isotopic form, including ¹²C, ¹³C, and ¹⁴C; O may be in any isotopic form, including ¹⁶O and ¹⁸O; and the like.

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly or partially) racemic and other mixtures thereof. Methods for the preparation (e.g. asymmetric synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

Unless otherwise specified, a reference to a particular compound also includes ionic, salt, solvate, and protected forms of thereof, for example, as discussed below.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge, *et al.*, *J. Pharm. Sci.*, **66**, 1-19 (1977).

5

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be -COO^-), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+ , alkaline earth cations such as Ca^{2+} and Mg^{2+} , and other cations such as Al^{3+} . Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+ , NH_2R_2^+ , NHR_3^+ , NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $\text{N}(\text{CH}_3)_4^+$.

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If the compound is cationic, or has a functional group which may be cationic (e.g., -NH_2 may be -NH_3^+), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulphuric, sulphurous, nitric, nitrous, phosphoric, and phosphorous. Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: acetic, propionic, succinic, glycolic, stearic, palmitic, lactic, malic, pantoic, tartaric, citric, gluconic, ascorbic, maleic, hydroxymaleic, phenylacetic, glutamic, aspartic, benzoic, cinnamic, pyruvic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, phenylsulfonic, toluenesulfonic, methanesulfonic, ethanesulfonic, ethane disulfonic, oxalic, pantothenic, isethionic, valeric, lactobionic, and gluconic. Examples of suitable polymeric anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

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It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g. active compound, salt of active compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

It may be convenient or desirable to prepare, purify, and/or handle the active compound in a chemically protected form. The term "chemically protected form", as used herein, pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions, that is, are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Green and P. Wuts, Wiley, 1999).

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH₃, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal or ketal, respectively, in which the carbonyl group (>C=O) is converted to a diether (>C(OR)₂), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

For example, an amine group may be protected, for example, as an amide or a urethane, for example, as: a methyl amide (-NHCO-CH₃); a benzyloxy amide (-NHCO-OCH₂C₆H₅, -NH-Cbz); as a t-butoxy amide (-NHCO-OC(CH₃)₃, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-OC(CH₃)₂C₆H₄C₆H₅, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), as a 2-phenylsulphonyl)ethyloxy amide (-NH-Psec); or, in suitable cases, as an N-oxide (>NO⁺).

For example, a carboxylic acid group may be protected as an ester for example, as: an C₁₋₇ alkyl ester (e.g. a methyl ester; a t-butyl ester); a C₁₋₇ haloalkyl ester (e.g., a C₁₋₇ trihaloalkyl ester); a triC₁₋₇ alkylsilyl-C₁₋₇ alkyl ester; or a C₅₋₂₀ aryl-C₁₋₇ alkyl ester (e.g. a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

For example, a thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-CH₂NHC(=O)CH₃).

It may be convenient or desirable to prepare, purify, and/or handle the active compound in the form of a prodrug. The term "prodrug", as used herein, pertains to a compound which, when metabolised (e.g. *in vivo*), yields the desired active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide advantageous handling, administration, or metabolic properties.

For example, some prodrugs are esters of the active compound (e.g. a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required. Examples of such metabolically labile esters include those wherein R is C₁₋₇ alkyl (e.g. -Me, -Et); C₁₋₇ aminoalkyl (e.g. aminoethyl; 2-(N,N-diethylamino)ethyl; 2-(4-morpholino)ethyl); and acyloxy-C₁₋₇ alkyl (e.g. acyloxymethyl; acyloxyethyl; e.g. pivaloyloxymethyl; acetoxymethyl; 1-acetoxyethyl; 1-(1-methoxy-1-methyl)ethyl-carboxyloxyethyl; 1-(benzoyloxy)ethyl; isopropoxy-carboxyloxymethyl; 1-isopropoxy-carboxyloxyethyl; cyclohexyl-carboxyloxymethyl; 1-cyclohexyl-carboxyloxyethyl; cyclohexyloxy-carboxyloxymethyl; 1-cyclohexyloxy-carboxyloxyethyl; (4-tetrahydropyranyloxy) carboxyloxymethyl; 1-(4-tetrahydropyranyloxy)carboxyloxyethyl; (4-tetrahydropyranyl)carboxyloxymethyl; and 1-(4-tetrahydropyranyl)carboxyloxyethyl).

Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound. For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

Selective Inhibition

'Selective inhibition' means the inhibition of one enzyme to a greater extent than the inhibition of one or more other enzymes. This selectivity is measurable by comparing the concentration of a compound required to inhibit 50% of the activity (IC₅₀) of one enzyme against the concentration of the same compound required to inhibit 50% of the activity (IC₅₀)

of the other enzyme (see below). The result is expressed as a ratio. If the ratio is greater than 1, then the compound tested exhibits some selectivity in its inhibitory action.

The compounds of the present invention preferably exhibit a selectivity of greater than 3, 10, 20, 50 or 100 against DNA-PK over PI 3-kinase.

It is preferred that the IC₅₀ values used to assess selectivity are determined using the methods described in the examples below.

10 Further Embodiments

R¹ and R²

In compounds of formula I, when R¹ and R² form, along with the nitrogen atom to which they are attached, a heterocyclic ring having from 4 to 8 atoms, this may form part of a C₄₋₂₀ heterocyclyl group defined above (except with a minimum of 4 ring atoms), which must contain at least one nitrogen ring atom. It is preferred that R¹ and R² form, along with the nitrogen atom to which they are attached, a heterocyclic ring having 5, 6 or 7 atoms, more preferably 6 ring atoms.

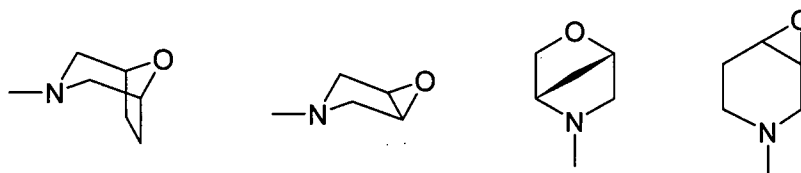
Single rings having one nitrogen atom include azetidine, azetidine, pyrrolidine (tetrahydropyrrole), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole), piperidine, dihydropyridine, tetrahydropyridine, and azepine; two nitrogen atoms include imidazolidine, pyrazolidine (diazolidine), imidazoline, pyrazoline (dihydropyrazole), and piperazine; one nitrogen and one oxygen include tetrahydrooxazole, dihydrooxazole, tetrahydroisoxazole, dihydroisoxazole, morpholine, tetrahydrooxazine, dihydrooxazine, and oxazine; one nitrogen and one sulphur include thiazoline, thiazolidine, and thiomorpholine.

Preferred rings are those containing one heteroatom in addition to the nitrogen, and in particular, the preferred heteroatoms are oxygen and sulphur. Thus preferred groups include morpholino, thiomorpholino, thiazolinyl. Preferred groups without a further heteroatom include pyrrolidino.

The most preferred groups are morpholino and thiomorpholino.

As mentioned above, these heterocyclic groups may themselves be substituted; a preferred class of substituent is a C₁₋₇ alkyl group. When the heterocyclic group is morpholino, the substituent group or groups are preferably methyl or ethyl, and more preferably methyl. A sole methyl substituent may be in the 2 or 3 position. If the morpholino group does bear a sole methyl substituent, the morpholino group has a chiral centre; thus, a racemic or enantiomeric group may be present.

As well as the single ring groups listed above, rings with bridges or cross-links are also envisaged. Examples of these types of ring where the group contains a nitrogen and an oxygen atom are:



These are named 8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl, 6-oxa-3-aza-bicyclo[3.1.0]hex-3-yl, 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl, and 7-oxa-3-aza-bicyclo[4.1.0]hept-3-yl, respectively.

Of these groups, 2-methylmorpholino and 8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl are of particular interest.

R^{N1}

R^{N1} is selected from hydrogen and an optionally substituted C₁₋₄ alkyl group.

In some embodiments, R^{N1} is hydrogen.

In other embodiments, R^{N1} is an optionally substituted C₁₋₄ alkyl group. The optional substituents may be selected from halo, hydroxy, nitro, cyano, -NH₂ and thiol. The substituents may be selected from halo and hydroxy. In some embodiments, the C₁₋₄ alkyl group is unsubstituted.

The C₁₋₄ alkyl group may be methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl or cyclopropylmethyl. In some embodiments, the group may be methyl, or cyclopropylmethyl.

Particular groups of interest are hydrogen, unsubstituted methyl and unsubstituted cyclopropylmethyl.

R^{C1} Alkyl

In some embodiments, R^{C1} is an optionally substituted C_{1-7} alkyl group.

5

In some embodiments, R^{C1} is an optionally substituted C_{1-4} alkyl group, e.g. methyl, ethyl, propyl, cyclopropyl, butyl, cyclobutyl.

10

The optional substituents when R^{C1} is an optionally substituted C_{1-7} alkyl, or C_{1-4} alkyl, group may be selected from: C_{5-20} aryl, C_{3-20} heterocyclyl, halo, hydroxy, ether, oxo, imino, formyl, acyl, carboxy, ester, acyloxy, amido, acylamido, acylureido, carbamate, thioamido, tetrazolyl, amino, imino, amidine, carbazoyl, nitro, nitroso, azido, cyano, isocyano, cyanato, thiocyanato, isothiocyano, thiol, thioether, disulfide, sulfone, sulfine, sulfonyloxy, sulfinyloxy, sulfamino, sulfonamino, sulfonamino, phosphoramidite and phosphoramidate.

15

In some embodiments, the optional substituents when R^{C1} is an optionally substituted C_{1-7} alkyl, or C_{1-4} alkyl, group may be selected from: C_{5-20} aryl, C_{3-20} heterocyclyl, halo, hydroxy, ether, carboxy, ester, acyloxy, amido, acylamido, amino, nitro, cyano, thiol and thioether.

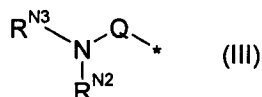
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In some of these embodiments, the optional substituents when R^{C1} is an optionally substituted C_{1-7} alkyl, or C_{1-4} alkyl, group may be selected from: amino, C_{5-20} aryl (e.g. C_6 aryl), cyano, carboxy and acylamido. In some instances, the C_6 aryl substituent may be phenyl or pyridyl.

25

In further embodiments, the optional substituents when R^{C1} is an optionally substituted C_{1-7} alkyl, or C_{1-4} alkyl, group may be selected from: C_{5-20} aryl (e.g. C_6 aryl), hydroxy, carboxy, ester, acylamido, amino, cyano and sulfone.

When the substituent on R^{C1} is amino, the R^{C1} group may be of formula III:



30

where Q represents a C_{1-7} or C_{1-4} alkylene group, and R^{N2} and R^{N3} are independently selected from hydrogen, an optionally substituted C_{1-7} alkyl group, an optionally substituted C_{3-20} heterocyclyl group, or an optionally substituted C_{5-20} aryl group, or may together form,

along with the nitrogen atom to which they are attached, an optionally substituted heterocyclic ring having from 4 to 8 ring atoms.

5 In some embodiments, R^{N2} and R^{N3} are independently selected from hydrogen and an optionally substituted C_{1-7} or C_{1-4} alkyl group. In these embodiments, the C_{1-7} or C_{1-4} alkyl group may be unsubstituted, and may be, for example, methyl or ethyl.

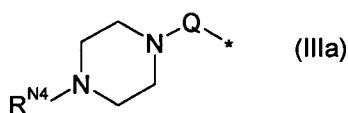
10 In some embodiments, where R^{N2} and R^{N3} together form, along with the nitrogen atom to which they are attached, an optionally substituted heterocyclic ring having from 4 to 8 ring atoms, the heterocyclic ring may have 5, 6 or 7 atoms, and in particular embodiments 6 ring atoms.

Single rings having one nitrogen atom include azetidine, azetidine, pyrrolidine (tetrahydropyrrole), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole), piperidine, dihydropyridine, tetrahydropyridine, and azepine; two
15 nitrogen atoms include imidazolidine, pyrazolidine (diazolidine), imidazoline, pyrazoline (dihydropyrazole), and piperazine; one nitrogen and one oxygen include tetrahydrooxazole, dihydrooxazole, tetrahydroisoxazole, dihydroisoxazole, morpholine, tetrahydrooxazine, dihydrooxazine, and oxazine; one nitrogen and one sulphur include thiazoline, thiazolidine,
20 and thiomorpholine.

Rings of particular interest are those containing one heteroatom in addition to the nitrogen, and in particular, oxygen, sulphur and nitrogen. Thus groups of particular interest include morpholino, thiomorpholino and piperaziny, with morpholino being of most interest. In some
25 embodiments, piperaziny is of interest.

As mentioned above, these heterocyclic groups may themselves be substituted; a class of substituent that may be present is a C_{1-7} , or C_{1-4} , alkyl group, e.g. methyl, ethyl. When R^{N2} and R^{N3} together form, along with the nitrogen atom to which they are attached, a
30 morpholino group, this may be unsubstituted or substituted with one or two methyl groups (i.e. methylmorpholino, dimethylmorpholino), or one or two ethyl groups (i.e. ethylmorpholino, diethylmorpholino).

When the ring is piperaziny, the R^{C1} group may be of formula IIIa:



where R^{N4} is an optionally substituted C_{1-7} or C_{1-4} alkyl group, and Q is as defined above. The optional substituents for R^{N4} may be selected from hydroxy, halo, cyano, and in some embodiments may be hydroxy.

5

Thus, in some embodiments, R^{N4} may be methyl, hydroxymethyl, ethyl and hydroxyethyl.

C_{1-7} alkyl groups of particular interest are those of formula III where R^{N2} and R^{N3} together form, along with the nitrogen atom to which they are attached, an optionally substituted morpholino group, where the optional substituents are C_{1-4} alkyl (e.g. methyl, ethyl). In these groups, it may be that Q is methylene or ethylene.

10

Another class of C_{1-7} alkyl groups of particular interest are pyridyl substituted methyl or ethyl. The pyridyl groups may themselves be unsubstituted.

15

Aryl

In some embodiments, R^{C1} is an optionally substituted C_{5-20} aryl group.

20

In some of these embodiments, R^{C1} is an optionally substituted C_{5-6} aryl group. The C_{5-6} aryl group may be a C_5 or C_6 aryl group.

25

The C_5 aryl group may be selected from furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, and oxatriazolyl. The C_5 aryl group may be selected from furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl and isothiazolyl. A C_5 aryl group of particular interest is oxazolyl.

30

The C_6 aryl group may be selected from phenyl, isoxazinyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl. In some embodiments it may be selected from phenyl and pyridinyl. In other embodiments, the C_6 aryl group may also be pyrimidinyl.

In some embodiments, the C_{5-6} aryl group may be selected from phenyl, pyrrolyl, oxazolyl and pyridyl. In some of these embodiments, the C_{5-6} aryl group may be selected from oxazolyl and pyridyl.

In some embodiments, R^{C1} is an optionally substituted C_{9-10} aryl group. The C_{9-10} aryl group may be a C_9 aryl group or a C_{10} aryl group.

5 The C_9 aryl groups may be derived from benzofuran, isobenzofuran, indole, isoindole, purine (e.g., adenine, guanine), benzothiophene and benzimidazole.

The C_{10} aryl groups may be derived from quinoline, isoquinoline, benzodiazine, pyridopyridine, quinoxaline and naphthalene.

10 In some embodiments, the C_{9-10} aryl group may be indolyl.

The optional substituents on the C_{5-20} aryl group (including C_{5-6} aryl and C_{9-10} aryl) may be selected from: hydroxy, C_{1-4} alkoxy, carboxy, C_{1-4} alkyl ester, cyano, nitro and halo. The optional substituents on the C_{5-20} aryl group (including C_{5-6} aryl and C_{9-10} aryl) may also be
15 selected from: C_{1-4} alkyl (e.g. methyl).

In some embodiments, these substituents may be hydroxy, cyano or carboxy, or the group may be unsubstituted.

20 C_{5-20} aryl groups of particular interest are oxazolyl and pyridyl, which may be unsubstituted. Other C_{5-20} aryl groups of particular interest are phenyl (optionally substituted by carboxy or methyl ester, pyrimidinyl (optionally substituted by methyl) and pyrrolyl (optionally substituted by cyano).

25 Heterocyclyl

In some embodiments, R^{C1} is an optionally substituted C_{3-20} heterocyclyl group.

In some of these embodiments, R^{C1} may be a C_{4-6} heterocyclic group. Thus, R^{C1} may be a C_4 , C_5 or C_6 heterocyclic group.

30 The C_4 heterocyclic groups may be derived from azetidine, oxetane, thietane, dioxetane and dithiethane.

The C_5 heterocyclic groups may be derived from pyrrolidine, oxolane, thiolane, imidazoline, oxazolidine, thiazolidine, dioxolane and dithiolane.

35

The C₆ heterocyclic groups may be derived from piperidine, tetrahydropyran, thiane, piperazine, oxazine, dithiane, dioxane and trioxane.

- 5 In some embodiments, R^{C1} may be selected from azetidiny and piperidiny (bound via a carbon atom). In some of these embodiments, R^{C1} may be piperidiny (bound via a carbon atom).

- 10 The optional substituents when R^{C1} is an optionally substituted C₃₋₂₀ heterocyclyl, or C₄₋₆ heterocyclyl, group may be selected from: C₁₋₂₀ alkyl (e.g. C₁₋₄ alkyl), C₅₋₂₀ aryl, halo, hydroxy, ether, oxo, imino, formyl, acyl, carboxy, ester, acyloxy, amido, acylamido, acylureido, carbamate, thioamido, tetrazolyl, amino, imino, amidine, carbazoyl, nitro, nitroso, azido, cyano, isocyano, cyanato, thiocyanato, isothiocyano, thiol, thioether, disulfide, sulfone, sulfine, sulfonyloxy, sulfinyloxy, sulfamino, sulfonamino, sulfonamino, 15 phosphoramidite and phosphoramidate.

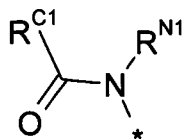
- In some embodiments, the optional substituents when R^{C1} is an optionally substituted C₃₋₂₀ heterocyclyl, or C₄₋₆ heterocyclyl, group may be selected from: C₁₋₂₀ alkyl (e.g. C₁₋₄ alkyl), C₅₋₂₀ aryl, halo, hydroxy, ether, carboxy, ester, acyloxy, amido, acylamido, amino, nitro, cyano, 20 thiol and thioether

In some of these embodiments, the optional substituents when R^{C1} is an optionally substituted C₃₋₂₀ heterocyclyl, or C₄₋₆ heterocyclyl, group may be C₁₋₄ alkyl (e.g. methyl).

- 25 C₃₋₂₀ heterocyclyl groups of particular interest are piperidiny (bound via a carbon atom) and in particular, N-methyl piperidiny.

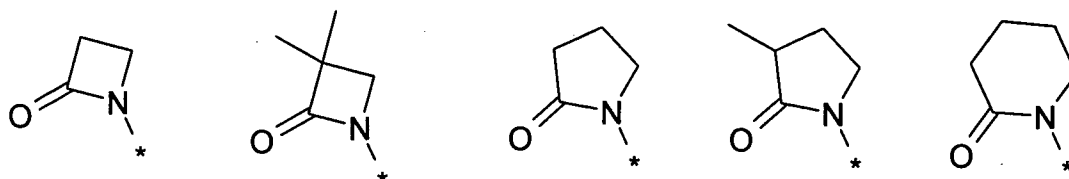
R^{N1} and R^{C1}

- 30 In some embodiments, R^{N1} and R^{C1} together form an optionally substituted C₂₋₄ alkylene group. In these embodiments, the group:

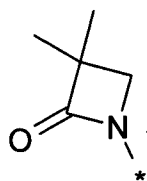


is a heterocyclic ring containing a nitrogen ring atom, and having from 4 to 6 ring atoms in total.

Possible groups include:



In some embodiments, the group is

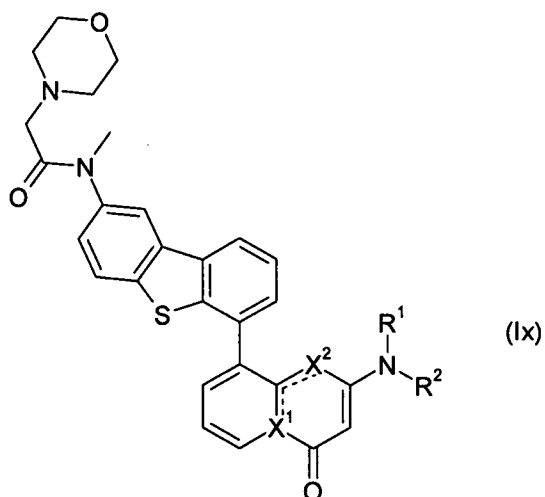


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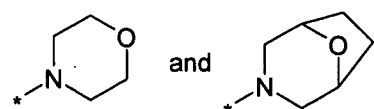
The C_{2-4} alkylene group may be unsubstituted. If the group is substituted, the substituents may be selected from: halo, hydroxy, nitro and cyano.

10 Compounds

In some embodiments, the compounds are of formula Ix:



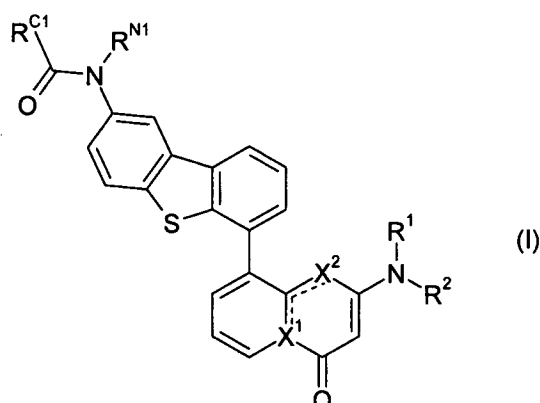
where X^1 and X^2 may be either (a) C and O, or (b) N and N, and NR^1R^2 is selected from:



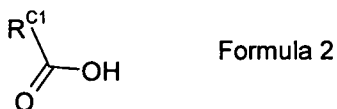
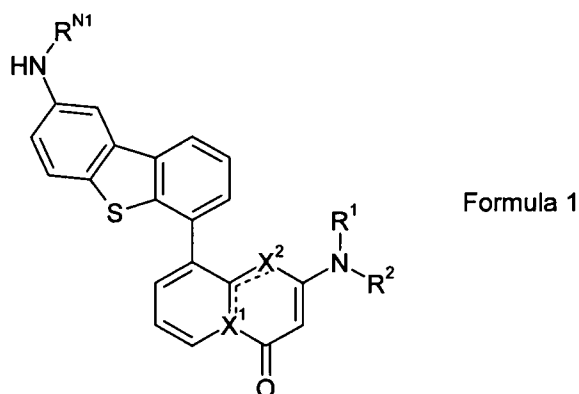
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General Synthesis Methods

Compounds of formula I:



can be synthesised by coupling compounds of formulae 1 and 2:



either by activating the compound of Formula 2 or with the assistance of an amide coupling reagent, e.g. HBTU, HATU, HOBt, or by activation of the acid of formula 2.

- 10 In some instances, the compound coupled to the compound of formula 1 may only form part of the compound of formula 2, and a further derivitisation may be required to achieve the desired compound.

- 15 Compounds of formula I where R^{N1} is not hydrogen can be derived from those where R^{N1} is hydrogen by treatment with a strong base, e.g. sodium hydride, followed by reaction with R^{N1} -X, where X is a halogen, e.g. I.

Examples of the synthesis of compounds of formula 1 are shown in the examples below.

Use of Compounds of the Invention

The present invention provides active compounds, specifically, active substituted dibenzothiophenyl, amino-chromen-4-ones, aminopyridopyrimidines or aminoquinolinones.

5 The term "active", as used herein, pertains to compounds which are capable of inhibiting DNA-PK activity, and specifically includes both compounds with intrinsic activity (drugs) as well as prodrugs of such compounds, which prodrugs may themselves exhibit little or no intrinsic activity.

10 One assay which may be used in order to assess the DNA-PK inhibition offered by a particular compound is described in the examples below.

The present invention further provides a method of inhibiting DNA-PK inhibition in a cell, comprising contacting said cell with an effective amount of an active compound, preferably in
15 the form of a pharmaceutically acceptable composition. Such a method may be practised *in vitro* or *in vivo*.

For example, a sample of cells (e.g. from a tumour) may be grown *in vitro* and an active compound brought into contact with said cells in conjunction with agents that have a known
20 curative effect, and the enhancement of the curative effect of the compound on those cells observed.

The present invention further provides active compounds which inhibit DNA-PK activity as well as methods of methods of inhibiting DNA-PK activity comprising contacting a cell with
25 an effective amount of an active compound, whether *in vitro* or *in vivo*.

Active compounds may also be used as cell culture additives to inhibit DNA-PK, for example, in order to sensitize cells to known chemotherapeutic agents or ionising radiation treatments
in vitro.

30 Active compounds may also be used as part of an *in vitro* assay, for example, in order to determine whether a candidate host is likely to benefit from treatment with the compound in question.

The invention further provides active compounds for use in a method of treatment of the human or animal body. Such a method may comprise administering to such a subject a therapeutically-effective amount of an active compound, preferably in the form of a pharmaceutical composition.

5

The term "treatment", as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g. in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e. prophylaxis) is also included.

10

The term "therapeutically-effective amount" as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio.

15

The term "adjunct" as used herein relates to the use of active compounds in conjunction with known therapeutic means. Such means include cytotoxic regimes of drugs and/or ionising radiation as used in the treatment of different cancer types. Examples of adjunct anti-cancer agents that could be combined with compounds from the invention include, but are not limited to, the following: alkylating agents: nitrogen mustards, mechlorethamine, cyclophosphamide, ifosfamide, melphalan, chlorambucil; Nitrosoureas: carmustine (BCNU), lomustine (CCNU), semustine (methyl-CCNU), ethylenimine/methylmelamine, thriethylenemelamine (TEM), triethylene thiophosphoramidate (thiotepa), hexamethylmelamine (HMM, altretamine); Alkyl sulfonates; busulfan; Triazines, dacarbazine (DTIC); Antimetabolites; folic acid analogs, methotrexate, trimetrexate, pyrimidine analogs, 5-fluorouracil, fluorodeoxyuridine, gemcitabine, cytosine arabinoside (AraC, cytarabine), 5-azacytidine, 2,2'-difluorodeoxycytidine; Purine analogs; 6-mercaptopurine, 6-thioguanine, azathioprine, 2'-deoxycoformycin (pentostatin, erythrohydroxynonyladenine (EHNA), fludarabine phosphate, 2-Chlorodeoxyadenosine (cladribine, 2-CdA); Topoisomerase I inhibitors; camptothecin, topotecan, irinotecan, rubitecan; Natural products; antimitotic drugs, paclitaxel, vinca alkaloids, vinblastine (VLB), vincristine, vinorelbine, TaxotereTM (docetaxel), estramustine, estramustine phosphate; epipodophylotoxins, etoposide, teniposide; Antibiotics; actinomycin D, daunomycin (rubidomycin), doxorubicin (adriamycin),

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mitoxantrone, idarubicin, bleomycins, plicamycin (mithramycin), mitomycin C, dactinomycin; Enzymes; L-asparaginase, RNase A; Biological response modifiers; interferon-alpha, IL-2, G-CSF, GM-CSF; Differentiation Agents; retinoic acid derivatives; Radiosensitizers; metronidazole, misonidazole, desmethylmisonidazole, pimonidazole, etanidazole, 5 nimorazole, RSU 1069, EO9, RB 6145, SR4233, nicotinamide, 5-bromodeoxyuridine, 5-iododeoxyuridine, bromodeoxycytidine; Platinum coordination complexes; cisplatin, carboplatin; Anthracenedione; mitoxantrone, AQ4N Substituted urea, hydroxyurea; Methylhydrazine derivatives, N-methylhydrazine (MIH), procarbazine; Adrenocortical suppressant, mitotane (*o.p'*-DDD), aminoglutethimide; Cytokines; interferon (α , β , γ), 10 interleukin; Hormones and antagonists; adrenocorticosteroids/antagonists, prednisone and equivalents, dexamethasone, aminoglutethimide; Progestins, hydroxyprogesterone caproate, medroxyprogesterone acetate, megestrol acetate; Estrogens, diethylstilbestrol, ethynyl estradiol/equivalents; Antiestrogen, tamoxifen; Androgens, testosterone propionate, fluoxymesterone/equivalents; Antiandrogens, flutamide, gonadotropin-releasing hormone 15 analogs, leuprolide; Nonsteroidal antiandrogens, flutamide; EGFR inhibitors, VEGF inhibitors; Proteasome inhibitors.

Cancer

The present invention provides active compounds which are anticancer agents or adjuncts 20 for treating cancer. One of ordinary skill in the art is readily able to determine whether or not a candidate compound treats a cancerous condition for any particular cell type, either alone or in combination.

Examples of cancers include, but are not limited to, lung cancer, small cell lung cancer, 25 gastrointestinal cancer, bowel cancer, colon cancer, breast carcinoma, ovarian carcinoma, prostate cancer, testicular cancer, liver cancer, kidney cancer, bladder cancer, pancreas cancer, brain cancer, sarcoma, osteosarcoma, Kaposi's sarcoma, melanoma and leukemias.

Any type of cell may be treated, including but not limited to, lung, gastrointestinal (including, 30 e.g., bowel, colon), breast (mammary), ovarian, prostate, liver (hepatic), kidney (renal), bladder, pancreas, brain, and skin.

The anti cancer treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or

chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:-

- (i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5 fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinese inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);
- (ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and idoxifene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuporelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase such as finasteride;
- (iii) anti-invasion agents (for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341) and N-(2-chloro-6-methylphenyl)-2-[6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino]thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase);
- (iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti erbB2 antibody trastuzumab [Herceptin[®]], the anti-EGFR antibody panitumumab, the anti erbB1 antibody cetuximab [Erbix[®], C225] and any growth factor or growth factor receptor antibodies disclosed by Stern et al. Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine

(erlotinib, OSI 774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib, inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived growth factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006)), inhibitors of cell signalling through MEK and/or AKT kinases, inhibitors of the hepatocyte growth factor family, c-kit inhibitors, abl kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti vascular endothelial cell growth factor antibody bevacizumab (AvastinT) and VEGF receptor tyrosine kinase inhibitors such as 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985) and SU11248 (sunitinib; WO 01/60814), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin avb3 function and angiostatin)];

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene directed enzyme pro drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex vivo and in vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte macrophage colony stimulating factor, approaches to decrease T cell anergy, approaches using transfected immune cells such as

cytokine transfected dendritic cells, approaches using cytokine transfected tumour cell lines and approaches using anti idiotypic antibodies

Administration

5 The active compound or pharmaceutical composition comprising the active compound may be administered to a subject by any convenient route of administration, whether systemically/ peripherally or at the site of desired action, including but not limited to, oral (e.g. by ingestion); topical (including e.g. transdermal, intranasal, ocular, buccal, and sublingual); pulmonary (e.g. by inhalation or insufflation therapy using, e.g. an aerosol, e.g. through mouth or nose); rectal; vaginal; parenteral, for example, by injection, including
10 subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot, for example, subcutaneously or intramuscularly.

15 The subject may be a eukaryote, an animal, a vertebrate animal, a mammal, a rodent (e.g. a guinea pig, a hamster, a rat, a mouse), murine (e.g. a mouse), canine (e.g. a dog), feline (e.g. a cat), equine (e.g. a horse), a primate, simian (e.g. a monkey or ape), a monkey (e.g. marmoset, baboon), an ape (e.g. gorilla, chimpanzee, orang-utan, gibbon), or a human.

20

Formulations

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation) comprising at least one active compound, as defined above, together with one or more pharmaceutically acceptable
25 carriers, adjuvants, excipients, diluents, fillers, buffers, stabilisers, preservatives, lubricants, or other materials well known to those skilled in the art and optionally other therapeutic or prophylactic agents.

Thus, the present invention further provides pharmaceutical compositions, as defined above,
30 and methods of making a pharmaceutical composition comprising admixing at least one active compound, as defined above, together with one or more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilisers, or other materials, as described herein.

The term "pharmaceutically acceptable" as used herein pertains to compounds, materials,
35 compositions, and/or dosage forms which are, within the scope of sound medical judgement,

suitable for use in contact with the tissues of a subject (e.g. human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

5

Suitable carriers, excipients, etc. can be found in standard pharmaceutical texts, for example, Remington's Pharmaceutical Sciences, 18th edition, Mack Publishing Company, Easton, Pa., 1990.

- 10 The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active compound with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active compound with liquid carriers or finely divided solid
- 15 carriers or both, and then if necessary shaping the product.

Formulations may be in the form of liquids, solutions, suspensions, emulsions, elixirs, syrups, tablets, lozenges, granules, powders, capsules, cachets, pills, ampoules, suppositories, pessaries, ointments, gels, pastes, creams, sprays, mists, foams, lotions, oils,

20 boluses, electuaries, or aerosols.

Formulations suitable for oral administration (e.g. by ingestion) may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or suspension in an aqueous or

25 non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion; as a bolus; as an electuary; or as a paste.

A tablet may be made by conventional means, e.g., compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing

30 in a suitable machine the active compound in a free-flowing form such as a powder or granules, optionally mixed with one or more binders (e.g. povidone, gelatin, acacia, sorbitol, tragacanth, hydroxypropylmethyl cellulose); fillers or diluents (e.g. lactose, microcrystalline cellulose, calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc, silica); disintegrants (e.g. sodium starch glycolate, cross-linked povidone, cross-linked sodium

35 carboxymethyl cellulose); surface-active or dispersing or wetting agents (e.g. sodium lauryl

sulfate); and preservatives (e.g. methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sorbic acid). Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active compound therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for topical administration (e.g. transdermal, intranasal, ocular, buccal, and sublingual) may be formulated as an ointment, cream, suspension, lotion, powder, solution, past, gel, spray, aerosol, or oil. Alternatively, a formulation may comprise a patch or a dressing such as a bandage or adhesive plaster impregnated with active compounds and optionally one or more excipients or diluents.

Formulations suitable for topical administration in the mouth include lozenges comprising the active compound in a flavoured basis, usually sucrose and acacia or tragacanth; pastilles comprising the active compound in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active compound in a suitable liquid carrier.

Formulations suitable for topical administration to the eye also include eye drops wherein the active compound is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active compound.

Formulations suitable for nasal administration, wherein the carrier is a solid, include a coarse powder having a particle size, for example, in the range of about 20 to about 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid for administration as, for example, nasal spray, nasal drops, or by aerosol administration by nebuliser, include aqueous or oily solutions of the active compound.

Formulations suitable for administration by inhalation include those presented as an aerosol spray from a pressurised pack, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichloro-tetrafluoroethane, carbon dioxide, or other suitable gases.

Formulations suitable for topical administration via the skin include ointments, creams, and emulsions. When formulated in an ointment, the active compound may optionally be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active compounds may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active compound through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogues.

When formulated as a topical emulsion, the oily phase may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Suitable emulgents and emulsion stabilisers include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulphate. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations may be very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as diisoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required.

Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active compound, such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration (e.g. by injection, including cutaneous, subcutaneous, intramuscular, intravenous and intradermal), include aqueous and non-aqueous isotonic, pyrogen-free, sterile injection solutions which may contain anti-oxidants, buffers, preservatives, stabilisers, bacteriostats, and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. Examples of suitable isotonic vehicles for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the active compound in the solution is from about 1 ng/ml to about 10 µg/ml, for example from about 10 ng/ml to about 1 µg/ml. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets. Formulations may be in the form of liposomes or other microparticulate systems which are designed to target the active compound to blood components or one or more organs.

Dosage

It will be appreciated that appropriate dosages of the active compounds, and compositions comprising the active compounds, can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects of the treatments of the present invention. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the

particular compound, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, and the age, sex, weight, condition, general health, and prior medical history of the patient. The amount of compound and route of administration will ultimately be at the discretion of the physician, although generally the dosage will be to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

Administration *in vivo* can be effected in one dose, continuously or intermittently (e.g. in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician.

In general, a suitable dose of the active compound is in the range of about 100 µg to about 250 mg per kilogram body weight of the subject per day. Where the active compound is a salt, an ester, prodrug, or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

Examples

Unless stated otherwise, starting materials were commercially available. All solvents and commercial reagents were of laboratory grade and were used as received.

The invention will now be illustrated in the following Examples in which, generally:

- (i) operations were carried out at room temperature (r.t.), *i.e.* in the range 17 to 25°C and under an atmosphere of an inert gas such as N₂ or Ar unless otherwise stated;
- (ii) in general, the course of reactions was followed by thin layer chromatography (TLC) and/or analytical high performance liquid chromatography (HPLC) which was usually coupled to a mass spectrometer (LCMS). The reaction times that are given are not necessarily the minimum attainable;
- (iii) when necessary, organic solutions were dried over anhydrous MgSO₄ or Na₂SO₄, work-up procedures were carried out using traditional phase separating techniques or by

using SCX as described in (xiii), evaporations were carried out either by rotary evaporation *in vacuo* or in a Genevac HT-4 / EZ-2;

(iv) yields, where present, are not necessarily the maximum attainable, and when necessary, reactions were repeated if a larger amount of the reaction product was required;

5 (v) in general, the structures of the end-products of the formula (I) were confirmed by nuclear magnetic resonance (NMR) and/or mass spectral techniques; electrospray mass spectral data were obtained using a Waters ZMD or Waters ZQ LC/mass spectrometer acquiring both positive and negative ion data, and generally, only ions relating to the parent structure are reported; proton NMR chemical shift values were measured on the delta scale using
10 either a Bruker DPX300 spectrometer operating at a field strength of 300 MHz, a Bruker DRX400 operating at 400 MHz, a Bruker DRX500 operating at 500 MHz or a Bruker AV700 operating at 700 MHz. Unless otherwise stated, NMR spectra were obtained at 400 MHz in *d*⁶-dimethylsulfoxide. The following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; qn, quintet;

15 (vi) Unless stated otherwise compounds containing an asymmetric carbon and/or sulphur atom were not resolved;

(vii) Intermediates were not necessarily fully purified but their structures and purity were assessed by TLC, analytical HPLC, infra-red (IR) and/or NMR analysis and/or mass spectrometry;

20 (viii) unless otherwise stated, flash column chromatography (FCC) was performed on Merck Kieselgel silica (Art. 9385) or on Silicycle cartridges (40-63 µm silica, 12 to 330 g mass) or on GraceResolv(TM) high res flash cartridges (35-45 µm silica, 4-120g mass) either manually or automated using an Isco Combi Flash Companion system;

(ix) Preparative reverse phase HPLC (RP HPLC) was performed on C18 reversed-phase
25 silica, for example on a Waters 'Xterra' or 'XBridge' preparative reversed-phase column (5µm silica, 19 mm diameter, 100 mm length) or on a Phenomenex "Gemini" or 'AXIA' preparative reversed-phase column (5µm silica, 110A, 21.1 mm diameter, 100 mm length) using decreasingly polar mixtures as eluent, for example [containing 1-5% formic acid or 1-5% aqueous ammonium hydroxide (d=0.88)] as solvent A and acetonitrile as solvent B; a
30 typical procedure would be as follows: a solvent gradient over 9.5 minutes, at 25 mL per minute, from a 85:15 (or alternative ratio as appropriate) mixture of solvents A and B respectively to a 5:95 mixture of solvents A and B;

(x) the following analytical HPLC methods were used; in general, reverse-phase silica was used with a flow rate of about 1 mL / minute and detection was by Electrospray Mass
35 Spectrometry and by UV absorbance at a wavelength of 254 nm. Analytical HPLC was

performed on C18 reverse-phase silica, on a Phenomenex "Gemini" preparative reversed-phase column (5µm silica, 110 Å, 2 mm diameter, 50 mm length) using decreasingly polar mixtures as eluent, for example decreasingly polar mixtures of water (containing 0.1% formic acid or 0.1% ammonia) as solvent A and acetonitrile as solvent B. A typical analytical HPLC method would be as follows: a solvent gradient over 4 minutes, at approximately 1 mL per minute, from a 95:5 mixture of solvents A and B respectively to a 5:95 mixture of solvents A and B;

(xi) Where certain compounds were obtained as an acid-addition salt, for example a mono-hydrochloride salt or a di-hydrochloride salt, the stoichiometry of the salt was based on the number and nature of the basic groups in the compound, the exact stoichiometry of the salt was generally not determined, for example by means of elemental analysis data;

(xii) Where reactions refer to the use of a microwave, one of the following microwave reactors were used: Biotage Initiator, Personal Chemistry Emrys Optimizer, Personal Chemistry Smithcreator or CEM Explorer;

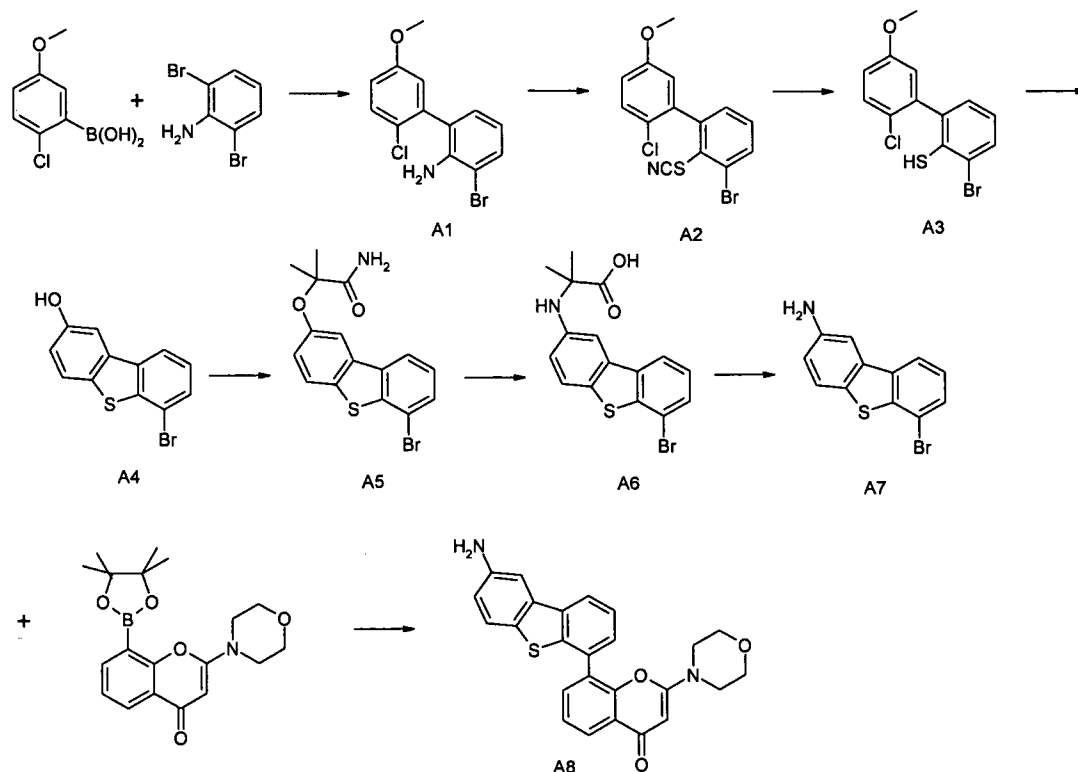
(xiii) Compounds were purified by strong cation exchange (SCX) chromatography using Isolute SPE flash SCX-2 column (International Sorbent Technology Limited, Mid Glamorgan, UK);

(xiv) In addition to the ones mentioned above, the following abbreviations have been used:

DMF	<i>N,N</i> -dimethylformamide	DMA	<i>N,N</i> -dimethylacetamide
DCM	dichloromethane	THF	tetrahydrofuran
conc.	concentrated	<i>m/z</i>	mass to charge ratio
TBAF	tetra <i>n</i> -butylammonium fluoride	NMP	1-methylpyrrolidin-2-one
EtOAc	ethyl acetate	DIPEA	<i>N,N</i> -diisopropylethylamine
DME	1,2-dimethoxyethane	MeOH	methanol
MeCN	acetonitrile	TBAB	tetra <i>n</i> -butylammonium bromide
h	hour(s)	EtOH	ethanol

Synthesis of Key Intermediates

A: 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one

Method 1

5 a) 3-bromo-2'-chloro-5'-methoxybiphenyl-2-amine (A1)

2-chloro-5-methoxyphenylboronic acid (1.25 g, 6.71 mmol), 2,6-dibromoaniline (1.851 g, 7.38 mmol), sodium carbonate (6.71 mL, 13.41 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.465 g, 0.40 mmol) were dissolved in dioxane (10 mL), degassed and sealed into a microwave tube. The reaction was heated to 150°C for 1

10 hour in the microwave reactor and cooled to room temperature.

The reaction mixture was poured into saturated aqueous NH_4Cl solution (100 mL), extracted with EtOAc (100 mL), and the organic layer was washed with water (50 mL) and saturated brine (50 mL). The organic layer was dried over MgSO_4 , filtered and evaporated to afford an orange oil. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford 3-bromo-2'-chloro-5'-methoxybiphenyl-2-amine (0.993 g, 47 %) as a white solid; ^1H NMR (400 MHz, CDCl_3) δ 3.73 (3H, s), 3.95 (2H, s), 6.61 (1H, t), 6.73 - 6.78 (1H, m), 6.83 (1H, d), 6.92 - 6.94 (1H, m), 7.31 - 7.34 (1H, m), 7.38 - 7.40 (1H, m).

15

b) 3-bromo-2'-chloro-5'-methoxy-2-thiocyanatobiphenyl (A2)

Concentrated HCl (20.07 mL, 660.61 mmol) was added dropwise at 0°C to a stirred suspension of 3-bromo-2'-chloro-5'-methoxybiphenyl-2-amine (A1, 2.95 g, 9.44 mmol) in methanol (60 mL). The reaction was stirred for 10 minutes. A solution of sodium nitrite (0.651 g, 9.44 mmol) in water (6 mL) was then added dropwise at 0°C over 10 minutes. The reaction was then stirred at 0°C for 15 minutes. The resulting cold orange solution was then added dropwise to a solution of potassium thiocyanate (2.93 g, 30.20 mmol) and iron(III)chloride (1.072 g, 6.61 mmol) in water (50 mL) at 0°C over 5 minutes. The dark solution was then stirred at room temperature for 4 hours under nitrogen. The reaction was then neutralised with 2 N aqueous sodium hydroxide solution (~ 150 mL) and extracted with ethyl acetate (4 x 150 mL). The combined organic extracts washed with water (200 mL) and saturated brine solution (100 mL). The organics were then dried over MgSO₄, filtered and evaporated to give the crude product as an oil. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% DCM in isohexane. Pure fractions were evaporated to dryness to afford 3-bromo-2'-chloro-5'-methoxy-2-thiocyanatobiphenyl (1.85 g, 55 %) as a colourless oil; ¹H NMR (400 MHz, CDCl₃) δ 3.76 (3H, s), 6.76 (1H, d), 6.86 - 6.89 (1H, m), 7.25 - 7.27 (1H, m), 7.32 (1H, t), 7.36 (1H, d), 7.73 - 7.75 (1H, m).

c) 3-bromo-2'-chloro-5'-methoxybiphenyl-2-thiol (A3)

A solution of lithium aluminium hydride (6.60 mL, 1M solution in THF, 6.60 mmol) was added dropwise over 5 minutes to a stirred solution of 3-bromo-2'-chloro-5'-methoxy-2-thiocyanatobiphenyl (A2, 2.11 g, 5.95 mmol) in THF (20 mL) at 0°C, under nitrogen. The resulting solution was stirred at room temperature for 3 hours. The reaction was then poured onto ice (150 g) - with caution! The mixture was stirred for 15 minutes and acidified to pH=2 with 2N HCl. The layers were separated and the aqueous phase extracted with ethyl acetate (3 x 75 mL). The combined organic extracts were then washed with saturated brine solution, dried over MgSO₄, filtered and evaporated to afford 3-bromo-2'-chloro-5'-methoxybiphenyl-2-thiol (1.907 g, 97 %) as a salmon pink oil; ¹H NMR (400 MHz, CDCl₃) δ 3.73 (3H, d), 3.85 (1H, s), 6.71 (1H, d), 6.82 - 6.85 (1H, m), 6.96 (1H, d), 7.02 - 7.04 (1H, m), 7.27 - 7.33 (1H, m), 7.49 - 7.51 (1H, m).

d) 6-bromodibenzo[b,d]thiophen-2-ol (A4)

Pyridine hydrochloride (9.33 g, 80.69 mmol) was added in one portion to 3-bromo-2'-chloro-5'-methoxybiphenyl-2-thiol (A3, 1.9 g, 5.76 mmol) and heated at 150°C under nitrogen. The resulting mixture was stirred at 150°C for 4 hours. The reaction was then cooled to 90°C and

poured into water (100 mL). The layers were separated and the aqueous phase extracted with DCM (3 x 100 mL). The combined organic extracts were washed with water (100 mL) and saturated brine solution (50 mL), dried over MgSO₄, filtered and evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 50 to 100% DCM in isohexane. Pure fractions were evaporated to dryness to afford 6-bromodibenzo[b,d]thiophen-2-ol (0.728 g, 45 %) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 4.82 (1H, s), 6.96 - 6.98 (1H, m), 7.25 (1H, t), 7.47 (1H, d), 7.52 - 7.54 (1H, m), 7.65 (1H, d), 7.92 - 7.94 (1H, m); *m/z* 278 (MH⁻).

e) 2-(6-bromodibenzo[b,d]thiophen-2-yloxy)-2-methylpropanamide (A5)

Sodium hydride (208 mg, 5.19 mmol) was added in one portion to a solution of 6-bromodibenzo[b,d]thiophen-2-ol (A4, 725 mg, 2.60 mmol) in dioxane (15 mL) at room temperature. The resulting mixture was heated at 30°C for 2 hours. 2-bromo-2-methylpropanamide (474 mg, 2.86 mmol) was added and the reaction mixture heated at 100°C for 18 hours. Additional NaH (60 mg) was added along with bromo-2-methylpropanamide (100 mg) after 3 hours as a significant amount of the benzothiophenol remained. The reaction was cooled to room temperature, filtered and the reaction mixture was diluted with EtOAc (50 mL). The organic phase was washed with 2N NaOH (20 mL), water (50 mL) and saturated brine solution (50 mL). The organic layer was dried over MgSO₄, filtered and evaporated to give crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-(6-bromodibenzo[b,d]thiophen-2-yloxy)-2-methylpropanamide (402 mg, 43 %) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.53 (6H, s), 5.44 (1H, s), 6.67 (1H, s), 7.07 - 7.10 (1H, m), 7.27 (1H, t), 7.54 - 7.56 (1H, m), 7.60 (1H, d), 7.69 - 7.71 (1H, m), 7.95 - 7.98 (1H, m).

f) N-(6-bromodibenzo[b,d]thiophen-2-yl)-2-hydroxy-2-methylpropanamide (A6)

2-(6-bromodibenzo[b,d]thiophen-2-yloxy)-2-methylpropanamide (A5, 400 mg, 1.10 mmol) was dissolved in a mixture of DMF (8 mL) and DMPU (0.800 mL). The resulting solution heated at 110°C for 4 hours. The reaction was then cooled to room temperature and poured into water (50 mL). The aqueous layer was then extracted with ethyl acetate (4 x 25 mL). The organic extracts were washed with water (100 mL) and saturated brine (50 mL). The organics were dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was then purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford N-(6-bromodibenzo[b,d]thiophen-

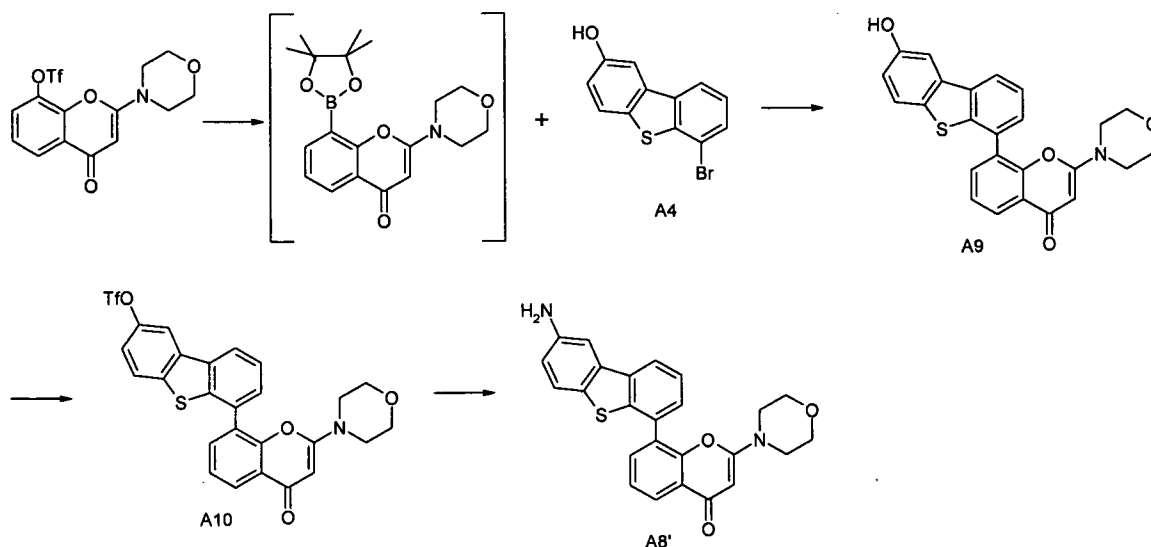
2-yl)-2-hydroxy-2-methylpropanamide (221 mg, 55 %) as a tan solid; ¹H NMR (400 MHz, CDCl₃) δ 1.52 (6H, m), 2.11 (1H, s), 7.27 (1H, t), 7.42 - 7.44 (1H, m), 7.53 - 7.55 (1H, m), 7.74 (1H, d), 8.03 - 8.05 (1H, m), 8.58 (1H, d), 8.80 (1H, s).

5 *g) 6-bromodibenzo[b,d]thiophen-2-amine (A7)*

N-(6-bromodibenzo[b,d]thiophen-2-yl)-2-hydroxy-2-methylpropanamide (A6, 221 mg, 0.61 mmol) was suspended in ethanol (5 mL) and 6N hydrochloric acid (2.5 mL). The reaction was then heated at reflux for 36 hours. The reaction was then cooled and diluted with water (20 mL) and neutralised with 2N aqueous NaOH solution. The aqueous phase was then
10 extracted with DCM (3 x 10 mL). The combined organic extracts were then purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford 6-bromodibenzo[b,d]thiophen-2-amine (145 mg, 86 %) as a cream solid; ¹H NMR (400 MHz, CDCl₃) δ 3.76 (2H, s), 6.82 - 6.85 (1H, m), 7.20 - 7.25 (1H, m), 7.32 (1H, d), 7.49 (1H, d),
15 7.55 (1H, d), 7.91 (1H, d).

h) 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8)

6-bromodibenzo[b,d]thiophen-2-amine (A7, 145 mg, 0.52 mmol), 2-morpholino-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-chromen-4-one (223 mg, 0.63 mmol) sodium
20 carbonate (0.782 mL of a 2M aqueous solution, 1.56 mmol) and Pd(Ph₃P)₄ (30.1 mg, 0.03 mmol) were suspended in dioxane (6 mL) and sealed into a microwave tube. The reaction was heated to 150°C for 1 hour in the microwave reactor and cooled to room temperature. The reaction was then quenched with saturated aqueous ammonium chloride solution (6 mL). The crude product was purified by ion exchange chromatography, using an SCX
25 column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (138 mg, 62 %) as a brown solid; ¹H NMR (400 MHz, CDCl₃) δ 3.01 (4H, t), 3.43 (4H, t), 3.76 (2H, d), 5.42 (1H, s), 6.80 - 6.83 (1H, m), 7.36 - 7.38 (1H, m), 7.37 - 7.41 (2H, m), 7.42 - 7.45 (1H, m), 7.49 (1H, d), 7.67 - 7.70 (1H, m), 8.00 - 8.03
30 (1H, m), 8.19 - 8.21 (1H, m); *m/z* 429.08 (MH⁺).

Method 2*a) 8-(8-hydroxydibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A9)*

- 5 1,1'-Bis(diphenylphosphino)ferrocenedichloropalladium(II) (0.47 g, 0.65 mmol) was added to a degassed solution of bis(pinacolato)diboron (6.89 g, 27.14 mmol), potassium acetate (7.61 g, 77.54 mmol) and 2-morpholino-4-oxo-4H-chromen-8-yl trifluoromethanesulfonate (10.00 g, 26.36 mmol) in anhydrous dioxane (80 ml) at 25°C. The resulting mixture was stirred under nitrogen at 110°C for 24 hours. 6-Bromodibenzo[b,d]thiophen-2-ol (A4, 5.77 g, 20.67 mmol), tetrakis(triphenylphosphine)palladium(0) (0.597 g, 0.52 mmol) and 2M aqueous Na₂CO₃ solution (52 ml, 104 mmol) were then added to cooled the reaction mixture and the resulting mixture stirred under nitrogen at 110 °C for a further 4 hours. The cooled reaction mixture was poured into water (500 ml) and acidified with 2N aqueous HCl solution. The formed precipitate was collected by vacuum filtration. The collected precipitate was taken up in saturated aqueous NH₄Cl solution (300 mL) and 9:1 DCM:MeOH (300 mL). The organic layer was removed and concentrated under reduced pressure, whereupon a solid dropped out of solution. This precipitate was slurried in methanol, collected by vacuum filtration, washing with MeOH (20 mL), and dried under vacuum to afford 8-(8-hydroxydibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (7.23 g, 81 %) as a brown solid, which was used without further purification; ¹H NMR (399.9 MHz, DMSO-d₆) δ 3.13 (4H, t), 3.44 (4H, t), 5.58 (1H, s), 7.03 - 7.05 (1H, m), 7.56 (1H, t), 7.60 - 7.63 (2H, m), 7.73 (1H, d), 7.76 (1H, d), 7.87 - 7.89 (1H, m), 8.06 - 8.08 (1H, m), 8.29 - 8.33 (1H, m), 9.68 (1H, s); m/z: 430.13 MH⁺.

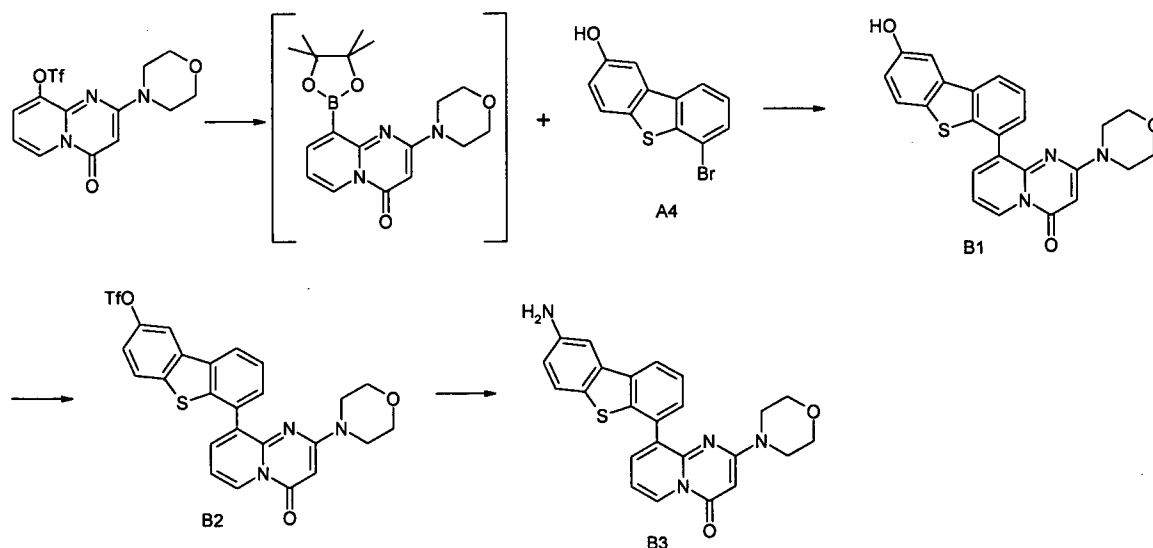
b) 6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl trifluoromethanesulfonate (A10)

1,1,1-Trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (6.99 g, 19.56 mmol) was added to 8-(8-hydroxydibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A9, 7.00 g, 16.30 mmol) and potassium carbonate (2.25 g, 16.30 mmol) in DMF (163 ml). The resulting solution was stirred under nitrogen at ambient temperature for 3 hours. The reaction was incomplete so the temperature was increased to 60°C and the reaction mixture was stirred for a further 2 hours. A fine precipitate was formed in the reaction mixture which was collected by vacuum filtration, washing with MeOH (50 mL), and dried under vacuum to afford 6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl trifluoromethanesulfonate (7.96 g, 87 %) as a beige solid, which was used without further purification; ¹H NMR (399.9 MHz, DMSO-d₆) δ 3.12 (4H, t), 3.43 (4H, t), 5.58 (1H, s), 7.58 (1H, t), 7.65 - 7.68 (1H, m), 7.72 - 7.78 (2H, m), 7.90 - 7.92 (1H, m), 8.08 - 8.11 (1H, m), 8.23 (1H, d), 8.63 - 8.66 (1H, m), 8.70 (1H, d); m/z: 562.06 MH⁺.

c) 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8')

Palladium(II) acetate (0.070 g, 0.31 mmol) was added to a stirred degassed solution of 6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl trifluoromethanesulfonate (A10, 7.00 g, 12.47 mmol), cesium carbonate (5.69 g, 17.45 mmol), benzophenone imine (2.51 ml, 14.96 mmol) and (rac)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.29 g, 0.47 mmol) in anhydrous dioxane (81 ml) at ambient temperature. The resulting solution was stirred under nitrogen at 100°C for 4 hours. The cooled reaction mixture was diluted with ethyl acetate (500 mL) and washed with water (500 mL). The aqueous was further extracted with EtOAc (2 x 200 mL) and the combined organics concentrated under reduced pressure. The residue was dissolved in THF (62 mL) and treated with 2M aqueous HCl solution (63 mL, 126 mmol). The resulting solution was stirred at ambient temperature for 15 minutes. The reaction mixture was then poured onto saturated aqueous NaHCO₃ solution (500 mL) and extracted with DCM (3 x 300 mL). The combined organics were dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (3.02 g, 57 %) as a pale yellow solid; ¹H NMR (399.9 MHz, DMSO-d₆) δ 3.13 (4H, t), 3.44 (4H, t), 5.27 (2H, s), 5.56 (1H, s), 6.85 - 6.88 (1H, m), 7.47 (1H, d), 7.53 - 7.62 (4H, m), 7.85 - 7.88 (1H, m), 8.05 - 8.07 (1H, m), 8.16 - 8.19 (1H, m); m/z: 429.15 MH⁺.

B: 9-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one



a) 9-(8-hydroxydibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (B1)

- 5 1,1'-Bis(diphenylphosphino)ferrocenedichloropalladium(II) (49 mg, 0.07 mmol) was added to a degassed solution of bis(pinacolato)diboron (362 mg, 1.43 mmol), potassium acetate (400 mg, 4.07 mmol) and 6-bromodibenzo[b,d]thiophen-2-ol (A4, 379 mg, 1.36 mmol) in dioxane (10 ml) at 25°C. The resulting mixture was stirred under nitrogen at 110°C for 24 hours. 2-Morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl trifluoromethanesulfonate (541 mg, 1.43
- 10 mmol), tetrakis(triphenylphosphine)palladium(0) (78 mg, 0.07 mmol) and 2M aqueous Na₂CO₃ solution (2.72 ml, 5.43 mmol) were then added to the cooled reaction mixture and the resulting mixture was stirred under nitrogen at 110°C for a further 3 hours. The cooled reaction mixture was poured into saturated aqueous NH₄Cl solution (50 mL) and extracted with EtOAc (3 x 25 mL). The combined organics were washed with saturated brine (50 mL),
- 15 dried over MgSO₄, filtered and evaporated to afford a brown oil. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness and the precipitate that formed slurried in DCM and collected by vacuum filtration to afford 9-(8-hydroxydibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (381 mg, 65 %) as a white solid. The filtrate also contained
- 20 desired product and was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford 9-(8-hydroxydibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (120 mg, 21 %, 89% pure) as a brown solid. Total yield of 9-(8-hydroxydibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (501 mg,
- 25 86 %); ¹H NMR (399.9 MHz, DMSO-d₆) δ 3.33 - 3.36 (4H, m), 3.46 - 3.48 (4H, m), 5.67 (1H,

s), 7.00 - 7.03 (1H, m), 7.22 (1H, t), 7.58 (1H, t), 7.60 - 7.62 (1H, m), 7.69 (1H, d), 7.73 (1H, d), 8.04 - 8.06 (1H, m), 8.25 - 8.28 (1H, m), 8.91 - 8.93 (1H, m), 9.63 (1H, s); m/z: 430.07 MH⁺.

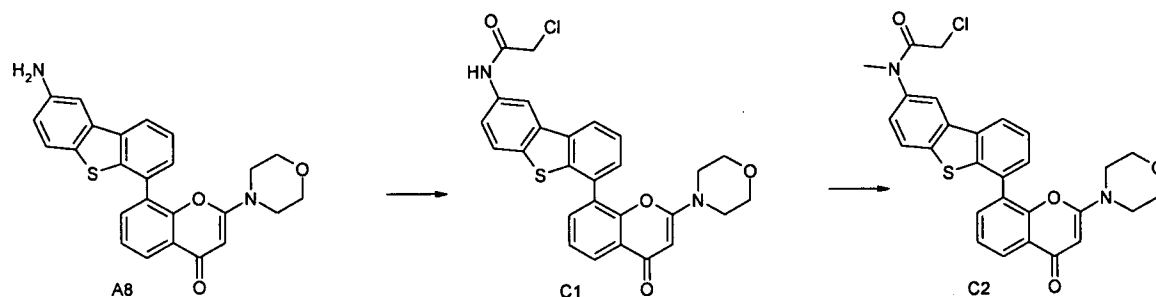
5 *b) 6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl trifluoromethanesulfonate (B2)*

1,1,1-Trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (541 mg, 1.51 mmol) was added to 9-(8-hydroxydibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (B1, 500 mg, 1.16 mmol) and potassium carbonate (161 mg, 1.16 mmol) in DMF (18 ml). The resulting solution was stirred under nitrogen at ambient temperature for 2 hours. A fine precipitate was formed in the reaction mixture which was collected by vacuum filtration, washing with MeOH (10 mL), and dried under vacuum to afford 6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl trifluoromethanesulfonate (579 mg, 89 %) as a beige solid, which was used without further purification; ¹H NMR (400.13 MHz, DMSO-d₆) δ 3.44 (4H, t), 5.67 (1H, s), 7.23 (1H, t), 7.61 - 7.64 (1H, m), 7.69 (1H, t), 7.72 - 7.74 (1H, m), 8.05 - 8.07 (1H, m), 8.19 (1H, d), 8.58 - 8.61 (1H, m), 8.65 (1H, d), 8.92 - 8.94 (1H, m), one 4H m obscured by solvent signal; m/z: 562.04 MH⁺.

20 *c) 9-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (B3)*
Palladium(II) acetate (0.096 g, 0.43 mmol) was added to a stirred, degassed solution of 6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl trifluoromethanesulfonate (B2, 4.82g, 8.58 mmol), cesium carbonate (3.92 g, 12.02 mmol), benzophenone imine (1.728 ml, 10.30 mmol) and (rac)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.401 g, 0.64 mmol) in anhydrous dioxane (84 ml) at ambient temperature. The resulting solution was stirred under nitrogen at 100°C for 4 hours. The cooled reaction mixture was poured into saturated aqueous NH₄Cl solution (500 mL) and extracted with EtOAc (3 x 250 mL). The combined organics were washed with water (500 mL), saturated brine (500 mL) and evaporated under reduced pressure to afford a yellow foam. The residue was dissolved in THF (86 mL) and treated with 2M aqueous HCl solution (86 mL, 172 mmol). The resulting solution was stirred at ambient temperature for 15 minutes. The reaction mixture was then poured onto saturated aqueous NaHCO₃ solution (250 mL) and extracted with DCM (3 x 200 mL). The combined organics were concentrated under reduced pressure to afford a yellow solid. This was slurried in methanol and the precipitate was collected by filtration, washing with MeOH (20 mL), and dried under vacuum to afford 9-(8-

aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (2.41 g, 66 %) as a yellow solid, which was used without further purification. The filtrate also contained desired product and was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 1:1 DCM/7M NH₃/MeOH and evaporated to dryness to afford a second batch of 9-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (0.68 g, 18 %) as a yellow solid, which was used without further purification. Total yield of 9-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (3.09 g, 84 %); ¹H NMR (399.9 MHz, DMSO-d₆) δ 3.48 (4H, t), 5.27 (2H, s), 5.67 (1H, s), 6.83 - 6.86 (1H, m), 7.22 (1H, t), 7.45 (1H, d), 7.53 - 7.58 (3H, m), 8.04 - 8.06 (1H, m), 8.12 - 8.14 (1H, m), 8.90 - 8.92 (1H, m), one (4H, m) obscured by solvent peak; m/z: 429.14 MH⁺.

C: 2-chloro-N-methyl-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide



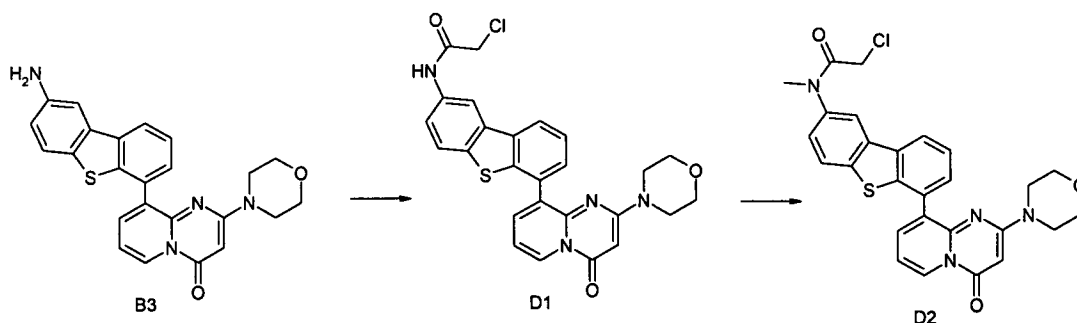
(a) 2-chloro-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (C1)

2-chloroacetyl chloride (0.149 mL, 1.87 mmol) dissolved in DMA (5ml) was added dropwise to a stirred solution of triethylamine (0.520 mL, 3.73 mmol), and 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8, 727mg, 1.70 mmol) in DMA (10ml) at room temperature under nitrogen atmosphere. The reaction was stirred at room temperature for 4 hours under nitrogen atmosphere. The reaction mixture was poured slowly into water (100ml) where a solid crashed out. This solid was filtered off under vacuum washed with water and left to dry overnight under high vacuum. This solid was then slurried in diethyl ether and then filtered under vacuum to give 2-chloro-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (808 mg, 94 %) a pale green solid; ¹H NMR (400 MHz, CDCl₃) δ 3.01 (4H, t), 3.44 (4H, t), 4.21 (2H, s), 5.43 (1H, s), 7.40 - 7.44 (3H, m), 7.52 (1H, t), 7.69 (2H, dd), 8.16 (1H, dd), 8.22 (1H, dd), 8.40 (1H, s), 8.56 - 8.57 (1H, m); m/z 505.03 (M⁺).

(b) 2-chloro-N-methyl-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (C2)

Sodium hydroxide (532 mg, 13.3 mmol) dissolved in water (1ml) was added to 2-chloro-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (C1, 800 mg, 1.58 mmol), N-benzyl-N,N-diethylethanaminium chloride (137 mg, 0.60 mmol) and dimethyl sulfate (220 mg, 1.74 mmol) in DCM (20ml). The starting material appeared to be quite insoluble so more DCM was added (30ml). The reaction was stirred at room temperature for 1 hour. The reaction mixture was diluted with DCM (50ml), and washed sequentially with water (50 mL), and saturated brine (50 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 2% MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-chloro-N-methyl-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (338 mg, 41.1 %) as a cream solid; ¹H NMR (400 MHz, CDCl₃) δ 3.05 (4H, t), 3.41 - 3.48 (7H, m), 3.84 (2H, s), 5.44 (1H, s), 7.29 (1H, dd), 7.41 - 7.45 (1H, m), 7.49 - 7.52 (1H, m), 7.54 - 7.58 (1H, m), 7.70 (1H, dd), 7.82 (1H, d), 8.02 (1H, d), 8.13 (1H, dd), 8.23 (1H, dd); *m/z* 519.07(M⁺).

D: 2-chloro-N-methyl-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide



(a) 2-chloro-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (D1)

2-Chloroacetyl chloride (0.041 mL, 0.51 mmol) dissolved in DMA (2ml) was added to a stirred solution of triethylamine (0.143 mL, 1.03 mmol), and 9-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (B3, 200 mg, 0.47 mmol) in DMA (5ml) at room temperature under nitrogen atmosphere. The reaction was stirred at room temperature for 4 hours under nitrogen atmosphere. The reaction mixture was poured slowly into water (100ml) where a solid crashed out. This solid was filtered off under vacuum washed with water and left to dry overnight under high vacuum. This solid was then slurried in diethyl ether and then filtered under vacuum to give 2-chloro-N-(6-(2-morpholino-4-oxo-4H-

pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (221 mg, 94 %) a pale green solid; ^1H NMR(400 MHz, CDCl_3) δ 3.35 (4H, t), 3.56 (4H, t), 4.27 (2H, s), 5.63 (1H, s), 7.02 (1H, t), 7.48 (1H, d), 7.54 - 7.58 (2H, m), 7.75 (1H, d), 7.86 (1H, dd), 8.22 (1H, dd), 8.43 (1H, s), 8.58 (1H, d), 9.04 (1H, d); m/z 505.00 (M^+).

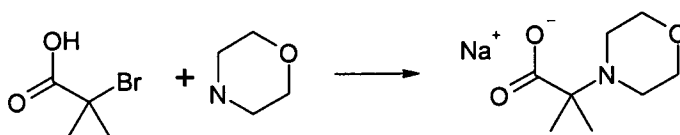
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(b) 2-chloro-N-methyl-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (D2)

Sodium hydroxide (50% in water w/v) (532 mg, 13.3 mmol) was added to 2-chloro-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (D1, 210 mg, 0.42 mmol), N-benzyl-N,N-diethylethanaminium chloride (36.0 mg, 0.16 mmol) and dimethyl sulfate (57.7 mg, 0.46 mmol) in DCM (20ml). The starting material appeared to be quite insoluble so more DCM was added (30ml). The reaction mixture was stirred at room temperature for 90 minutes. The reaction mixture was diluted with DCM (10ml), and washed sequentially with water (50 mL), and saturated brine (50 mL). The organic layer was dried over Na_2SO_4 , filtered and evaporated to afford crude product. The crude product was purified by crystallisation from $\text{Et}_2\text{O}/\text{MeOH}$ to afford 2-chloro-N-methyl-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (157 mg, 72.7 %) as a cream solid. ^1H NMR(400 MHz, CDCl_3) δ 3.37 (4H, t), 3.43 (3H, s), 3.58 (4H, t), 3.91 (2H, s), 5.64 (1H, s), 7.03 (1H, t), 7.34 (1H, dd), 7.59 - 7.65 (2H, m), 7.85 - 7.87 (2H, m), 8.07 (1H, d), 8.19 (1H, dd), 9.06 (1H, d); m/z 519.04 (M^+).

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E: Sodium 2-methyl-2-morpholinopropanoate

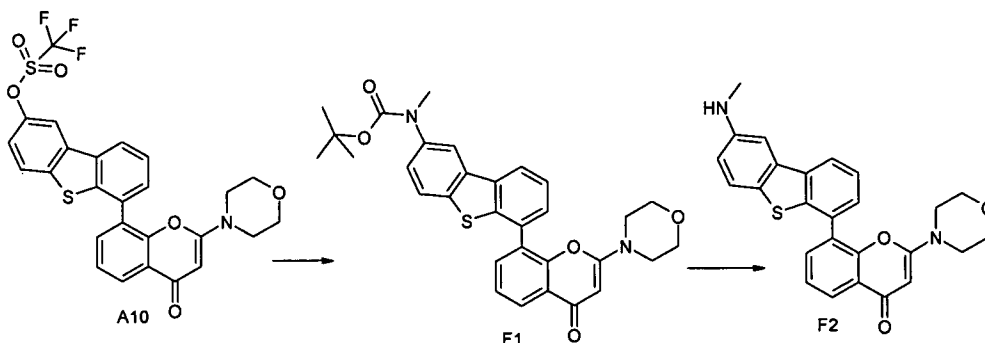


E1

Triethylamine (1.103 mL, 7.91 mmol) was added to 2-bromo-2-methylpropanoic acid (1.0165 g, 6.09 mmol) and Morpholine (1.221 mL, 14.00 mmol) in butan-1-ol (3 mL). The resulting solution was stirred at 80°C for 24 hours. The reaction was cooled to room temperature then sodium hydroxide (0.325 mL, 6.09 mmol) was added and the resulting mixture was evaporated to dryness and the residue was azeotroped with toluene to afford crude sodium 2-methyl-2-morpholinopropanoate (E1, 1.60 g, 135 %); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.20 (s, 6H), 2.59 (t, 4H), 2.78 (t, 3H), 3.55 - 3.60 (m, 8H).

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F: 8-[8-(Methylamino)dibenzothiophen-4-yl]-2-morpholin-4-ylchromen-4-one
tert-butyl N-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]carbamate



5

(a) *Tert-butyl N-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]carbamate (F1)*

A solution of tert-butyl methylcarbamate (35.0 mg, 0.27 mmol) in dioxane (1.7 mL) was added to a stirred mixture of [6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl] trifluoromethanesulfonate (A10, 100 mg, 0.18 mmol),

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tris(dibenzylideneacetone)dipalladium(0) (4.08 mg, 4.45 μ mol), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (5.15 mg, 8.90 μ mol) and cesium carbonate (232 mg, 0.71 mmol). The resulting mixture was stirred under nitrogen at 110°C for 3 hours.

The cooled reaction mixture was diluted with methanol and the residue was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3/MeOH and evaporated to dryness to afford tert-butyl N-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]carbamate (97 mg, 100 %) as an orange residue. 100% assumed and this was progressed to the next stage with no further purification; ^1H NMR (400 MHz, CDCl_3) δ 1.48 (9H, s), 3.09 (4H, t), 3.38 (3H, s), 3.51 (4H, t), 5.50 (1H, s), 7.36 (1H, s), 7.45 - 7.52 (2H, m), 7.57 (1H, t), 7.73 - 7.77 (2H, m), 8.06 (1H, s), 8.18 (1H, d), 8.28 (1H, d); m/z : 543.09 (MH^+).

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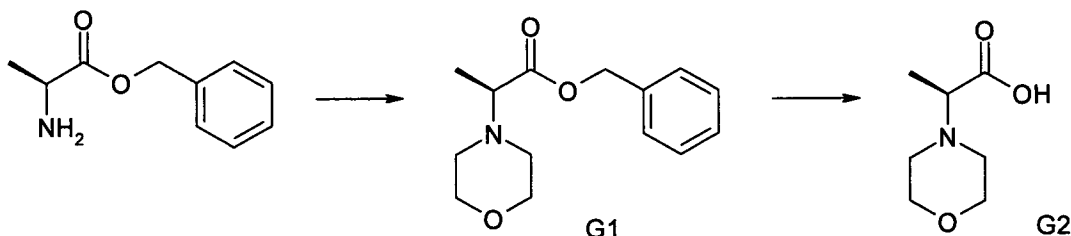
(b) *8-[8-(methylamino)dibenzothiophen-4-yl]-2-morpholin-4-ylchromen-4-one (F2)*

A solution of trifluoroacetic acid (0.20 mL, 2.60 mmol) in DCM (1.7 mL) was added to tert-butyl N-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]carbamate (F1, 97 mg, 0.18 mmol). The resulting solution was stirred under nitrogen at ambient temperature for 3 hours. The crude product was diluted with methanol and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3/MeOH and evaporated to dryness to afford 8-[8-

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(methylamino)dibenzothiophen-4-yl]-2-morpholin-4-ylchromen-4-one (77 mg, 98 %) as a yellow solid. This was used directly with no further purification.

G: (S)-2-Morpholinopropanoic acid



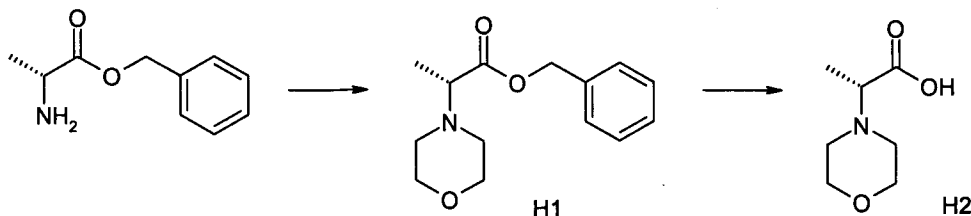
(a) *Benzyl (2S)-2-morpholin-4-ylpropanoate (G1)*

Ozone gas was passed into a mixture of 2,5-dihydrofuran (1.402 g, 20.00 mmol), methanol (8 mL), DCM (32.0 mL) at -60°C , (containing a trace of sudan red), until the red colour disappeared leaving a greyish solution. After removal of excess ozone with nitrogen, sodium cyanotrihydroborate (0.880 g, 14 mmol) was added to the solution and the mixture stirred at -50°C for 10 mins. A solution of (S)-benzyl 2-aminopropanoate hydrochloride (2.157 g, 10 mmol) in methanol (40 mL) was added dropwise and the stirring continued at 0°C overnight. Acetic acid (0.572 mL, 10.00 mmol) added and mixture evaporated. The residue was dissolved in DCM (200 mL) and washed with saturated aqueous NaHCO_3 solution. The organic layer was dried over Na_2SO_4 , filtered and evaporated to give an oil. The crude product was purified by flash silica chromatography, elution gradient 10 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford benzyl (2S)-2-morpholin-4-ylpropanoate (2.390 g, 96 %) as a yellow oil contained small amount of solvent; ^1H NMR (400 MHz, DMSO) δ 1.21 (3H, d), 2.47 - 2.60 (4H, m), 3.36 (1H, q), 3.52 - 3.61 (4H, m), 5.16 (2H, s), 7.36 - 7.43 (5H, m); m/z : 250.34 (MH^+).

(b) *(S)-2-morpholinopropanoic acid (G2)*

(S)-benzyl 2-morpholinopropanoate (G1, 2.39 g, 9.59 mmol), palladium, 10% on charcoal (200 mg, 1.88 mmol) in ethanol (40 mL) was stirred under an atmosphere of hydrogen at 21°C for 3 hours. The reaction mixture was filtered through celite and evaporated. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3/MeOH and pure fractions were evaporated to dryness to afford (S)-2-morpholinopropanoic acid (1.200 g, 79 %) as a brown crystalline solid. Chiral nmr showed 100% one isomer; ^1H NMR (400 MHz, DMSO) δ 1.21 (3H, d), 2.59 - 2.66 (4H, m), 3.14 (1H, q), 3.58 - 3.66 (4H, m).

H : (R)-2-Morpholinopropanoic acid



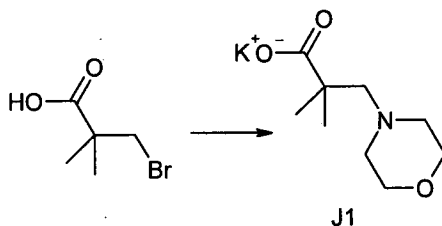
(a) Benzyl (2R)-2-morpholin-4-ylpropanoate (H1)

Ozone gas was passed into a mixture of 2,5-dihydrofuran (1.994 g, 28.46 mmol), methanol (24 mL), DCM (100 mL) at -60°C, (containing a trace of sudan red), until the red colour disappeared leaving a greyish solution. After removal of excess ozone with nitrogen, sodium cyanotrihydroborate (1.252 g, 19.92 mmol) was added to the solution and the mixture stirred at -50°C for 10 mins. A solution benzyl (2R)-2-aminopropanoate p-toluenesulfonate salt (5 g, 14.23 mmol) in methanol (100 mL) was added dropwise and the stirring continued at 0°C overnight. Acetic acid (0.815 mL, 14.23 mmol) was added and the mixture evaporated. The residue was dissolved in DCM (200 mL) and washed with saturated aqueous NaHCO₃ solution. The organic extracts were dried over Na₂SO₄, filtered and evaporated to an oil. The crude product was purified by flash silica chromatography, elution gradient 15 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford benzyl (2R)-2-morpholin-4-ylpropanoate (2.75 g, 78 %) as a orange oil; m/z: 250.17 (MH⁺).

(b) (R)-2-Morpholinopropanoic acid (H2)

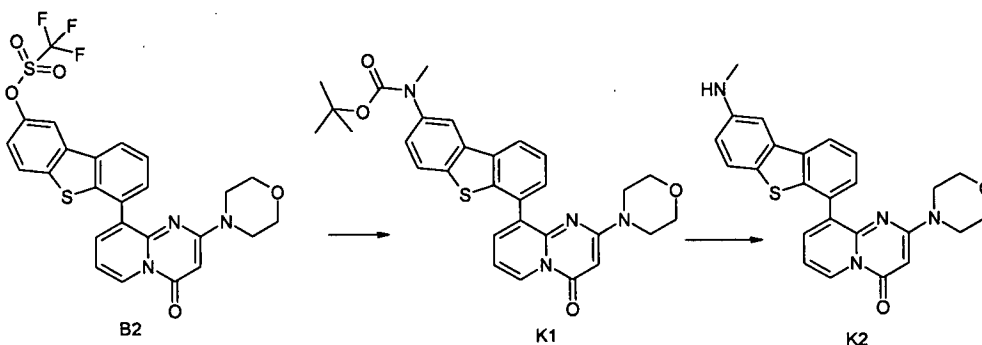
(2)-2-morpholin-4-ylpropanoate (H1, 3.5 g, 14.04 mmol), palladium, 10% On charcoal (0.374 g, 3.51 mmol) in ethanol (40 mL) was stirred under an atmosphere of hydrogen at 21°C for 2 hours then left at ambient temperature overnight. The reaction mixture was filtered through celite and evaporated. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford a brown semi-crystalline solid. NMR showed some starting material remained and so the reaction was hydrogenated for a further 2 hours and worked up in same way. Evaporation provided the product (S)-2-morpholinopropanoic acid (1.81g, 81%) as a cream solid; ¹H NMR (400 MHz, DMSO) δ 1.16 (3H, d), 2.52 - 2.59 (4H, m), 3.13 (1H, q), 3.48 - 3.66 (4H, m).

J : Potassium 2,2-dimethyl-3-morpholinopropanoate



Morpholine (68.7 mg, 0.79 mmol) was added to 3-bromo-2,2-dimethylpropanoic acid (119 mg, 0.66 mmol), and potassium carbonate (109 mg, 0.79 mmol) in acetonitrile (2 mL). The resulting suspension was stirred at room temperature for 18 hours. The white solid was filtered off and washed with diethyl ether to give potassium 2,2-dimethyl-3-morpholinopropanoate (165 mg, 111 %); ^1H NMR (400 MHz, DMSO) δ 0.95 (6H, s), 2.32 (2H, s), 2.38 (4H, t), 3.50 (4H, t).

K: 9-[8-(Methylamino)dibenzothiophen-4-yl]-2-morpholin-4-ylpyrido[1,2-a]pyrimidin-4-one



(a) *Tert-butyl N-methyl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]carbamate (K1)*

tert-butyl methylcarbamate (467 mg, 3.56 mmol) dissolved in dioxane (5mL) was added in one portion to [6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl] trifluoromethanesulfonate (B2, 1000 mg, 1.78 mmol), tris (dibenzylideneacetone)dipalladium(0) (40.8 mg, 0.04 mmol) and (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (51.5 mg, 0.09 mmol) and cesium carbonate (2321 mg, 7.12 mmol) in dioxane (18mL) at 110°C. The reaction flask was evacuated and blanketed with nitrogen four times. The resulting suspension was stirred at 110°C for 3 hours.

The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M $\text{NH}_3/\text{MeOH}/\text{DCM}$ (50/50) and pure fractions were evaporated to dryness to afford tert-butyl N-methyl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]carbamate (771 mg, 80 %) as a yellow solid; m/z : 543.51 (MH^+).

(b) 9-[8-(Methylamino)dibenzothiophen-4-yl]-2-morpholin-4-ylpyrido[1,2-a]pyrimidin-4-one (K2)

A solution of 10% TFA in DCM (10 mL) was added to tert-butyl N-methyl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]carbamate (K1, 771 mg, 1.42 mmol) at 25°C. The resulting solution was stirred at 25°C for 2 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford 9-[8-(methylamino)dibenzothiophen-4-yl]-2-morpholin-4-ylpyrido[1,2-a]pyrimidin-4-one (607 mg, 97 %) as a yellow solid; ¹H NMR (400 MHz, CDCl₃) δ 2.91 (3H, s), 3.30 (4H, t), 3.50 (4H, t), 5.55 (1H, s), 6.75 (1H, dd), 6.93 (1H, t), 7.28 (1H, d), 7.43 - 7.48 (3H, m), 7.81 (1H, dd), 8.06 (1H, dd), 8.96 (1H, dd); m/z: 443.43 (MH⁺).

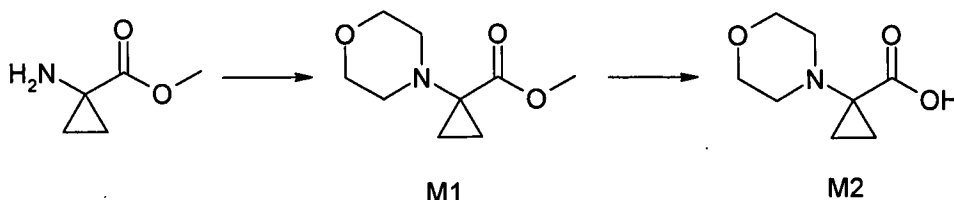
L : 1-(Dimethylamino)cyclopropane-1-carboxylic acid



L1

10% Pd-C (0.506 g, 4.76 mmol), formaldehyde (37% aqueous solution, 1.520 mL, 20.41 mmol) and 1-aminocyclopropanecarboxylic acid (1.013 g, 10.02 mmol) in water (40 mL) were stirred under an atmosphere of hydrogen (balloon pressure) at room temperature for 18 hours. The reaction mixture was filtered through celite and washed with water. The filtrate was evaporated to give a white wet solid. Water (50mL) was added to this and the mixture re-evapoated. Toluene was added and then removed by evaporation. More toluene was added and evaporated to leave dry 1-(dimethylamino)cyclopropanecarboxylic acid (1.198 g, 93 %) as a white solid; ¹H NMR (400 MHz, D₂O) δ 1.33 - 1.38 (4H, m), 2.91 (6H, d).

M : 1-morpholin-4-ylcyclopropane-1-carboxylic acid hydrochloride



(a) Methyl 1-morpholin-4-ylcyclopropane-1-carboxylate (M1)

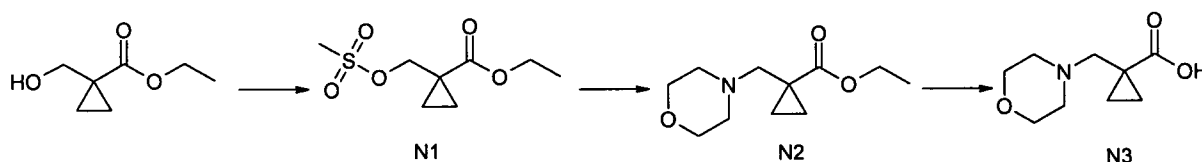
A solution of 1-bromo-2-(2-bromoethoxy)ethane (314 mg, 1.35 mmol) in acetonitrile (2 mL) was added dropwise to a boiling stirred suspension of methyl 1-aminocyclopropane-1-

carboxylate (130 mg, 1.13 mmol), potassium carbonate (655 mg, 4.74 mmol) and tetrabutylammonium bromide (47.3 mg, 0.15 mmol) in acetonitrile (2 mL). The resulting suspension was stirred at 80°C for 18 hours under nitrogen atmosphere. The reaction mixture was filtered to remove inorganics and washed with acetonitrile. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford methyl 1-morpholin-4-ylcyclopropane-1-carboxylate (82 mg, 39.2 %) as a colourless oil; ¹H NMR (400 MHz, CDCl₃) δ 0.86 - 0.90 (2H, m), 1.20 - 1.23 (2H, m), 2.88 (4H, s), 3.51 - 3.53 (4H, m), 3.61 (3H, s).

(b) 1-Morpholin-4-ylcyclopropane-1-carboxylic acid hydrochloride (M2)

Methyl 1-morpholin-4-ylcyclopropane-1-carboxylate (M1, 80 mg, 0.43 mmol) was added to water (1 mL) and hydrochloric acid, 37% (1 mL) and the reaction heated at 100°C for 48 hours. The reaction was concentrated under vacuum and toluene was added twice to azeotrope any water off to give 1-morpholin-4-ylcyclopropane-1-carboxylic acid hydrochloride (85 mg, 95 %); ¹H NMR (400 MHz, D₂O) δ 1.36 - 1.39 (2H, m), 1.41 - 1.43 (2H, m), 3.43 (4H, s), 3.84 (4H, s).

N: 1-(morpholin-4-ylmethyl)cyclopropane-1-carboxylic acid



(a) Ethyl 1-(methylsulfonyloxymethyl)cyclopropane-1-carboxylate (N1)

Triethylamine (0.734 g, 7.26 mmol) was added dropwise to ethyl 1-(hydroxymethyl)cyclopropane-1-carboxylate (0.959 g, 6.65 mmol), and methanesulfonyl chloride (0.762 g, 6.65 mmol) in dry dichloromethane (40 mL). The resulting solution was stirred at room temperature for 18 hours. The reaction mixture was washed sequentially with diluted saturated Na₂CO₃ (25 mL), 2M NaH₂PO₄ solution (25 mL), and saturated brine (25 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated to afford ethyl 1-(methylsulfonyloxymethyl)cyclopropane-1-carboxylate (0.931 g, 69%) as a pale yellow oil. This was used without purification for the next step; ¹H NMR (400 MHz, CDCl₃) δ 0.97 - 0.99 (2H, m), 1.19 (3H, t), 1.35 - 1.38 (2H, m), 3.01 (3H, s), 4.10 (2H, q), 4.27 (2H, s).

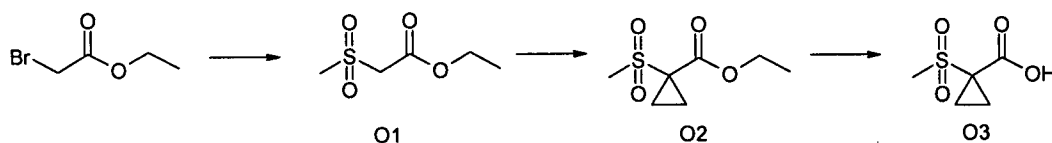
(b) Ethyl 1-(morpholin-4-ylmethyl)cyclopropane-1-carboxylate (N2)

Morpholine (216 mg, 2.47 mmol) was added ethyl 1-(methylsulfonyloxymethyl)cyclopropane-1-carboxylate (N1, 500 mg, 2.25 mmol), and potassium carbonate (342 mg, 2.47 mmol) in acetonitrile (10 mL). The resulting suspension was stirred at 80°C for 4 hours and then at room temperature overnight. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with water (50 mL), and saturated brine (25 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford ethyl 1-(morpholin-4-ylmethyl)cyclopropane-1-carboxylate (244 mg, 50.9 %) as a colourless oil; ¹H NMR (400 MHz, CDCl₃) δ 0.73 - 0.75 (2H, m), 1.15 - 1.19 (5H, m), 2.41 (4H, t), 2.54 (2H, s), 3.60 (4H, t), 4.05 (2H, q).

(c) 1-(Morpholin-4-ylmethyl)cyclopropane-1-carboxylic acid (N3)

Lithium hydroxide (129 mg, 5.39 mmol) was added to ethyl 1-(morpholin-4-ylmethyl)cyclopropane-1-carboxylate (N2, 230 mg, 1.08 mmol) in MeOH (5 mL), THF (5.00 mL) and a few drops of water. The resulting solution was stirred at 60°C for 18 hours. The reaction was then allowed to stand at room temp for the weekend. The reaction was evaporated to dryness and then water (5mL) was added and aqueous HCl (2molar) was added dropwise to neutral pH. The remaining gum was dissolved in water and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 10% Et₃N in methanol and pure fractions were evaporated to dryness to afford 1-(morpholin-4-ylmethyl)cyclopropane-1-carboxylic acid (139 mg, 70%) as a white oil which crystallised on standing; ¹H NMR (400 MHz, CDCl₃) δ 0.57 - 0.60 (2H, m), 1.32 - 1.35 (2H, m), 2.47 (2H, s), 2.53 (2H, s), 3.12 (2H, s), 3.74 (4H, s).

O : 1-methylsulfonylcyclopropane-1-carboxylic acid

*(a) Ethyl 2-methylsulfonylacetate (O1)*

To a solution of ethyl 2-bromoacetate (330 g, 1.98 mol) in DMF (1500 mL) was added MeSO₂Na (240 g, 2.35 mol). The mixture was stirred at room temperature for 24 hours. Then water was added, and the resulted mixture was extracted with ethyl acetate. The separated organic layer was washed with brine, dried over Na₂SO₄, and concentrated in

vacuo to give ethyl 2-methylsulfonylacetate (280 g, 85%); ¹H NMR (400 MHz, CDCl₃) δ 4.20 (2H, q), 3.95 (2H, s), 3.13 (3H, s), 1.23~1.25 (3H).

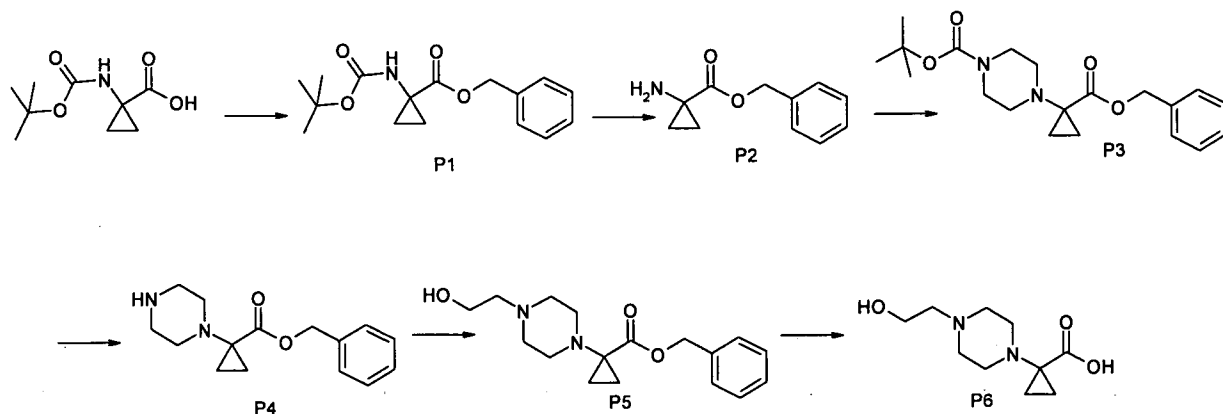
(b) Ethyl 1-methylsulfonylcyclopropane-1-carboxylate (O2)

5 To a solution of compound ethyl 2-methylsulfonylacetate (O1, 166 g, 1.0 mol) in DMF (1500 mL) was added 1,2-dibromoethane (265 g, 1.4 mol) and K_2CO_3 (207 g, 1.5 mol). The reaction mixture was stirred at 60°C for 24 hours. Water and ethyl acetate was added while stirring, the separated organic layer was washed with brine, dried over Na_2SO_4 , and concentrated in vacuo to give ethyl 1-methylsulfonylcyclopropane-1-carboxylate (150 g, 78%); 1H NMR (400 MHz, $CDCl_3$) δ 4.27 (2H, q, CH_2), 3.15 (3H, s, CH_3), 1.80 (2H, m, CH_2), 1.65 (2H, m, CH_2), 1.31 (3H, t, CH_3).

(c) 1-methylsulfonylcyclopropane-1-carboxylic acid (O3)

15 A mixture of compound ethyl 1-methylsulfonylcyclopropane-1-carboxylate (O2, 60 g, 0.31mol) and KOH (35 g, 0.62 mol) in ethanol/H₂O (500 mL/ 500 mL) was stirred at reflux for 10 hours. The solvent was removed in vacuo, the residue was partitioned between diluted HCl and ethyl acetate. The separated organic layer was washed with brine, dried over Na₂SO₄, and concentrated in vacuo, to give the product (41 g, 80%) as a solid; ¹H NMR (400 MHz, MeOD) δ 3.22 (3H, s, CH₃), 1.69 (2H, m, CH₂), 1.64 (2H, m, CH₂).

P: 1-[4-(2-hydroxyethyl)piperazin-1-yl]cyclopropane-1-carboxylic acid



(a) Benzyl 1-[(2-methylpropan-2-yl)oxycarbonylamino]cyclopropane-1-carboxylate (P1)

25 (Bromomethyl)benzene (3.55 mL, 29.82 mmol) was added dropwise to 1-[(2-methylpropan-2-yl)oxycarbonylamino]cyclopropane-1-carboxylic acid (2.5 g, 12.42 mmol), and triethylamine (4.14 mL, 29.82 mmol) in DMF (50 mL). The resulting suspension was stirred at room temperature for 18 hours under nitrogen atmosphere. The reaction mixture was

diluted with Et₂O (200 mL), and washed sequentially with saturated NH₄Cl (200 mL), and saturated brine (150 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford benzyl 1-[(2-methylpropan-2-yl)oxycarbonylamino]cyclopropane-1-carboxylate (2.88 g, 80 %) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.12 (2H, s), 1.37 (9H, s), 1.48 (2H, s), 5.06 (2H, s), 7.19 - 7.30 (5H, m).

(b) Benzyl 1-aminocyclopropane-1-carboxylate (P2)

TFA (25mL) was added dropwise to a solution benzyl 1-[(2-methylpropan-2-yl)oxycarbonylamino]cyclopropane-1-carboxylate (P1, 2.377 g, 8.16 mmol) in DCM (25 mL) at 0°C. The reaction mixture was allowed to stir at 0°C for 2 hours. The reaction mixture was concentrated and diluted with DCM (100 mL), and washed sequentially with saturated NaHCO₃ (100 mL), and saturated brine (100 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated to afford benzyl 1-aminocyclopropane-1-carboxylate (1.287 g, 82 %) as a colourless oil; ¹H NMR (400 MHz, CDCl₃) δ 0.93 - 0.97 (2H, m), 1.24 - 1.27 (2H, m), 1.99 (2H, bs), 5.05 (2H, s), 7.25 - 7.32 (5H, m).

(c) Tert-butyl 4-(1-phenylmethoxycarbonylcyclopropyl)piperazine-1-carboxylate (P3)

Ozone gas was passed into a mixture of tert-butyl 2,5-dihydro-1H-pyrrole-1-carboxylate (177 mg, 1.05 mmol), methanol (5 mL), DCM (5.00 mL) at -60°C, (containing a trace of sudan red), until red colour disappeared leaving a yellow solution (this took less than 5 minutes). After removal of excess ozone with nitrogen, sodium cyanotrihydroborate (46.0 mg, 0.73 mmol) was added to the soln and the mixture stirred at -50°C for 10mins. A solution of benzyl 1-aminocyclopropane-1-carboxylate (P2, 100 mg, 0.52 mmol) in methanol (2mL) was added dropwise and the stirring continued at 0°C overnight. Acetic acid (0.030 mL, 0.52 mmol) was then added dropwise. The reaction mixture was concentrated and diluted with DCM (25 mL), and washed sequentially with saturated NaHCO₃ (50 mL), and saturated brine (25 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated to afford crude product as an orange oil. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford tert-butyl 4-(1-phenylmethoxycarbonylcyclopropyl)piperazine-1-carboxylate (52.0 mg, 27.6 %) as a colourless oil; ¹H NMR (400 MHz, CDCl₃) δ 0.88 - 0.91 (2H, m), 1.24 - 1.28 (2H, m), 1.38 (9H, s), 2.84 (4H, s), 3.44 (4H, s), 5.03 (2H, s), 7.21 - 7.31 (5H, m).

(d) *Benzyl 1-piperazin-1-ylcyclopropane-1-carboxylate (P4)*

TFA (3mL) was added dropwise to a solution of tert-butyl 4-(1-phenylmethoxycarbonylcyclopropyl)piperazine-1-carboxylate (P3, 1.08 g, 3.00 mmol) in DCM (30mL) at room temperature. The reaction mixture was allowed to stir at room temperature for 2 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford benzyl 1-piperazin-1-ylcyclopropane-1-carboxylate (0.756 g, 97 %) as yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 0.87 - 0.90 (2H, m), 1.22 - 1.25 (2H, m), 2.70 - 2.71 (4H, m), 2.86 (4H, s), 5.04 (2H, s), 7.22 - 7.31 (5H, m)

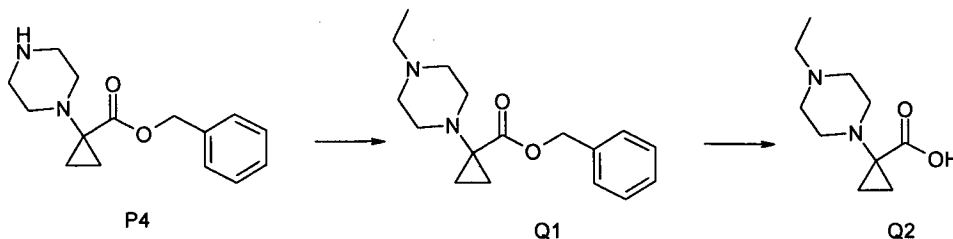
(e) *1-[4-(2-Hydroxyethyl)piperazin-1-yl]cyclopropane-1-carboxylic acid (P5)*

2-Bromoethanol (190 mg, 1.52 mmol) was added in one portion to benzyl 1-piperazin-1-ylcyclopropane-1-carboxylate (P4, 360 mg, 1.38 mmol) and potassium carbonate (382 mg, 2.77 mmol) in acetonitrile (5 mL). The resulting suspension was stirred at 80°C for 18 hours under nitrogen atmosphere. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and fractions were evaporated to dryness to afford crude product as an orange oil. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford benzyl 1-[4-(2-hydroxyethyl)piperazin-1-yl]cyclopropane-1-carboxylate (345 mg, 82 %) as a yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 0.86 - 0.89 (2H, m), 1.24 - 1.26 (2H, m), 2.34 (4H, s), 2.43 (2H, t), 2.93 (4H, s), 3.51 (2H, t), 5.05 (2H, s), 7.23 - 7.32 (5H, m).

(f) *1-[4-(2-hydroxyethyl)piperazin-1-yl]cyclopropane-1-carboxylic acid (P6)*

Palladium, 10% on charcoal (119 mg, 0.11 mmol) and benzyl 1-[4-(2-hydroxyethyl)piperazin-1-yl]cyclopropane-1-carboxylate (P5, 340 mg, 1.12 mmol) in ethanol (10 mL) were stirred under an atmosphere of hydrogen at balloon pressure and room temperature for 90 minutes. The reaction mixture was filtered through celite and washed with ethanol (30mL) and DCM (10mL). The filtrate was concentrated to give 1-[4-(2-hydroxyethyl)piperazin-1-yl]cyclopropane-1-carboxylic acid (80 mg, 33.4 %) as a white solid; ¹H NMR (400 MHz, D₂O) δ 0.76 - 0.79 (2H, m), 1.02 - 1.04 (2H, m), 2.75 - 3.51 (10H, m), 3.80 (2H, t).

Q: 1-[4-(2-hydroxyethyl)piperazin-1-yl]cyclopropane-1-carboxylic acid



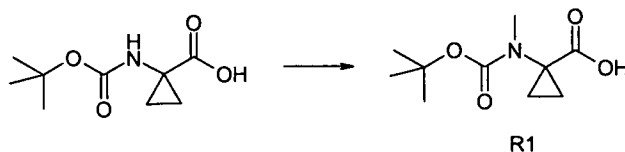
(a) *Benzyl 1-(4-ethylpiperazin-1-yl)cyclopropane-1-carboxylate (Q1)*

Bromoethane (166 mg, 1.52 mmol) was added in one portion to benzyl 1-piperazin-1-ylcyclopropane-1-carboxylate (P4, 360 mg, 1.38 mmol) and potassium carbonate (382 mg, 2.77 mmol) in acetonitrile (5 mL). The resulting suspension was stirred at 80°C for 18 hours under nitrogen atmosphere. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3/MeOH and fractions were evaporated to dryness to afford crude product as an orange oil. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford benzyl 1-(4-ethylpiperazin-1-yl)cyclopropane-1-carboxylate (358 mg, 90 %) as a colourless oil; ^1H NMR (400 MHz, CDCl_3) δ 0.85 - 0.88 (2H, m), 0.98 - 1.02 (3H, m), 1.22 - 1.25 (2H, m), 2.18 - 2.34 (6H, m), 2.94 (4H, s), 5.06 (2H, s), 7.21 - 7.30 (5H, m)

(b) *1-[4-(2-Hydroxyethyl)piperazin-1-yl]cyclopropane-1-carboxylic acid (Q2)*

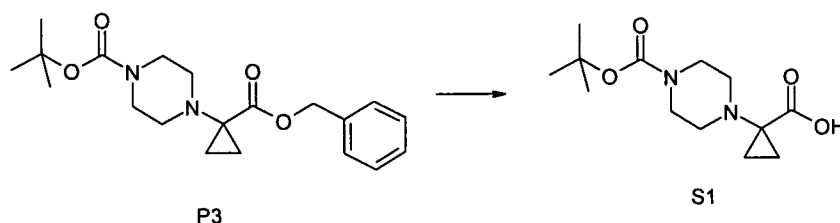
Palladium, 10% on charcoal (35 mg, 0.03 mmol) and benzyl 1-(4-ethylpiperazin-1-yl)cyclopropane-1-carboxylate (Q1, 354 mg, 1.23 mmol) in ethanol (10 mL) were stirred under an atmosphere of hydrogen at balloon pressure and room temperature for 90 minutes. The reaction mixture was filtered through celite and washed with ethanol (30mL) and DCM (10mL). The filtrate was concentrated to give a sticky white solid which was triturated in diethyl ether and then diethyl ether removed by evaporation to give 1-[4-(2-hydroxyethyl)piperazin-1-yl]cyclopropane-1-carboxylic acid (240 mg, 99 %) as a white solid; ^1H NMR (400 MHz, CDCl_3) δ 0.70 - 0.74 (2H, m), 1.19 - 1.21 (2H, m), 1.38 (3H, t), 2.46 (2H, s), 2.76 - 2.91 (4H, m), 3.21 (2H, s), 4.11 (2H, s)

R : 1-[methyl-[(2-methylpropan-2-yl)oxycarbonyl]amino]cyclopropane-1-carboxylic acid



Sodium hydride, 60% dispersion in mineral oil (284 mg, 7.11 mmol) was added portionwise to 1-[(2-methylpropan-2-yl)oxycarbonylamino]cyclopropane-1-carboxylic acid (260 mg, 1.29 mmol) and Methyl iodide (0.644 mL, 10.34 mmol). The resulting suspension was stirred at 0°C for 1 hour under nitrogen atmosphere. The suspension was then stirred at room temperature for 18 hours. The reaction was quenched by adding a few drops of water and ethyl acetate (6mL). Most of the solvent was then removed by evaporation and water (10 mL) and diethyl ether (4 mL) were added. The ether layer was washed with 5% NaHCO₃aq solution. The pH of the combined aqueous layers were adjusted to pH3 by addition of solid citric acid. The solid was filtered off and dissolved in EtOAc and dried over Na₂SO₄. The EtOAc was evaporated to give 1-(tert-butoxycarbonyl(methyl)amino)cyclopropanecarboxylic acid (155 mg, 56 %) as a cream solid; ¹H NMR (400 MHz, CDCl₃) δ 1.19 - 1.34 (2H, m), 1.45 (9H, s), 1.59 - 1.80 (2H, m), 2.89 (3H, s).

S: 1-[4-[(2-methylpropan-2-yl)oxycarbonyl]piperazin-1-yl]cyclopropane-1-carboxylic acid



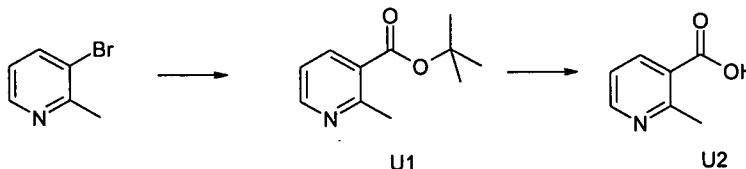
Palladium, 10% on charcoal (40mg, 0.04 mmol) and tert-butyl 4-(1-phenylmethoxycarbonylcyclopropyl)piperazine-1-carboxylate (P3, 396 mg, 1.10 mmol) in ethanol (10 mL) were stirred under an atmosphere of hydrogen at balloon pressure and room temperature for 90 minutes. The reaction mixture was filtered through celite and washed with ethanol (30 mL) and DCM (10 mL). The filtrate was concentrated to give 1-[4-[(2-methylpropan-2-yl)oxycarbonyl]piperazin-1-yl]cyclopropane-1-carboxylic acid (277 mg, 93 %) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.08 - 1.11 (2H, m), 1.36 - 1.39 (2H, m), 1.46 (9H, s), 2.73 (4H, s), 3.39 (4H, s).

T: 2-(6-Methylpyrimidin-4-yl)acetic acid



n-Butyllithium (1.6M in Hexanes) (20.81 mL, 33.29 mmol) was added dropwise, at -78°C, under nitrogen, to a solution of 4,6-dimethylpyrimidine (3.00 g, 27.74 mmol) and 2,2'-bipyridine (10.00 mg, 0.06 mmol) (as an organometallic indicator) in dry THF (50 mL) with the formation of an orange solution. The mixture was stirred at -78°C for 20 minutes before gaseous Carbon Dioxide (24.42 g, 554.83 mmol) was introduced, slowly bubbled through a needle (produced from melting dry ice) for 15 minutes at -78°C and over the period of 1 hour during which time the mixture was allowed to warm slowly to room temperature. The excess of BuLi was quenched by addition of water (2mL) and the resultant mixture was evaporated in vacuo, with toluene (50.0 mL x 2) to give the crude product 2-(6-methylpyrimidin-4-yl)acetic acid (4.66 g, 106 %) as a white solid as the lithium salt which was used in subsequent reactions without further purification; ¹H NMR (400 MHz, D₂O) δ 2.50 (3H, s), 3.66 (2H, s), 7.35 (1H, s), 8.85 (1H, s); m/z: 150.95 (MH⁺).

U: 2-methylpyridine-3-carboxylic acid



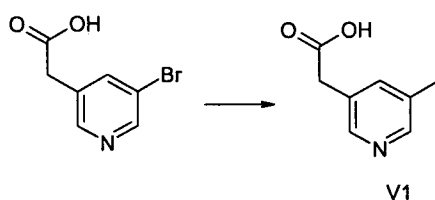
(a) *Tert-butyl 2-methylpyridine-3-carboxylate (U1)*

1,2,3,4,5-Pentaphenyl-1'-(di-*t*-butylphosphino)ferrocene (0.083 g, 0.12 mmol) and bis(dibenzylideneacetone)palladium (0.067 g, 0.12 mmol) were added to a partial solution of (2-*tert*-butoxy-2-oxoethyl)zinc(II) bromide (4.54 g, 17.44 mmol) and 3-bromo-2-methylpyridine (2 g, 11.63 mmol) in dry THF (10mL), stirred under nitrogen, at room temperature. The mixture was then heated to reflux with dissolution of the reactants observed and the heating continued for 6 hours. After cooling the mixture was evaporated onto silica and purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in isohexane. Pure fractions were evaporated to dryness and then azeotroped with toluene (20mL) to dryness to give *tert*-butyl 2-methylpyridine-3-carboxylate (2.3 g, 95 %) as a white foam; ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.41 (9H, s), 2.43 (3H, s), 3.65 (2H, s), 7.20 - 7.23 (1H, m), 7.59 - 7.61 (1H, m), 8.35 - 8.37 (1H, m).

(b) 2-methylpyridine-3-carboxylic acid (U2)

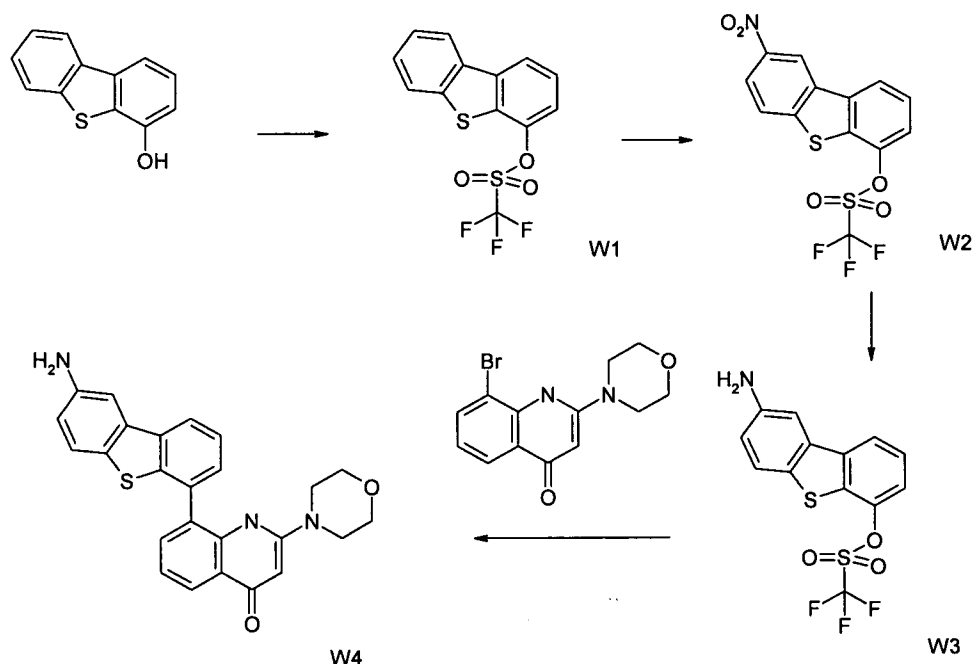
Tert-butyl 2-methylpyridine-3-carboxylate (U1, 2.26 g, 10.90 mmol) was added to a solution of hydrogen chloride (4.0M in Dioxane) (10.90 mL, 43.61 mmol) and the suspension heated to 60°C for 1 hour. The solvents were removed in vacuo and the resultant oil stirred in diethyl ether (250 mL) overnight with the formation of a fine white suspension. The solid was filtered and suction dried under nitrogen to give the product 2-methylpyridine-3-carboxylic acid hydrochloride salt as a white solid (2.0 g, 98 %); ¹H NMR (400 MHz, DMSO-d₆) δ 2.66 (3H, s), 3.70 (1H, br s), 3.94 (2H, s), 7.85 (1H, t), 8.38 (1H, d), 8.70 (1H, d), 12.85 (1H, br s).

10 V: 2-(5-methylpyridin-3-yl)acetic acid



Dimethylzinc (2.0M in Toluene) (2.467 mL, 4.93 mmol) was added dropwise to a solution of 2-(5-bromopyridin-3-yl)acetic acid (533 mg, 2.47 mmol) and 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (39.7 mg, 0.06 mmol) in dry tetrahydrofuran (20 mL) with an exotherm and gas evolution observed during addition. The mixture was stirred at ambient temperature for 4 hours. The reaction mixture was quenched by the addition of silica (Merck 9385 grade, 10g) and after stirring for 1 hour when gas evolution had ceased the solvents were removed in vacuo and the crude product was purified by flash silica chromatography, elution gradient 0 to 10% (5% Et₃N in MeOH) in DCM. Pure fractions were evaporated to dryness to afford 2-(5-methylpyridin-3-yl)acetic acid (67 mg, 18%) as a white solid; ¹H NMR (400 MHz, D₂O) δ 0.89 - 1.01 (3H, m), 3.39 (5H, m), 3.56 (2H, d), 7.62 (1H, s), 8.24 (1H, s), 8.30 (1H, s).

W: 8-(8-aminodibenzothiophen-4-yl)-2-morpholin-4-yl-1H-quinolin-4-one



(a) Dibenzothiophen-4-yl trifluoromethanesulfonate (W1)

- 5 Dibenzothiophen-4-ol (500 mg, 2.50 mmol), 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (1160 mg, 3.25 mmol) and potassium carbonate (0.151 mL, 2.50 mmol) were dissolved in DMF (25 mL) and stirred at ambient temperature under nitrogen for 18 hours. The reaction mixture was concentrated and diluted with EtOAc (50 mL). The mixture was washed with water (100 mL) and the aqueous layer
- 10 further extracted with EtOAc (1 x 100 mL). The organic layers were combined and washed with saturated brine solution (100 mL), dried over MgSO_4 , filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford dibenzothiophen-4-yl trifluoromethanesulfonate (774 mg, 93 %) as a colourless oil; ^1H NMR
- 15 (400 MHz, CDCl_3) δ 7.44 - 7.46 (1H, m), 7.50 - 7.56 (3H, m), 7.88 - 7.90 (1H, m), 8.14 - 8.19 (2H, m); m/z : 330.97 (MH^+).

(b) (8-Nitrodibenzothiophen-4-yl) trifluoromethanesulfonate (W2)

- 20 Sulfuric acid (approx 15 mg), followed by fuming nitric acid (approx 60 mg) was added to a stirred solution of dibenzothiophen-4-yl trifluoromethanesulfonate (W1, 199 mg, 0.60 mmol) in acetic acid (0.5 mL) at 100°C . Sulfuric acid (approx 15 mg), followed by fuming nitric acid (approx 60 mg) was added to a stirred solution of dibenzothiophen-4-yl trifluoromethanesulfonate (W1, 205 mg, 0.62 mmol) in acetic acid (1.0 mL) at 100°C .

Sulfuric acid (approx 15 mg), followed by fuming nitric acid (approx 60 mg) was added to a stirred solution of dibenzothiophen-4-yl trifluoromethanesulfonate (W1, 210 mg, 0.63 mmol) in acetic acid (2.0 mL) at 100°C. The reactions were incomplete and further sulfuric acid (15 mg, 0.15 mmol) and fuming nitric acid (60 mg, 0.95 mmol) were added and the solution was stirred at 100°C for a further 2 to 20 hours. The reaction mixtures were combined and added carefully to water (150 mL) and stirred for 15 mins. The aqueous was then extracted with DCM (3 x 100 mL), the combined organics dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash silica chromatography, elution gradient 0 to 8% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford (8-nitrodibenzothiophen-4-yl) trifluoromethanesulfonate (280 mg, 41 %) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 7.58 (1H, d), 7.66 (1H, t), 8.04 (1H, d), 8.28 (1H, d), 8.40 - 8.43 (1H, m), 9.05 (1H, d).

(c) (8-Aminodibenzothiophen-4-yl) trifluoromethanesulfonate (W3)

Zinc dust (357 mg, 5.46 mmol) was added portionwise to (8-nitrodibenzothiophen-4-yl) trifluoromethanesulfonate (W2, 206 mg, 0.55 mmol) in glacial acetic acid (2 mL) at ambient temperature over a period of 2 minutes. The resulting suspension was stirred at ambient temperature for 4 hours and the sat at ambient temperature for 3 days (weekend). The reaction mixture was diluted with methanol, decanting off the liquid and the solid washed with more methanol (2 x 5 mL). The combined liquids were further diluted with methanol (10 mL) and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford (8-aminodibenzothiophen-4-yl) trifluoromethanesulfonate (136 mg, 71.7 %) as a pale brown solid; ¹H NMR (400 MHz, CDCl₃) δ 3.70 (2H, br s), 6.92 - 6.95 (1H, m), 7.39 - 7.41 (1H, m), 7.43 (1H, d), 7.46 (1H, t), 7.63 (1H, d), 8.01 - 8.03 (1H, m).

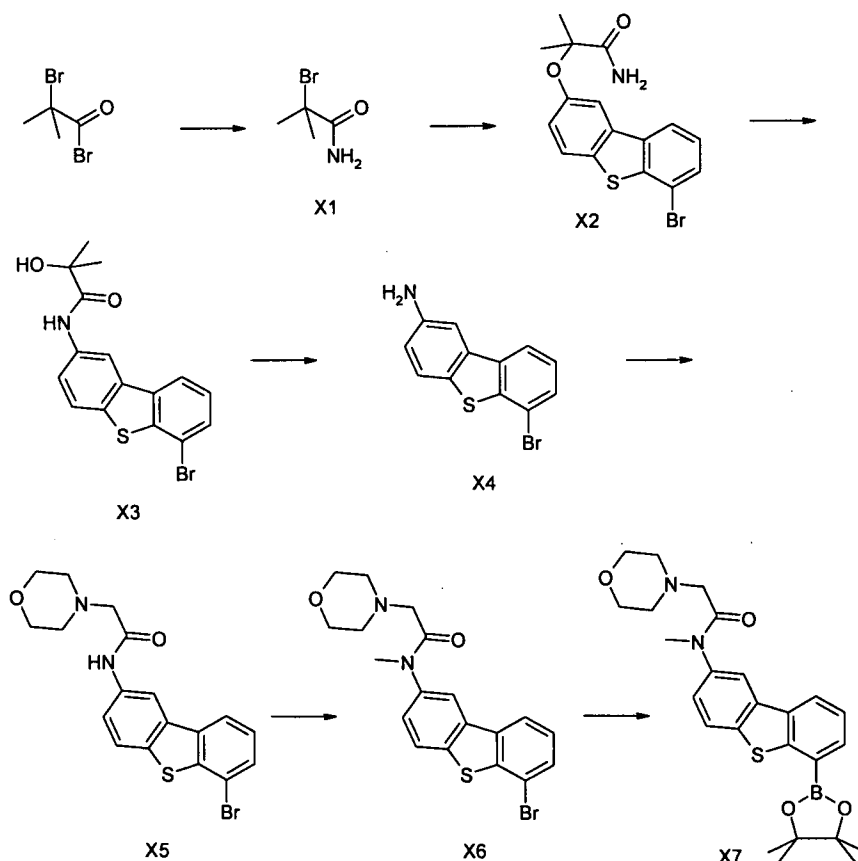
(d) 8-(8-Aminodibenzothiophen-4-yl)-2-morpholin-4-yl-1H-quinolin-4-one (W4)

(8-Aminodibenzothiophen-4-yl) trifluoromethanesulfonate (W3, 130 mg, 0.37 mmol), potassium acetate (110 mg, 1.12 mmol) and bis(pinacolato)diboron (105 mg, 0.41 mmol) were suspended in degassed dioxane (20 mL). 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) (15.27 mg, 0.02 mmol) was added in one portion. The resulting suspension was stirred under nitrogen at reflux for 4 hours.

The reaction was then cooled to room temperature and

tetrakis(triphenylphosphine)palladium(0) (21.38 mg, 0.02 mmol) was added followed by 8-bromo-2-morpholin-4-yl-1H-quinolin-4-one (*Org. Biomol. Chem.*, 2007, **5**, 2670, 114 mg, 0.37 mmol), sodium carbonate (0.555 mL, 1.11 mmol) and copper(I) chloride (36.6 mg, 0.37 mmol) in degassed dioxane (10 mL) under nitrogen. The resulting suspension was stirred at reflux for 18 hours. The reaction mixture was diluted with EtOAc (200 mL), filtered through celite and washed with water (100 mL). The organic layer was dried over MgSO₄, filtered and evaporated onto silica gel (5 g). The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford 8-(8-aminodibenzothiophen-4-yl)-2-morpholin-4-yl-1H-quinolin-4-one (37.0 mg, 23%) as a brown solid; ¹H NMR (400 MHz, CDCl₃) δ 3.01 (4H, t), 3.65 (4H, t), 5.78 (1H, s), 6.92 (1H, dd), 7.40 (1H, t), 7.46 (1H, d), 7.51 - 7.64 (4H, m), 7.68 (1H, dd), 8.16 (1H, dd), 8.39 (1H, d); m/z: 428.38 (MH⁺).

X: N-methyl-2-morpholin-4-yl-N-[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dibenzothiophen-2-yl]acetamide



(a) *2-bromo-2-methylpropanamide (X1)*

2-bromo-2-methylpropanoyl bromide (13.44 mL, 108.74 mmol) was added dropwise from a pressure equalising dropping funnel to a stirred solution of ammonium hydroxide (17.85 mL, 128.35 mmol) in water (22 mL) cooled to below 5°C. The internal temperature was not allowed to rise above 15°C. The resulting solution was stirred at between 0 and 5°C for 1 hour until the reaction was complete. The precipitate was filtered and washed with water (100 mL) to give 2-bromo-2-methylpropanamide (13.69 g, 64.2 %); ¹H NMR (500 MHz, DMSO) δ 1.85 (6H, s), 7.28 (1H, s), 7.53 (1H, s); m/z: 166/168 (MH⁺).

(b) *2-(6-bromodibenzothiophen-2-yl)oxy-2-methylpropanamide (X2)*

Sodium hydride (1.185 g, 29.64 mmol) was added portionwise to 6-bromodibenzothiophen-2-ol (A4, 4.1365 g, 14.82 mmol) in 1,4-dioxane (200 mL) at room temperature. The resulting solution was stirred at room temperature for 15 minutes. 2-bromo-2-methylpropanamide (X1, 2.460 g, 14.82 mmol) was then added and the reaction heated to 100 °C for 40 hours. The reaction mixture was concentrated under reduced pressure and taken up in water (100 mL) and DCM (100 mL). Methanol was added to try and aid full solubilisation of material. The organic layer was removed and the aqueous further extracted with DCM (2 x 50 mL). The combined organics were filtered and then washed with water (100 mL) and concentrated under reduced pressure. The cream solid which formed was slurried in methanol (approx 100 mL) and the precipitate was collected by filtration, washed with MeOH (25 mL) and dried under vacuum to give 2-(6-bromodibenzothiophen-2-yl)oxy-2-methylpropanamide (2.428 g, 45%); ¹H NMR (400 MHz, DMSO) δ 1.49 (6H, s), 7.20 (1H, dd), 7.48 (1H, t), 7.77 (1H, dd), 7.91 (1H, d), 8.00 (1H, d), 8.30 - 8.33 (1H, m).

(c) *N-(6-bromodibenzothiophen-2-yl)-2-hydroxy-2-methylpropanamide (X3)*

Sodium hydride, 60% dispersion in mineral oil (0.800 g, 20.00 mmol) was added portionwise to 2-(6-bromodibenzothiophen-2-yl)oxy-2-methylpropanamide (X2, 2.428 g, 6.67 mmol) dissolved in DMF (50 mL) and DMPU (5 mL) at ambient temperature. The resulting solution was stirred under nitrogen at 110°C for 4 hours. The reaction mixture was poured into water (100 mL), and extracted with EtOAc (3 x 50 mL). The organic layers were combined and washed with water (100 mL) dried over MgSO₄, filtered and evaporated to yield N-(6-bromodibenzothiophen-2-yl)-2-hydroxy-2-methylpropanamide as a brown gum which was reacted on without further purification; m/z: 364.00 (MH⁺).

(d) 6-bromodibenzothiophen-2-amine (X4)

Hydrochloric acid, 37% concentrated aqueous solution (25 mL, 822.80 mmol) was added dropwise to N-(6-bromodibenzothiophen-2-yl)-2-hydroxy-2-methylpropanamide (X3, 2.430 g, 6.67 mmol) in ethanol (30 mL) at ambient temperature. The resulting solution was stirred under nitrogen at 100°C for 18 hours. The precipitate was collected by filtration, washed with EtOH (20 mL) and air dried to afford 6-bromodibenzothiophen-2-amine (1.792 g, 85 %) as the HCl salt and a white solid, which was used without further purification; ¹H NMR (400 MHz, DMSO) δ 7.54 (2H, dt), 7.83 (1H, dd), 8.21 (2H, dd), 8.37 (1H, dd).

(e) N-(6-bromodibenzothiophen-2-yl)-2-morpholin-4-ylacetamide (X5)

Chloroacetyl chloride (0.499 mL, 6.27 mmol) was added to 6-bromodibenzothiophen-2-amine, HCl salt (X4, 1.792 g, 5.70 mmol) and triethylamine (2.382 mL, 17.09 mmol) in anhydrous DMA (24 mL) at ambient temperature. The resulting mixture was stirred at ambient temperature for 30 minutes. The reaction was incomplete and further chloroacetyl chloride (0.25 mL) was added and the solution was stirred at ambient temperature for a further 20 minutes. Morpholine (1.987 mL, 22.78 mmol) was then added and the reaction mixture stirred for 3 hours. The reaction mixture was diluted with EtOAc (100 mL) and washed with water (200 mL). The aqueous was further extracted with EtOAc (2 x 100 mL) and the combined organics washed with saturated brine, dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness and then slurried in methanol. The precipitate was collected by filtration, washed with MeOH (20 mL) and air dried to afford N-(6-bromodibenzothiophen-2-yl)-2-morpholin-4-ylacetamide (1.572 g, 68%) as a green solid; ¹H NMR (400 MHz, DMSO) δ 2.55 (4H, dd), 3.64 - 3.70 (4H, m), 4.12 (2H, q), 7.48 (1H, t), 7.76 (1H, s), 7.81 (1H, dt), 8.02 (1H, d), 8.26 (1H, d), 8.63 (1H, dd), 10.00 (1H, s); m/z: 404.98 (MH⁺).

(f) N-(6-bromodibenzothiophen-2-yl)-N-methyl-2-morpholin-4-ylacetamide (X6)

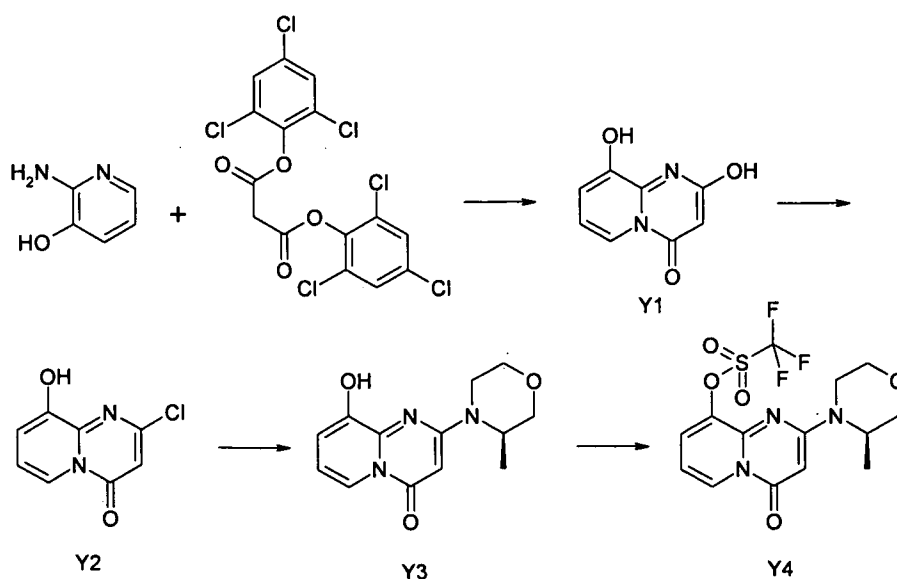
Sodium Bis(trimethylsilyl)amide (4.07 mL, 4.07 mmol) was added to N-(6-bromodibenzothiophen-2-yl)-2-morpholin-4-ylacetamide (X5, 1.5722 g, 3.88 mmol) in THF (35 mL) at 0°C. The resulting mixture was stirred under nitrogen at 0°C for 30 minutes then iodomethane (0.266 mL, 4.27 mmol) was added and the reaction mixture stirred for a further 20 minutes at room temperature. The reaction mixture was quenched with water (1 mL) then concentrated and diluted with EtOAc (100 mL), and washed with water (100 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product.

The crude product was purified by flash silica chromatography, elution gradient 0 to 3% MeOH in DCM. Pure fractions were evaporated to dryness to afford N-(6-bromodibenzothiophen-2-yl)-N-methyl-2-morpholin-4-ylacetamide (1.482 g, 91 %) as a white foam; ¹H NMR (400 MHz, DMSO) δ 2.30 (4H, d), 2.95 (2H, s), 3.27 (3H, s), 3.40 (4H, d), 7.51 (1H, t), 7.56 (1H, d), 7.79 (1H, d), 8.16 (1H, d), 8.44 (2H, d); m/z: 419.00 (MH⁺).

(g) N-methyl-2-morpholin-4-yl-N-[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dibenzothiophen-2-yl]acetamide (X7)

1,1'-Bis(diphenylphosphino)ferrocenedichloropalladium(II) (0.116 g, 0.16 mmol) was added to N-(6-bromodibenzothiophen-2-yl)-N-methyl-2-morpholin-4-ylacetamide (X6, 1.343 g, 3.20 mmol), bis(pinacolato)diboron (0.854 g, 3.36 mmol), potassium acetate (0.943 g, 9.61 mmol) in 1,4-dioxane (100 mL) under nitrogen. The resulting suspension was stirred at 110°C for 3 days. The reaction mixture was evaporated to dryness and redissolved in EtOAc (250 mL), and washed with water (250 mL). The organic layer was dried over MgSO₄, filtered and evaporated on to silica gel (10 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford N-methyl-2-morpholin-4-yl-N-[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dibenzothiophen-2-yl]acetamide (1.303 g, 87 %) as a yellow solid; ¹H NMR (400 MHz, DMSO) δ 1.38 (12H, s), 2.19 - 2.37 (5H, m, 4 protons for desired product), 2.94 (2H, s), 3.26 (3H, s), 3.33 (4H, s), 3.40 (5H, s, 4 protons for desired product), 7.53 (3H, s), 7.87 (1H, d), 7.97 - 8.14 (2H, m), 8.40 (1H, d), 8.54 (1H, d); m/z: 476.21 (MH⁺).

Y: [[2-[(3R)-3-methylmorpholin-4-yl]-4-oxo-1,9a-dihydropyrido[1,2-a]pyrimidin-9-yl]trifluoromethanesulfonate



(a) *2,9-dihydroxy-1,9a-dihydropyrido[1,2-a]pyrimidin-4-one (Y1)*

2-aminopyridin-3-ol (4.12 g, 37.45 mmol) and bis(2,4,6-trichlorophenyl) propanedioate (17.338 g, 37.45 mmol) in bromobenzene (37 mL, 352.31 mmol) were stirred at reflux for 3 hours then allowed to cool to room temperature. The precipitate was collected by filtration and washed with EtOH (20 mL). The solid was dissolved in 1M NaOH (75 mL) then glacial acetic acid (4 mL) was added with stirring and the resulting precipitate was collected by filtration and dried under vacuum to afford 2,9-dihydroxy-1,9a-dihydropyrido[1,2-a]pyrimidin-4-one (1.950 g, 29.2 %) as a pale yellow solid, which was used without further purification. The filtrate (NaOH/Acetic acid mix) was freeze dried to yield 2,9-dihydroxy-1,9a-dihydropyrido[1,2-a]pyrimidin-4-one (9.92 g, 149 %) as a beige solid; ¹H NMR (400 MHz, DMSO) δ 4.87 (1H, s), 6.90 (1H, d), 6.96 - 7.05 (1H, m), 8.02 (1H, d); m/z: 179.00 (MH⁺).

(b) *2-chloro-9-hydroxy-1,9a-dihydropyrido[1,2-a]pyrimidin-4-one (Y2)*

2,9-dihydroxy-1,9a-dihydropyrido[1,2-a]pyrimidin-4-one (Y1, 9.92 g, 27.84 mmol) was treated with phosphorous oxychloride (100 mL). The resulting solution was stirred at reflux for 30 hours. The reaction mixture was evaporated and the residue carefully treated with saturated NaHCO₃ (1 L). The mixture was extracted with DCM (4 x 250 mL) and the combined organic layers dried over MgSO₄, filtered and evaporated to afford 2-chloro-9-hydroxy-1,9a-dihydropyrido[1,2-a]pyrimidin-4-one (1.95 g, 36%) as a yellow solid; ¹H NMR (400 MHz, DMSO) δ 6.54 (1H, s), 7.35 - 7.42 (1H, m), 7.46 (1H, dd), 8.58 (1H, dd), 10.90 (1H, s); m/z: 196.97 (MH⁺).

(c) *9-hydroxy-2-[(3R)-3-methylmorpholin-4-yl]-1,9a-dihydropyrido[1,2-a]pyrimidin-4-one (Y3)*

2-chloro-9-hydroxy-1,9a-dihydropyrido[1,2-a]pyrimidin-4-one (Y2, 500 mg, 2.54 mmol), N-ethyl-N-isopropylpropan-2-amine (0.886 mL, 5.09 mmol) and (R)-3-methylmorpholine (283 mg, 2.80 mmol) were dissolved in ethanol (10 mL) and sealed into a microwave tube. The reaction was heated to 150°C for 2 hours in the microwave reactor and cooled to room temperature. The reaction was incomplete and further (R)-3-methylmorpholine (283 mg, 2.80 mmol) was added and the solution was stirred at 150°C for a further 1 hour. The reaction mixture was filtered, then purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 9-hydroxy-2-[(3R)-3-methylmorpholin-4-yl]-1,9a-dihydropyrido[1,2-a]pyrimidin-4-one (85 mg, 12.79 %) as a white solid; ¹H NMR (400 MHz, DMSO) δ 1.18 (3H, d), 3.09 (1H, td), 3.40 - 3.48 (1H, td), 3.59 (1H, dd), 3.71 (1H, d),

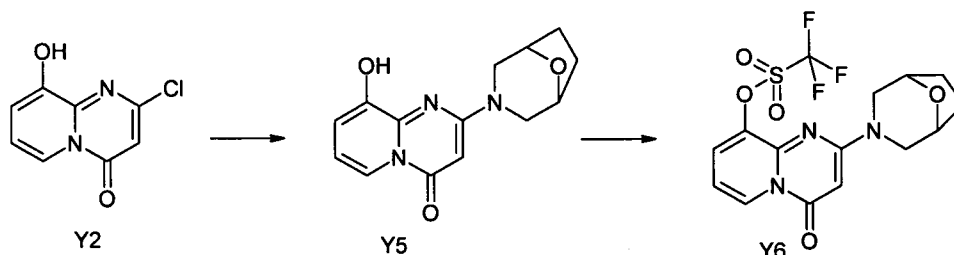
3.92 (1H, dd), 4.31 (1H, s), 4.56 (1H, s), 5.54 (1H, s), 6.93 (1H, t), 7.12 (1H, dd), 8.29 (1H, dd), 9.51 (1H, s); m/z : 262.04 (MH^+).

(d) [[2-[(3R)-3-methylmorpholin-4-yl]-4-oxo-1,9a-dihydropyrido[1,2-a]pyrimidin-9-yl]

5 trifluoromethanesulfonate (Y4)

9-hydroxy-2-[(3R)-3-methylmorpholin-4-yl]-1,9a-dihydropyrido[1,2-a]pyrimidin-4-one (Y4, 83 mg, 0.32 mmol), 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (148 mg, 0.41 mmol) and potassium carbonate (43.9 mg, 0.32 mmol) were suspended in tetrahydrofuran (3 mL) and sealed into a microwave tube. The reaction was heated to 120°C
10 for 12 minutes in the microwave reactor and cooled to room temperature. The reaction mixture was filtered, and then purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford [[2-[(3R)-3-methylmorpholin-4-yl]-4-oxo-
15 1,9a-dihydropyrido[1,2-a]pyrimidin-9-yl] trifluoromethanesulfonate (75 mg, 60%) as a white solid; 1H NMR (400 MHz, DMSO) δ 1.21 (3H, d), 3.19 (1H, td), 3.45 (1H, td), 3.55 - 3.64 (1H, m), 3.73 (1H, d), 3.94 (1H, dd), 4.02 (1H, d), 4.52 (1H, s), 5.65 (1H, s), 7.11 (1H, t), 8.09 (1H, dd), 8.78 (1H, dd); m/z : 394.09 (MH^+).

20 [2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-4-oxopyrido[1,2-a]pyrimidin-9-yl] trifluoromethanesulfonate



(e) 9-hydroxy-2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrido[1,2-a]pyrimidin-4-one (Y5)

2-chloro-9-hydroxy-1,9a-dihydropyrido[1,2-a]pyrimidin-4-one (Y2, 383 mg, 1.95 mmol), N-ethyl-N-isopropylpropan-2-amine (0.407 mL, 2.34 mmol) and (8-oxa-3-
25 azabicyclo[3.2.1]octane (350 mg, 2.34 mmol) were dissolved in ethanol (10 mL) and sealed into a microwave tube. The reaction was heated to 150°C for 2 hours in the microwave reactor and cooled to room temperature. The reaction mixture was filtered then purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100
30 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness

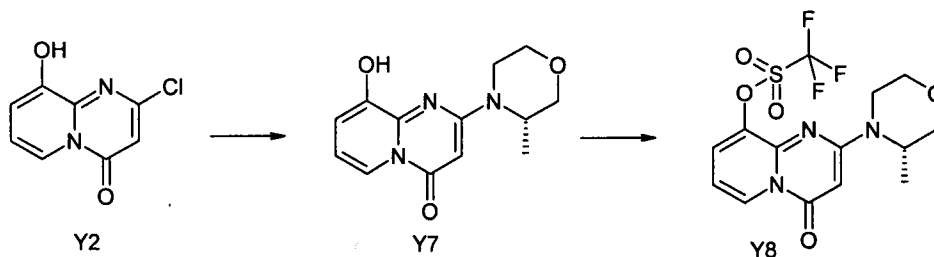
to afford 9-hydroxy-2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrido[1,2-a]pyrimidin-4-one (270 mg, 50.7 %) as a white solid; ¹H NMR (400 MHz, DMSO) δ 1.75 (4H, ddd), 3.01 (2H, d), 4.21 (2H, br s), 4.41 (2H, d), 5.49 (1H, s), 6.93 (1H, t), 7.12 (1H, dd), 8.29 (1H, dd), 9.47 (1H, s); m/z: 274.07 (MH⁺).

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(f) [2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-4-oxopyrido[1,2-a]pyrimidin-9-yl] trifluoromethanesulfonate (Y6)

9-hydroxy-2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrido[1,2-a]pyrimidin-4-one (Y5, 266 mg, 0.97 mmol), 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (452 mg, 1.27 mmol) and potassium carbonate (135 mg, 0.97 mmol) were suspended in tetrahydrofuran (3 mL) and sealed into a microwave tube. The reaction was heated to 120°C for 12 minutes in the microwave reactor and cooled to room temperature. The reaction mixture was filtered, then evaporated to dryness and redissolved in EtOAc (100 mL), and washed with water (100 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford [2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-4-oxopyrido[1,2-a]pyrimidin-9-yl] trifluoromethanesulfonate (560 mg, 142 %); ¹H NMR (400 MHz, DMSO) δ 1.72 (2H, dd), 1.86 (2H, dd), 3.18 (2H, dd), 3.75 - 4.32 (2H, m), 4.43 (2H, d), 5.65 (1H, s), 7.15 (1H, t), 8.14 (1H, d), 8.82 (1H, d); m/z: 406.05 (MH⁺).

20 [2-[(3S)-3-methylmorpholin-4-yl]-4-oxopyrido[1,2-a]pyrimidin-9-yl] trifluoromethanesulfonate



(g) 9-hydroxy-2-[(3S)-3-methylmorpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one (Y7)

2-chloro-9-hydroxy-2,3,4,9-tetrahydropyrido[1,2-a]pyrimidin-4-one (Y2, 590 mg, 3.00 mmol) and (S)-3-methylmorpholine (607 mg, 6 mmol) were dissolved in ethanol (10 mL) and sealed into a microwave tube. The reaction was heated to 150°C for 3 hours in the microwave reactor and cooled to room temperature. The reaction was incomplete and further (S)-3-methylmorpholine (0.202 g, 2 mmol) was added and the solution was stirred at 150 °C for a further 1 hour. The reaction mixture was filtered then purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 9-hydroxy-

2-[(3S)-3-methylmorpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one (352 mg, 45%) as an off white solid; ^1H NMR (400 MHz, DMSO) δ 1.18 (3H, d), 3.09 (1H, td), 3.43 (1H, td), 3.59 (1H, dd), 3.71 (1H, d), 3.92 (1H, dd), 4.30 (1H, d), 4.56 (1H, s), 5.54 (1H, s), 6.93 (1H, t), 7.12 (1H, dd), 8.29 (1H, dd), 9.49 (1H, s); m/z: 262.09 (MH^+).

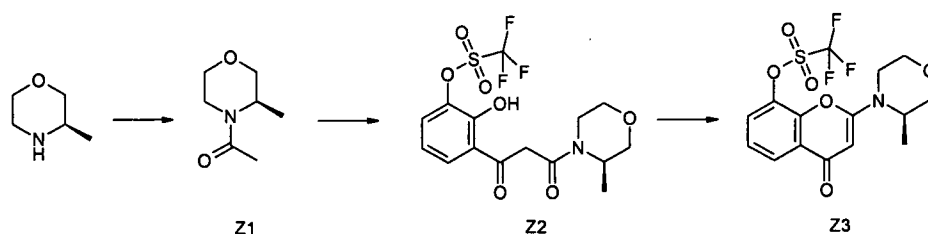
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(h) [2-[(3S)-3-methylmorpholin-4-yl]-4-oxopyrido[1,2-a]pyrimidin-9-yl] trifluoromethanesulfonate (Y8)

9-hydroxy-2-[(3S)-3-methylmorpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one (Y7, 348 mg, 1.33 mmol), 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (619 mg, 1.73 mmol) and potassium carbonate (184 mg, 1.33 mmol) were suspended in tetrahydrofuran (3 mL) and sealed into a microwave tube. The reaction was heated to 120 °C for 12 minutes in the microwave reactor and cooled to room temperature. The reaction mixture was filtered, then evaporated to dryness and redissolved in EtOAc (100 mL), and washed with water (100 mL). The organic layer was dried over MgSO_4 , filtered and evaporated to afford 2-[(3S)-3-methylmorpholin-4-yl]-4-oxopyrido[1,2-a]pyrimidin-9-yl trifluoromethanesulfonate (822 mg, 157 %); m/z: 394.09 (MH^+).

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Z: [2-[(3R)-3-methylmorpholin-4-yl]-4-oxochromen-8-yl] trifluoromethanesulfonate



(b) [2-hydroxy-3-[3-[(3R)-3-methylmorpholin-4-yl]-3-oxopropanoyl]phenyl] trifluoromethanesulfonate (Z2)

A solution of butyllithium (7.00 mL, 11.20 mmol) in hexanes was added to a stirred solution of diisopropylamine (1.583 mL, 11.20 mmol) in tetrahydrofuran (50 mL) at -78°C under nitrogen. The resulting solution was allowed to warm to -50°C then cooled back down to -77°C and stirred for 30 minutes. A solution of (1-[(3R)-3-methylmorpholin-4-yl]ethanone (Z1, 0.458 g, 3.2 mmol) in tetrahydrofuran (20 mL) was added dropwise. The reaction mixture was stirred at -70°C for 30 minutes. A solution of methyl 2-hydroxy-3-(trifluoromethylsulfonyloxy)benzoate (J. Med. Chem., **2005**, 48, 7829, 0.961 g, 3.20 mmol) in tetrahydrofuran (10 mL) was added dropwise and the resulting solution was stirred at -77°C for 2 hours then allowed to warm slowly to room temperature. The reaction mixture was cooled to 0°C and quenched with saturated NH₄Cl (10 mL). The reaction mixture was evaporated to dryness and redissolved in EtOAc (200 mL), and washed sequentially with water (200 mL) and saturated brine (50 mL). The organic layer was dried over MgSO₄, filtered and evaporated and the residue was azeotroped with toluene to afford crude [2-hydroxy-3-[3-[(3R)-3-methylmorpholin-4-yl]-3-oxopropanoyl]phenyl] trifluoromethanesulfonate (0.00 µg). The product was used as is in the next step.

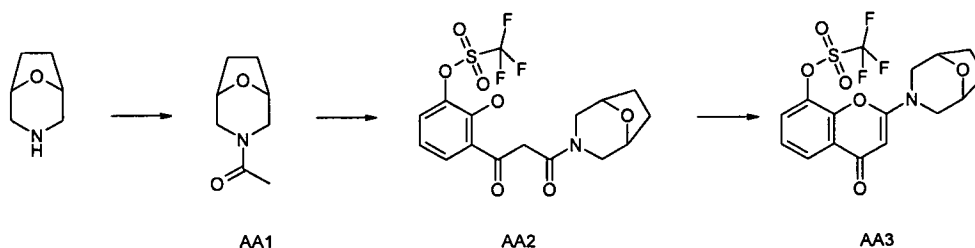
(c) (i) [2-[(3R)-3-methylmorpholin-4-yl]-4-oxochromen-8-yl] trifluoromethanesulfonate (Z3) and 8-hydroxy-2-[(3R)-3-methylmorpholin-4-yl]chromen-4-one

Trifluoromethanesulfonic anhydride (1.541 mL, 9.12 mmol) was added dropwise to ([2-hydroxy-3-[3-[(3R)-3-methylmorpholin-4-yl]-3-oxopropanoyl]phenyl] trifluoromethanesulfonate (Z2, 1316 mg, 3.2 mmol) in dichloromethane (100 mL) at 0°C over a period of 5 minutes under nitrogen. The resulting solution was stirred at room temperature for 18 hours. The reaction mixture was evaporated onto silica gel (10 g) then purified by flash silica chromatography, elution gradient 0 to 20% MeOH in DCM. Pure fractions were evaporated to dryness to afford [2-[(3R)-3-methylmorpholin-4-yl]-4-oxochromen-8-yl] trifluoromethanesulfonate (10.80 mg, 0.858 %) as a brown solid (m/z: 394.02 (MH⁺)), and (8-hydroxy-2-[(3R)-3-methylmorpholin-4-yl]chromen-4-one (76 mg, 9.09 %) as a brown solid m/z: 262.04 (MH⁺).

(ii) [2-[(3R)-3-methylmorpholin-4-yl]-4-oxochromen-8-yl] trifluoromethanesulfonate (8-hydroxy-2-[(3R)-3-methylmorpholin-4-yl]chromen-4-one (76 mg, 0.29 mmol), from the previous step, 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (135 mg, 0.38 mmol) and potassium carbonate (40.2 mg, 0.29 mmol) were suspended in

tetrahydrofuran (3 mL) and sealed into a microwave tube. The reaction was heated to 120°C for 12 minutes in the microwave reactor and cooled to room temperature. The reaction mixture was filtered, then evaporated to dryness and redissolved in EtOAc (100 mL), and washed with water (100 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford [2-[(3R)-3-methylmorpholin-4-yl]-4-oxochromen-8-yl] trifluoromethanesulfonate (24.80 mg, 22%); m/z: 394.02 (MH⁺).

AA: [2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-4-oxochromen-8-yl] trifluoromethanesulfonate



(a) 1-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)ethanone (AA1)

Acetic anhydride (0.628 mL, 6.68 mmol) was added to 8-oxa-3-azabicyclo[3.2.1]octane hydrochloride (1 g, 6.68 mmol), MP-carbonate (8.88 g, 20.05 mmol) and diisopropylamine (0.043 mL, 0.33 mmol) in THF (70 mL) under nitrogen. The resulting suspension was stirred very slowly at room temperature for 18 hours. The reaction mixture was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using THF (30 mL) and pure fractions were evaporated to dryness to afford 1-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)ethanone (1.1 g, 106 %) as a colourless oil; ¹H NMR (400 MHz, CDCl₃) δ 1.66 - 1.83 (2H, m), 1.85 - 2.02 (2H, m), 2.06 (3H, dd), 2.90 (1H, t), 3.33 - 3.46 (2H, m), 4.14 (1H, t), 4.30 - 4.43 (2H, m).

(b) [2-hydroxy-3-[3-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-3-oxopropanoyl]phenyl] trifluoromethanesulfonate (AA2)

A solution of butyllithium (14.62 mL, 23.39 mmol) in hexanes was added to a stirred solution of diisopropylamine (3.31 mL, 23.39 mmol) in tetrahydrofuran (100 mL) at -78°C under nitrogen. The resulting solution was stirred at -70°C for 30 minutes. A solution of 1-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)ethanone (AA1, 1.037 g, 6.68 mmol) in tetrahydrofuran (20 mL) was added dropwise and the resulting solution was stirred at -70°C for 30 minutes. A solution of methyl 2-hydroxy-3-(trifluoromethylsulfonyloxy)benzoate (2.006 g, 6.68 mmol) in tetrahydrofuran (20 mL) was added dropwise and the resulting solution was stirred at -77°C for 2 hours then allowed to warm to room temperature. The reaction mixture was cooled to 0°C and quenched with saturated NH₄Cl (10 mL). The reaction mixture was evaporated to

dryness and redissolved in EtOAc (200 mL), and washed sequentially with water (200 mL) and saturated brine (50 mL). The organic layer was dried over MgSO_4 , filtered and evaporated and the residue was azeotroped with toluene to afford crude product that was used as is; m/z : 422.05 (MH^+).

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(c) [2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-4-oxochromen-8-yl] trifluoromethanesulfonate (AA3)

Trifluoromethanesulfonic anhydride (3.22 mL, 19.04 mmol) was added dropwise to [2-hydroxy-3-[3-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-3-oxopropanoyl]phenyl]

10 trifluoromethanesulfonate (AA2, 2.83 g, 6.68 mmol) in dichloromethane (100 mL) at 0°C over a period of 5 minutes under nitrogen. The resulting solution was stirred at room temperature for 18 hours. Silica gel (10 g) was added and the mixture evaporated to dryness. The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford [2-(8-oxa-3-

15 azabicyclo[3.2.1]octan-3-yl)-4-oxochromen-8-yl] trifluoromethanesulfonate

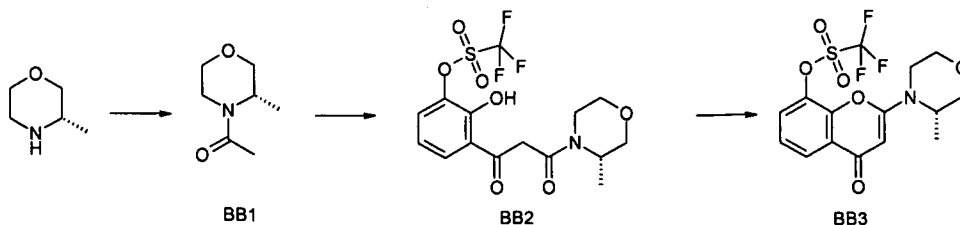
(0.700 g, 25.9 %) as a brown solid. One mixed fraction from the column was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford [2-

20 (8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-4-oxochromen-8-yl] trifluoromethanesulfonate (0.019 g, 0.7 %) as a yellow solid. The two samples were combined and dissolved in a mixture of DME:water:ACN (2:1:1) (20 mL) then purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. Fractions containing

25 the desired compound were evaporated to dryness to afford [2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-4-oxochromen-8-yl] trifluoromethanesulfonate (0.250 g, 9.23 %) as a white solid; ^1H NMR (400 MHz, CDCl_3) δ 1.82 - 1.92 (2H, m), 2.01 - 2.11 (2H, m), 3.35 (2H, dd), 3.65 (2H, d), 4.52 (2H, d), 5.45 (1H, s), 7.37 (1H, t), 7.47 (1H, dd), 8.16 (1H, dd); m/z : 406.05 (MH^+).

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BB: [2-[(3S)-3-methylmorpholin-4-yl]-4-oxochromen-8-yl] trifluoromethanesulfonate



5 was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was washed with saturated NaHCO₃ (75 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford 1-[(3S)-3-methylmorpholin-4-yl]ethanone (1.520 g, 35.8 %) as a colourless
10 liquid; ¹H NMR (400 MHz, CDCl₃, NB mixture of rotamers) δ 1.15 - 1.41 (6H, m), 2.08 (6H, dd), 2.91 - 3.08 (1H, m), 3.33 - 3.65 (6H, m), 3.70 (2H, d), 3.80 (1H, t), 3.91 (2H, dd), 4.26 (1H, d), 4.59 (1H, d).

15 *trifluoromethanesulfonate (BB2)*

20 (trifluoromethylsulfonyloxy)benzoate (2.097 g, 6.98 mmol) in tetrahydrofuran (5 mL) was added dropwise and the resulting solution was stirred at -70°C for 30 minutes then allowed to warm to room temperature. The reaction mixture was quenched with saturated NH₄Cl (5 mL) and diluted with water (100 mL). The mixture was adjusted to pH 7 with 2M HCl (5 mL) then extracted with EtOAc (2 x 100 mL), the organic layer was dried over MgSO₄, filtered
25 and evaporated onto silica gel (10 g). The resulting powder was purified by flash silica chromatography, elution gradient 30 to 100% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford [2-hydroxy-3-[3-[(3S)-3-methylmorpholin-4-yl]-3-oxopropanoyl]phenyl] trifluoromethanesulfonate (1.250 g, 44%) as a yellow solid; m/z : 412.08 (MH⁺).

30 (c) 2-[(3S)-3-methylmorpholin-4-yl]-4-oxochromen-8-yl] trifluoromethanesulfonate and 8-hydroxy-2-[(3S)-3-methylmorpholin-4-yl]chromen-4-one (BB3)

35 trifluoromethanesulfonate (BB2, 1.25 g, 3.04 mmol) in dichloromethane (100 mL) at 0°C over

trifluoromethanesulfonate (BB2, 1.25 g, 3.04 mmol) in dichloromethane (100 mL) at 0°C over

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Chloroacetyl chloride (42.2 mL, 529.53 mmol) was added dropwise to a suspension of Potassium carbonate (95 g, 688.38 mmol) and (2R)-2-aminobutan-1-ol (50 mL, 529.53 mmol) in water (0.143 mL, 7.94 mmol) and dichloromethane (472 mL) at 0°C, adjusting the addition rate to keep the reaction temperature kept below 10°C during addition. The reaction mixture was stirred at 0°C for 1.5 hours, filtered through a celite pad and the filter cake washed with dichloromethane (472 mL) and tetrahydrofuran (500 mL). The combined organics were evaporated to dryness to give 2-chloro-N-[(2R)-1-hydroxybutan-2-yl]acetamide (86 g, 519 mmol, 98 %) as a pale oil (crystallised on standing) which was reacted on directly.

(b) (5R)-5-ethylmorpholin-3-one (CC2)

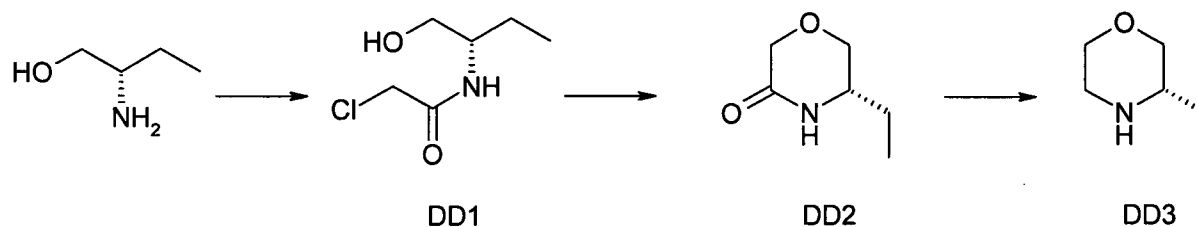
A solution of sodium tert-butoxide (49.9 g, 519.27 mmol) in tetrahydrofuran (430 mL) was added dropwise to a solution of 2-chloro-N-[(2R)-1-hydroxybutan-2-yl]acetamide (CC1, 86 g, 519.27 mmol) in tetrahydrofuran (1290 mL) at 0°C over 30 minutes. The reaction mixture was stirred at 0°C for 1 hour then warmed to 20°C for 1 hour. TLC implied that there was still starting material present. The reaction was cooled to 15°C and further sodium tert-butoxide (25.96 g, 270.03 mmol) added portionwise as a solid (slight exotherm). The reaction mixture was filtered through celite pad, washing the filter cake well with tetrahydrofuran (3 x 430 mL). The combined organics were concentrated to dryness to give a pale oil. The crude product was purified by chromatography on silica, eluting with EtOAc to afford (5R)-5-ethylmorpholin-3-one (30.35 g, 235 mmol, 45.3 %) as a pale oil that crystallised on standing; ¹H NMR (400 MHz, CDCl₃) δ 0.97 (3H, t), 1.52 - 1.62 (2H, m), 3.43 - 3.50 (2H, m), 3.88 - 3.94 (1H, m), 4.11 (1H, d), 4.19 (1H, d), 6.45 (1H, s).

(c) (3R)-3-ethylmorpholine hemi oxalate salt (CC3)

A solution of (5R)-5-ethylmorpholin-3-one (CC2, 17.8 g, 137.82 mmol) in tetrahydrofuran (89 mL) was added dropwise to Lithium aluminum hydride (1.0M in THF) (138 mL, 137.82 mmol) at 5°C (Exothermic, effervescence, addition rate adjusted to keep reaction temperature <10°C, added over 25 minutes). The reaction mixture was allowed to warm to room temperature over 16 hours. TLC showed traces of starting material remaining so further Lithium aluminum hydride (2.0M in THF) (17.23 mL, 34.45 mmol) was added. The reaction mixture was stirred for a further five hours, diluted with addition of tetrahydrofuran (89 mL) and cooled to 5°C. A solution of potassium sodium (2R,3R)-2,3-tartrate tetrahydrate (24.31 g, 86.14 mmol) in water (0.5 w/w of tartrate salt) (12.40 mL, 689.08 mmol) prepared by heating to 50°C, cooled before addition) was added dropwise to the reaction mixture. The resulting suspension was filtered, washing the solid residue with tetrahydrofuran (2 x 89 mL). The combined organics were evaporated to near dryness, then dissolved in ethyl acetate (178 mL), dried over MgSO₄ and filtered. A solution of oxalic acid (6.20 g, 68.91 mmol) in ethanol (26.7 mL, 206.73 mmol) was added dropwise to the ethyl acetate solution of product with stirring, the reaction was stirred for 45 minutes, then a solid product collected by filtration. This was washed well with EtOAc, dried under vacuum at room temperature for 24 hours to give (3R)-3-ethylmorpholine, hemi oxalate (13.20 g, 82 mmol, 60%) as an off-white solid; ¹H NMR (400 MHz, D₂O) δ 0.97 (3H, t), 1.58 - 1.66 (2H, m), 3.20 - 3.33 (2H, m), 3.33 - 3.38 (1H, m), 3.52 - 3.58 (1H, m), 3.73 - 3.80 (1H, m), 4.02 - 4.11 (2H, m)

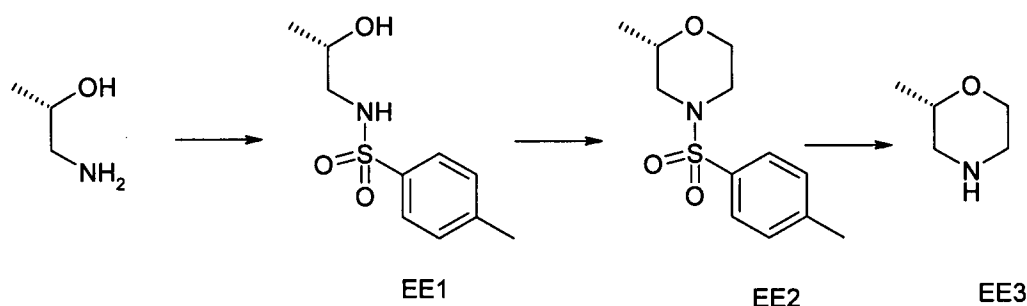
(exchangeables not observed); ^{13}C NMR (176.0 MHz, D_2O) δ 8.71, 21.87, 43.03, 56.03, 63.42, 67.73, 169.33

DD: (3S)-3-ethylmorpholine hemi oxalate salt



(3S)-3-ethylmorpholine hemi oxalate salt (DD3) was prepared in the same manner to that described above for CC3. The yields were 92, 58 and 44% for the 3 steps.

EE: (2S)-2-methylmorpholine



(a) *N*-[(2S)-2-hydroxypropyl]-4-methylbenzenesulfonamide (EE1)

4-methylbenzene-1-sulfonyl chloride (42.2 g, 221.28 mmol) was added portionwise to a stirred solution of triethylamine (93 mL, 663.83 mmol) and (2S)-1-aminopropan-2-ol (17.42 mL, 221.28 mmol) in CH_2Cl_2 (1326 mL) at 0°C , over a period of 1 hour under air. The resulting solution was stirred at room temperature for 4 hours. The reaction mixture was washed with 2M HCl (1L) followed by saturated NaHCO_3 (1L) and then with saturated brine (1L). The organic layer was collected, dried with MgSO_4 and evaporated to yield *N*-[(2S)-2-hydroxypropyl]-4-methylbenzenesulfonamide (44.8 g, 88 %) which was used without further purification; ^1H NMR (400 MHz, CDCl_3) δ 1.08 (3H, d), 2.36 (3H, s), 2.92 - 3.01 (1H, m), 3.77 - 3.88 (1H, m), 5.04 - 5.16 (1H, m), 7.24 (2H, d), 7.68 (2H, d); m/z : 230.34 (MH^+).

(b) (2S)-2-methyl-4-(4-methylphenyl)sulfonylmorpholine (EE2)

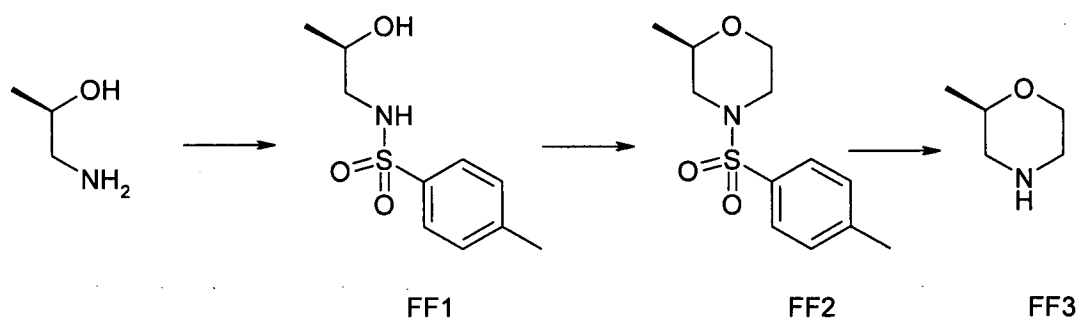
Sodium hydride (11.84 g, 296.08 mmol) was added portionwise to *N*-[(2S)-2-hydroxypropyl]-4-methylbenzenesulfonamide (EE1, 19.40 g, 84.59 mmol) in CH_2Cl_2 (2 L) at 0°C under nitrogen. The resulting suspension was stirred at 0°C for 15 minutes, after this time (2-bromoethyl)diphenylsulfonium trifluoromethanesulfonate (45 g, 101.51 mmol) was added

and the solution stirred at 0°C for 1 hours. The cooling bath was removed and the reaction mixture allowed to warm to room temperature and stirred for 5 hours. The reaction mixture was quenched with saturated NH₄Cl (2 L), extracted with CH₂Cl₂ (2 x 1 L), the organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford (2S)-2-methyl-4-(4-methylphenyl)sulfonylmorpholine (13.29 g, 61.5 %) as an orange oil which crystallised on standing; ¹H NMR (400 MHz, CDCl₃) δ 1.06 (3H, d), 1.91 - 2.00 (1H, m), 2.26 - 2.35 (1H, m), 2.37 (3H, s), 3.40 - 3.51 (2H, m), 3.56 - 3.65 (2H, m), 3.77 - 3.83 (1H, m), 7.27 (2H, d), 7.56 (2H, d); m/z: 256.19 (MH⁺).

(c) (2S)-2-methylmorpholine (EE3)

A solution of (2S)-2-methyl-4-(4-methylphenyl)sulfonylmorpholine (EE2, 13.26 g, 51.93 mmol), phenol (9.77 g, 103.86 mmol) and 33% HBr in acetic acid (89 mL, 363.52 mmol) was stirred at room temperature for 6 hours. The reaction mixture was evaporated to dryness. The crude oil was triturated with Et₂O to give a solid which was collected by filtration and dried under vacuum to give (2S)-2-methylmorpholine hydrobromide (6.77 g, 72%) as a white solid; ¹H NMR (400 MHz, DMSO) δ 1.18 (3H, d), 2.74 (1H, t), 3.01 (1H, td), 3.23 (1H, d), 3.26 (1H, d), 3.73 (1H, td), 3.79 (1H, dqd), 3.98 (1H, dd), 8.86 (2H, s).

FF: (2R)-2-methylmorpholine



(a) N-[(2R)-2-hydroxypropyl]-4-methylbenzenesulfonamide (FF1)

4-methylbenzene-1-sulfonyl chloride (49.9 g, 261.88 mmol) was added portionwise to a stirred solution of triethylamine (110 mL, 785.65 mmol) and (2R)-1-aminopropan-2-ol (19.67 g, 261.88 mmol) in CH₂Cl₂ (1569 mL) at 0°C, over a period of 1 hour under air. The resulting solution was stirred at room temperature for 4 hours. The reaction mixture was diluted with CH₂Cl₂ and washed with 2M HCl (1L) followed by saturated NaHCO₃ (1L) and then with saturated brine (1L). The organic layer was collected, dried with MgSO₄ and evaporated to yield N-[(2R)-2-hydroxypropyl]-4-methylbenzenesulfonamide (57.0 g, 95 %) which was used

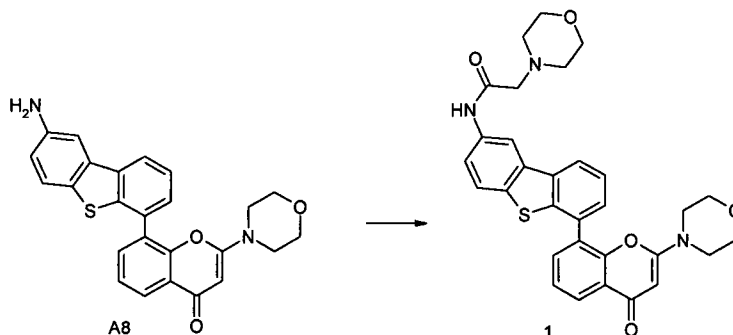
without further purification; ^1H NMR (400 MHz, CDCl_3) δ 1.06 (3H, d), 2.35 (3H, s), 2.64 - 2.76 (1H, m), 2.91 - 3.00 (1H, m), 3.83 (1H, s), 7.23 (2H, d), 7.68 (2H, d); m/z : 252.24 (MH^+).

(b) (2R)-2-methyl-4-(4-methylphenyl)sulfonylmorpholine (FF2)

- 5 Sodium hydride (11.84 g, 296.08 mmol) was added portionwise to N-[(2R)-2-hydroxypropyl]-4-methylbenzenesulfonamide (FF1, 19.40 g, 84.59 mmol) in CH_2Cl_2 (2 L) at 0°C under nitrogen. The resulting suspension was stirred at 0°C for 5 minutes, after this time (2-bromoethyl)diphenylsulfonium trifluoromethanesulfonate (45 g, 101.51 mmol) was added and the solution stirred at 0°C for 1 hours. The cooling bath was removed and the reaction
- 10 mixture allowed to warm to room temperature and stirred for 5 hours. The reaction mixture was quenched with saturated NH_4Cl (2 L), extracted with CH_2Cl_2 (2 x 1 L), the organic layer was dried over MgSO_4 , filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford (2R)-2-methyl-4-(4-
- 15 methylphenyl)sulfonylmorpholine (13.74 g, 63.6 %) as an orange oil which crystallised on standing; ^1H NMR (400 MHz, CDCl_3) δ 1.06 (3H, d), 1.97 (1H, t), 2.31 (1H, t), 2.38 (3H, s), 3.46 (2H, t), 3.61 (2H, t), 3.78 - 3.83 (1H, m), 7.27 (2H, d), 7.56 (2H, d); m/z : 256.26 (MH^+).

(c) (2R)-2-methylmorpholine (FF3)

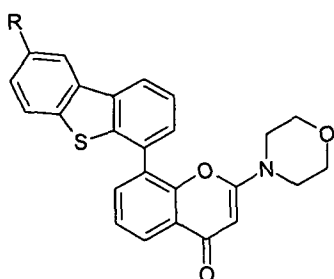
- 20 A solution of (2R)-2-methyl-4-(4-methylphenyl)sulfonylmorpholine (FF2, 13.5 g, 52.87 mmol), phenol (9.95 g, 105.74 mmol) and 33% HBr in acetic acid (91 mL, 370.10 mmol) was stirred at room temperature for 16 hours. The reaction mixture was evaporated to dryness, The crude oil was triturated with Et_2O to give a solid which was collected by filtration and dried under vacuum to give (2R)-2-methylmorpholine hydrobromide (8.28 g, 86 %) as a pink solid ;
- 25 ^1H NMR (400 MHz, DMSO) δ 1.17 (3H, d), 2.73 (1H, t), 3.01 (1H, td), 3.23 (1H, d), 3.26 (1H, d), 3.74 (1H, td), 3.79 (1H, dqd), 3.98 (1H, dd), 8.89 (2H, s).

Example 1

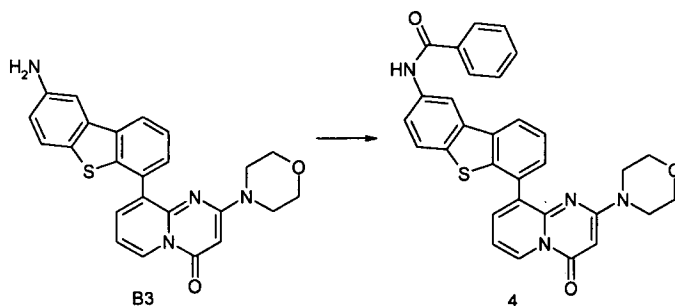
(a) 2-morpholino-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (1)

2-chloroacetyl chloride (16 μ L, 0.18 mmol) was added dropwise to a stirred solution of 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8, 76 mg, 0.18 mmol) in DMA (2 mL) at room temperature. After stirring for 4 hours, the reaction mixture was then treated with a solution of morpholine (47 μ L, 0.53 mmol) in DMA (2 mL) and stirred at room temperature for a further 5 hours. The reaction was then diluted with methanol (2mL). The crude reaction mixture was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3 /MeOH and pure fractions were evaporated to dryness to afford crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 2-morpholino-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (61 mg, 61 %) as a white solid; ^1H NMR (500 MHz, CDCl_3) δ 2.76 (4H, s), 3.05 (4H, t), 3.30 (2H, s), 3.48 (4H, t), 3.86 (4H, s), 5.49 (1H, s), 7.45 - 7.50 (2H, m), 7.45 - 7.51 (1H, m), 7.55 (1H, d), 7.72 (2H, d), 8.22 (1H, d), 8.25 - 8.27 (1H, m), 8.69 (1H, d), 9.32 (1H, s); m/z 556.46 (MH^+).

(b) The procedure described above was repeated using the appropriate amine and 2-chloroacetyl chloride with 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8). The compounds described below were thus obtained:



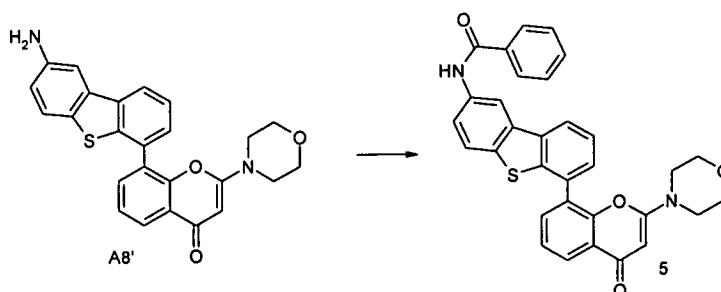
Compound	R	Name and Analytical Data
2		2-(4-ethylpiperazin-1-yl)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide ¹H NMR (500 MHz, CDCl₃) δ 1.18 (3H, s), 2.58 (2H, s), 2.66 (4H, s), 2.79 (4H, s), 3.05 (4H, t), 3.25 (2H, d), 3.48 (4H, t), 5.47 (1H, s), 7.39 - 7.41 (1H, m), 7.46 - 7.48 (2H, m), 7.56 (1H, t), 7.70 - 7.75 (2H, m), 8.22 - 8.27 (2H, m), 8.71 (1H, d), 9.24 (1H, s); m/z: 583.59 (MH⁺).
3		2-(4-(2-hydroxyethyl)piperazin-1-yl)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide ¹H NMR (400 MHz, CDCl₃) δ 2.69 (2H, s), 2.77 (8H, s), 3.00 (4H, t), 3.20 (2H, s), 3.42 (4H, t), 3.68 (2H, s), 5.42 (1H, s), 7.33 - 7.36 (1H, m), 7.41 - 7.44 (2H, m), 7.51 (1H, t), 7.65 (1H, s), 7.68 - 7.70 (2H, m), 8.16 - 8.22 (2H, m), 8.66 (1H, d), 9.14 (1H, s); m/z: 599.53 (MH⁺).

Example 2

N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)benzamide (4)

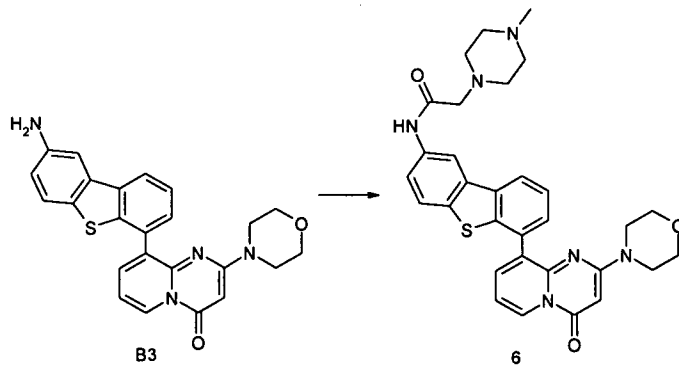
- 5 O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (49 mg, 0.13 mmol) was added in one portion to 9-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (B3, 50 mg, 0.12 mmol), benzoic acid (14 mg, 0.12 mmol) and N,N-diisopropylethylamine (0.051 mL, 0.29 mmol) in DMA (1 mL) at ambient temperature. The resulting solution was stirred at ambient temperature for 3 days. The crude product was
- 10 purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure material.

- The impure material was then purified by preparative LCMS (Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of
- 15 water (containing 1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford *N*-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)benzamide (13 mg, 21 %) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 3.36 (4H, t), 3.57 (4H, t), 5.64 (1H, s), 7.02 (1H, t), 7.52 - 7.62 (6H, m), 7.76 (1H, d), 7.86 - 7.89 (1H, m), 7.94 - 7.96 (2H, m), 8.03 (1H, s), 8.22 - 8.26 (1H, m), 8.77 (1H, d), 9.03 - 9.05 (1H, m); *m/z*: 533.90 MH⁺.
- 20

Example 3

N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)benzamide (5)

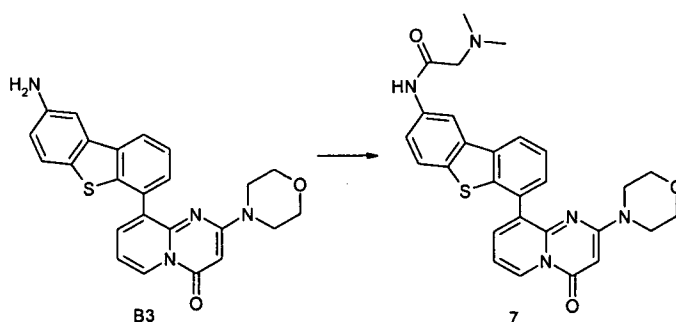
O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (80 mg, 0.21 mmol) was added in one portion to 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8', 75 mg, 0.18 mmol), benzoic acid (24 mg, 0.20 mmol) and N,N-diisopropylethylamine (0.076 mL, 0.44 mmol) in DMA (1.5 mL) at ambient temperature. The resulting solution was stirred at ambient temperature for 3 hours. The reaction was incomplete and further O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (20 mg, 0.05 mmol) was added in one portion and the solution was stirred at ambient temperature for a further 3 days. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)benzamide (37 mg, 40 %) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 3.10 (4H, t), 3.51 (4H, t), 5.60 (1H, s), 7.48 - 7.63 (7H, m), 7.73 - 7.79 (2H, m), 7.95 - 7.97 (2H, m), 8.08 (1H, s), 8.25 - 8.30 (2H, m), 8.83 (1H, d); *m/z*: 533.90 MH⁺.

Example 4*2*-(4-methylpiperazin-1-yl)-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (6)

Chloroacetyl chloride (13 μ l, 0.16 mmol) was added to 9-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (B3, 62 mg, 0.14 mmol) and triethylamine (61 μ l, 0.43 mmol) in anhydrous DMA (1.3 mL) at ambient temperature. The resulting solution was stirred under nitrogen at ambient temperature for 30 minutes. N-Methylpiperazine (64 μ l, 0.58 mmol) was then added and the reaction mixture stirred at ambient temperature for 18 hours. The reaction mixture was diluted with methanol to a total volume of 4 mL, filtered and purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH₃)

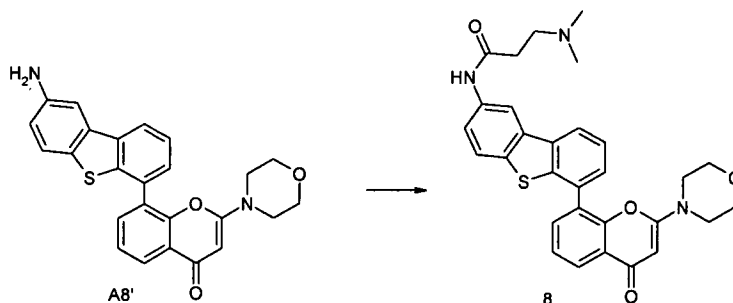
and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 2-(4-methylpiperazin-1-yl)-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (45 mg, 55 %) as a cream solid; ¹H NMR (400 MHz, CDCl₃) δ 2.43 (3H, s), 2.67 (4H, br s), 2.79 (4H, br s), 3.25 (2H, s), 3.35 (4H, t), 3.56 (4H, t), 5.63 (1H, s), 7.02 (1H, t), 7.43 - 7.45 (1H, m), 7.55 - 7.57 (2H, m), 7.72 (1H, d), 7.85 - 7.88 (1H, m), 8.21 - 8.26 (1H, m), 8.66 (1H, d), 9.03 - 9.05 (1H, m), 9.23 (1H, br s); *m/z*: 570.08 MH⁺.

Example 5



2-(dimethylamino)-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (7)

Chloroacetyl chloride (0.020 mL, 0.26 mmol) was added to 9-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (B3, 100 mg, 0.23 mmol) and triethylamine (0.098 mL, 0.70 mmol) in anhydrous DMA (2.88 mL) at ambient temperature. The resulting solution was stirred under nitrogen at ambient temperature for 1 hour. An aliquot of this material, 2-chloro-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide, (1.5 mL, 0.12 mmol) was then added to a 2M solution of dimethylamine in THF (0.176 mL, 0.35 mmol) at ambient temperature and the resulting solution was stirred for 18 hours. The solution was diluted with methanol to a total volume of 4 mL, filtered and purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 2-(dimethylamino)-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (35 mg, 58 %) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.35 (6H, s), 3.15 (2H, s), 3.32 (4H, m), 3.46 (4H, t), 5.67 (1H, s), 7.23 (1H, t), 7.64 (2H, d), 7.78 - 7.81 (1H, m), 7.89 (1H, d), 8.05 - 8.08 (1H, m), 8.25 - 8.28 (1H, m), 8.69 (1H, d), 8.92 - 8.94 (1H, m), 9.93 (1H, s); *m/z*: 514.94 MH⁺.

Example 6

(a) 3-(dimethylamino)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)propanamide (8)

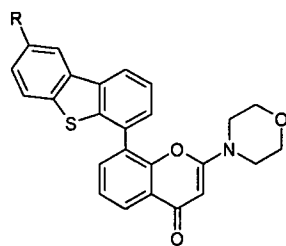
5 β -Bromopropionyl chloride (0.13 mL, 1.29 mmol) was added dropwise to 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8', 500 mg, 1.17 mmol) and triethylamine (0.36 mL, 2.58 mmol) in anhydrous DMA (9.5 mL) at ambient temperature. The resulting solution was stirred under nitrogen at ambient temperature for 90 minutes. An aliquot of this material (2 mL, 0.23 mmol) was added in one portion to an MPS tube

10 containing 2M solution of dimethylamine in THF (0.35 mL, 0.70 mmol) at ambient temperature. The resulting solution was then stirred at 100 °C for 18 hours. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents. Fractions containing the desired compound

15 were evaporated to dryness to afford impure product. The residue was further purified by flash silica chromatography, isocratic elution of 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford 3-(dimethylamino)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)propanamide (59 mg, 47 %) as a cream solid; ¹H NMR (400 MHz, CDCl₃) δ 2.52 (6H, s), 2.69 (2H, t), 2.86 (2H, t), 3.07 (4H, t), 3.48 - 3.50

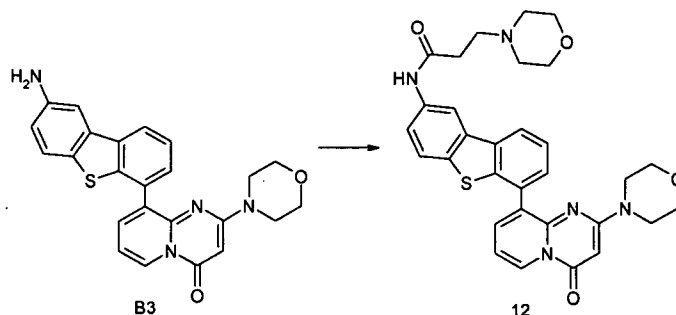
20 (4H, m), 5.50 (1H, s), 7.37 - 7.40 (1H, m), 7.46 - 7.50 (2H, m), 7.56 (1H, t), 7.69 (1H, d), 7.74 - 7.77 (1H, m), 8.22 - 8.24 (1H, m), 8.26 - 8.29 (1H, m), 8.71 (1H, d), 10.94 (1H, s); *m/z*: 528.17 MH⁺.

(b) The procedure described above was repeated using the appropriate amine (0.70 mmol) and beta-bromopropionyl chloride with 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8') (2 mL, 0.23 mmol). The compounds described below were thus obtained:



Compound	R	Name and Analytical Data
9		<i>3-morpholino-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)propanamide</i> ¹H NMR (400 MHz, CDCl₃) δ 2.69 (2H, t), 2.74 (4H, br s), 2.88 (2H, t), 3.07 (4H, t), 3.48 - 3.51 (4H, m), 3.91 (4H, t), 5.50 (1H, s), 7.34 - 7.37 (1H, m), 7.46 - 7.50 (2H, m), 7.57 (1H, t), 7.71 (1H, d), 7.75 - 7.77 (1H, m), 8.21 - 8.24 (1H, m), 8.27 - 8.29 (1H, m), 8.75 (1H, d), 10.86 (1H, s); <i>m/z</i>: 570.17 MH⁺
10		<i>3-(4-ethylpiperazin-1-yl)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)propanamide</i> ¹H NMR (400 MHz, CDCl₃) δ 1.19 (3H, t), 2.57 (2H, q), 2.64 (2H, t), 2.78 (8H, s), 2.86 (2H, t), 3.07 (4H, t), 3.50 (4H, t), 5.49 (1H, s), 7.32 - 7.35 (1H, m), 7.46 - 7.52 (2H, m), 7.57 (1H, t), 7.70 (1H, d), 7.75 - 7.77 (1H, m), 8.21 - 8.24 (1H, m), 8.27 - 8.29 (1H, m), 8.80 (1H, d), 11.01 (1H, br s); <i>m/z</i>: 597.24 MH⁺
11		<i>3-(4-(2-hydroxyethyl)piperazin-1-yl)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)propanamide</i> ¹H NMR (400 MHz, CDCl₃) δ 2.67 (2H, t), 2.71 (2H, t), 2.80 (8H, s), 2.88 (2H, t), 3.07 (4H, t), 3.49 (4H, t), 3.72 (2H, t), 5.49 (1H, s), 7.31 - 7.33 (1H, m), 7.46 - 7.50 (2H, m), 7.57 (1H, t), 7.70 (1H, d), 7.75 - 7.77 (1H, m), 8.21

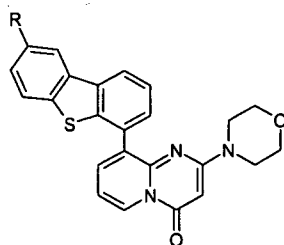
		- 8.24 (1H, m), 8.27 - 8.29 (1H, m), 8.79 (1H, d), 10.82 (1H, s). OH not observed; m/z : 613.21 MH^+
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Example 7

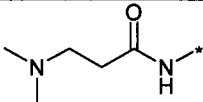
(a) 3-morpholino-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)propanamide (12)

β -Bromopropionyl chloride (0.052 mL, 0.51 mmol) was added dropwise to 9-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (B3, 200 mg, 0.47 mmol) and triethylamine (0.143 mL, 1.03 mmol) in anhydrous DMA (6 mL) at ambient temperature. The resulting solution was stirred under nitrogen at ambient temperature for 90 minutes. An aliquot of this material (1.2 mL, 0.09 mmol) was added to an MPS tube containing morpholine (24 mg, 0.27 mmol) at ambient temperature. The resulting mixture was then stirred at 100°C for 18 hours. The reaction mixture was diluted with methanol to make the total volume up to 4 mL, filtered and purified by preparative HPLC (Waters XBridge Ppep O18 OBD column, 5 μ silica, 19 mm diameter, 100 -i length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 3-morpholino-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)propanamide (23 mg, 45%); 1H NMR (400 MHz, $CDCl_3$) δ 2.91 (6H, s), 3.10 (2H, s), 3.35 (4H, t), 3.56 (4H, t), 3.98 (4H, t), 5.63 (1H, s), 7.01 (1H, t), 7.47 (1H, d), 7.51 - 7.56 (2H, m), 7.70 (1H, d), 7.85 - 7.87 (1H, m), 8.19 - 8.21 (1H, m), 8.67 (1H, d), 9.03 - 9.05 (1H, m), 10.40 (1H, br s); m/z : 571.11 MH^+

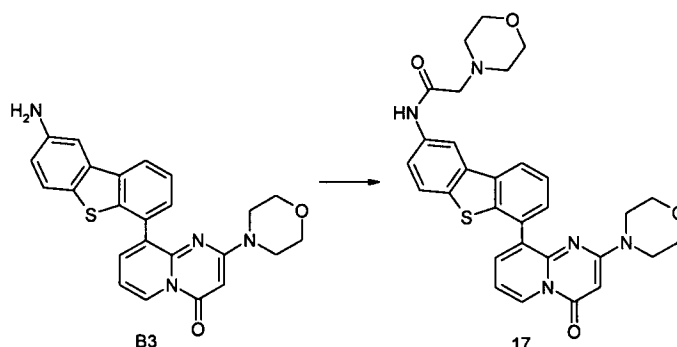
(b) The procedure described above was repeated using the appropriate amine (0.27 mmol) and beta-bromopropionyl chloride with 9-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (B3, 1.2 mL, 0.09 mmol). The compounds described below were thus obtained:



Compound	R	Name and Analytical Data
13		<i>3-(4-methylpiperazin-1-yl)-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)propanamide</i> ¹H NMR (400 MHz, CDCl₃) δ 2.48 (3H, s), 2.71 (2H, t), 2.79 (4H, s), 2.84 - 2.88 (4H, m), 2.94 (2H, t), 3.35 (4H, t), 3.56 (4H, t), 5.62 (1H, s), 7.01 (1H, t), 7.38 - 7.41 (1H, m), 7.52 - 7.56 (2H, m), 7.69 (1H, d), 7.85 - 7.87 (1H, m), 8.19 - 8.23 (1H, m), 8.71 (1H, d), 9.03 - 9.05 (1H, m), 10.48 (1H, br s); <i>m/z</i>: 584.15 MH⁺.
14		<i>3-(4-ethylpiperazin-1-yl)-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)propanamide</i> ¹H NMR (400 MHz, CDCl₃) δ 1.27 (3H, t), 2.61 - 3.05 (14H, m), 3.35 (4H, t), 3.56 (4H, t), 5.62 (1H, s), 7.01 (1H, t), 7.39 - 7.42 (1H, m), 7.52 - 7.56 (2H, m), 7.69 (1H, d), 7.85 - 7.87 (1H, m), 8.19 - 8.23 (1H, m), 8.71 (1H, d), 9.03 - 9.05 (1H, m), 10.20 (1H, br s); <i>m/z</i>: 598.21 MH⁺.
15		<i>3-(4-(2-hydroxyethyl)piperazin-1-yl)-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)propanamide</i> ¹H NMR (400 MHz, CDCl₃) δ 2.71 - 2.73 (4H, m), 2.81 - 2.95 (10H, m), 3.28 (4H, t), 3.49 (4H, t), 3.70 (2H, t), 5.55 (1H, s), 6.94 (1H, t), 7.32 - 7.35 (1H, m), 7.45 - 7.49 (2H, m), 7.62

		(1H, d), 7.78 - 7.80 (1H, m), 8.11 - 8.16 (1H, m), 8.63 (1H, d), 8.95 - 8.98 (1H, m), 10.21 (1H, br s) OH not observed; m/z : 614.17 MH^+ .
16		<i>3-(dimethylamino)-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)propanamide</i> 1H NMR (400 MHz, $CDCl_3$) δ 2.63 (6H, s), 2.87 (2H, t), 3.06 (2H, t), 3.35 (4H, t), 3.54 - 3.57 (4H, m), 5.62 (1H, s), 7.01 (1H, t), 7.46 - 7.55 (3H, m), 7.68 (1H, d), 7.84 - 7.86 (1H, m), 8.18 - 8.23 (1H, m), 8.64 - 8.66 (1H, m), 9.02 - 9.05 (1H, m), 10.51 (1H, br s); m/z: 529.01 MH^+.

Example 8

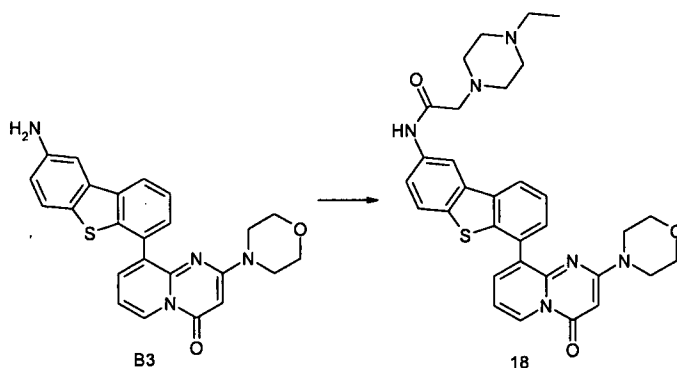


2-morpholino-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (17)

Chloroacetyl chloride (15 μ l, 0.19 mmol) in anhydrous DMA (1 mL) was added to 9-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (75 mg, 0.18 mmol) and triethylamine (B3, 49 μ l, 0.35 mmol) in anhydrous DMA (1 mL) at ambient temperature. The resulting solution was stirred under nitrogen at ambient temperature for 3 hours and then morpholine (183 μ l, 2.10 mmol) was added and the reaction mixture stirred at ambient temperature for a further 1 hour. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3 /MeOH and evaporated to dryness to afford impure product. The residue was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to

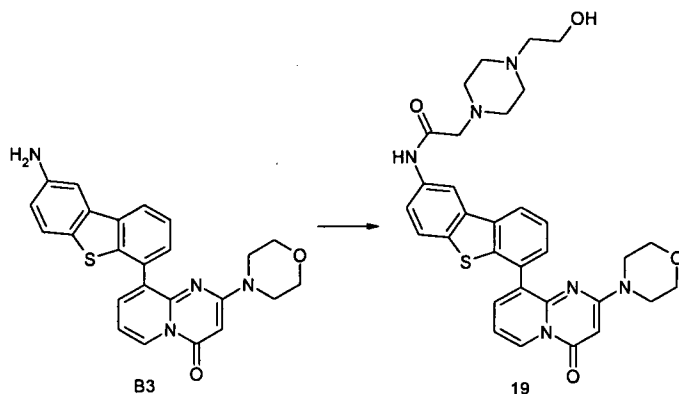
dryness to afford 2-morpholino-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (54 mg, 56 %) as a white solid; ^1H NMR (400 MHz, DMSO- d_6) δ 2.57 (4H, t), 3.21 (2H, s), 3.31 (4H, t), 3.45 (4H, t), 3.69 (4H, t), 5.68 (1H, s), 7.23 (1H, t), 7.61 - 7.66 (1H, m), 7.65 (1H, s), 7.73 - 7.76 (1H, m), 7.91 (1H, d), 8.06 - 8.08 (1H, m), 8.27 - 8.29 (1H, m), 8.66 (1H, d), 8.92 - 8.94 (1H, m), 9.98 (1H, s); m/z : 556.77 MH^+ .

Example 9



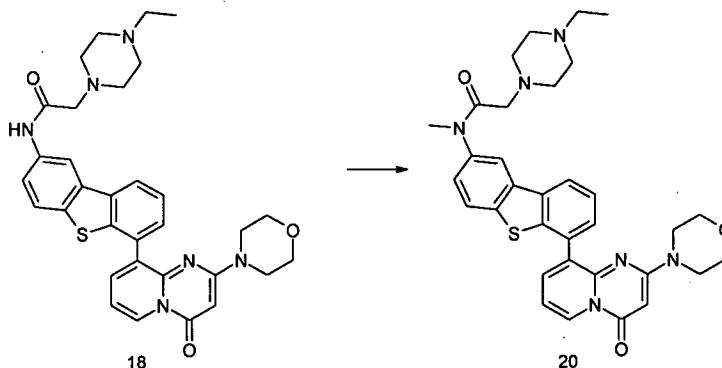
2-(4-ethylpiperazin-1-yl)-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (18)

Chloroacetyl chloride (132 μl , 1.66 mmol) in anhydrous DMA (1 mL) was added to 9-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (B3, 71 mg, 0.17 mmol) and triethylamine (46 μl , 0.33 mmol) in anhydrous DMA (1 mL) at ambient temperature. The resulting solution was stirred under nitrogen at ambient temperature for 3 hours and then N-ethylpiperazine (631 μl , 4.97 mmol) added and the reaction mixture stirred at ambient temperature for a further 1 hour. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3/MeOH and evaporated to dryness to afford impure product. The residue was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 2-(4-ethylpiperazin-1-yl)-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (59 mg, 61 %) as a white solid; ^1H NMR δ 1.01 (3H, t), 2.35 (2H, q), 2.46 (4H, s), 2.58 (4H, s), 3.19 (2H, s), 3.32 (4H, t), 3.45 (4H, t), 5.68 (1H, s), 7.23 (1H, t), 7.61 - 7.66 (1H, m), 7.65 (1H, s), 7.73 - 7.76 (1H, m), 7.91 (1H, d), 8.06 - 8.08 (1H, m), 8.28 - 8.30 (1H, m), 8.66 (1H, d), 8.92 - 8.94 (1H, m), 9.92 (1H, s); m/z : 583.89 MH^+ .

Example 10

2-(4-(2-hydroxyethyl)piperazin-1-yl)-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (19)

- 5 Chloracetyl chloride (93 μ L, 1.17 mmol) in anhydrous DMA (1 mL) was added to 9-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (B3, 50 mg, 0.12 mmol) and triethylamine (33 μ L, 0.23 mmol) in anhydrous DMA (1 mL) at ambient temperature. The resulting solution was stirred under nitrogen at ambient temperature for 3 hours and then 1-(2-hydroxyethyl)piperazine (456 mg, 3.50 mmol) added and the reaction mixture stirred at ambient temperature for a further 1 hour. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3 /MeOH and evaporated to dryness to afford impure product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 2-(4-(2-hydroxyethyl)piperazin-1-yl)-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (57 mg, 82 %) as a white solid; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 2.42 (2H, t), 2.57 (4H, s), 3.18 (2H, s), 3.32 (4H, t), 3.46 (4H, t), 3.49 - 3.53 (2H, m), 4.41 (1H, t), 5.68 (1H, s), 7.23 (1H, t), 7.61 - 7.66 (1H, m), 7.65 (1H, s), 7.73 - 7.76 (1H, m), 7.91 (1H, d), 8.06 - 8.08 (1H, m), 8.28 - 8.30 (1H, m), 8.66 (1H, d), 8.92 - 8.94 (1H, m), 9.91 (1H, s), one x (4H, m) obscured by solvent; m/z : 599.95 MH^+ .

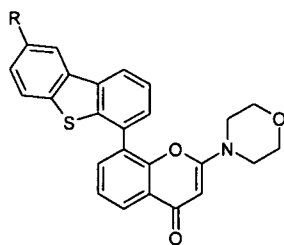
Example 11

2-(4-ethylpiperazin-1-yl)-N-methyl-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (20)

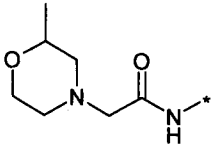
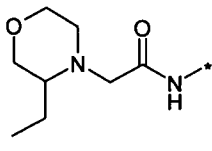
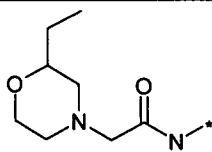
- 5 Sodium hydride, 60% dispersion in mineral oil (7.6 mg, 0.19 mmol) was added portionwise to 2-(4-ethylpiperazin-1-yl)-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (18, 94 mg, 0.16 mmol) in anhydrous DMF (1.6 ml) cooled to 0°C. The resulting mixture was stirred under nitrogen at 0°C for 30 minutes then methyl iodide (11 μ l, 0.17 mmol) was added and the reaction mixture allowed to warm to
- 10 ambient temperature and stirred for a further 1 hour. The reaction mixture was poured into water (50 mL) and diluted with EtOAc (50 mL). The aqueous layer was removed and the organics further washed with water (2 x 50 mL) and saturated brine (50 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ
- 15 silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 2-(4-ethylpiperazin-1-yl)-N-methyl-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (25 mg, 26 %) as a cream solid; ¹H NMR (400 MHz, DMSO-d₆) δ 0.93 (3H, t), 2.21 - 2.35 (9H, m), 2.94 (2H, s), 3.46 (4H, t), 5.68 (1H, s), 7.24 (1H, t), 7.48 (1H, d), 7.63 - 7.68 (2H, m), 8.02 (1H, d), 8.06 - 8.08 (1H, m), 8.42 (1H, s), 8.44 - 8.46 (1H, m), 8.93 - 8.95 (1H, m) 2 x (4H, m) obscured by solvent; m/z: 598.06 MH⁺.
- 20

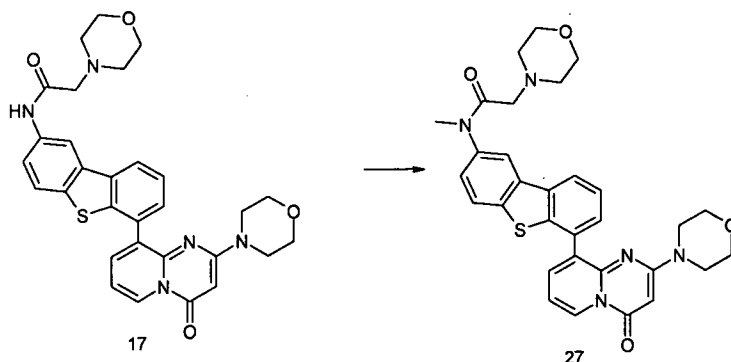
Example 12

- 25 The procedure described above in Example 1 was repeated using the appropriate amine and 2-chloroacetyl chloride with 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8'). The compounds described below were thus obtained:



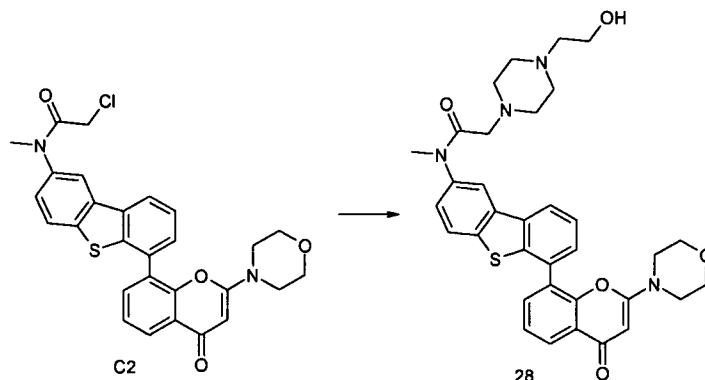
Compound	R	Name and Analytical Data
21		<i>2-(Dimethylamino)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide</i> ¹H NMR (400 MHz, CDCl₃) δ 2.45 (s, 6H), 3.08 (t, 4H), 3.16 (s, 2H), 3.50 (t, 4H), 5.49 (s, 1H), 7.46 - 7.50 (m, 3H), 7.57 (t, 1H), 7.72 - 7.77 (m, 2H), 8.24 (d, 1H), 8.28 (dd, 1H), 8.72 (dd, 1H), 9.33 (s, 1H); <i>m/z</i>: 514 (MH⁺).
22		<i>2-(4-Methylpiperazin-1-yl)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide</i> ¹H NMR (400 MHz, CDCl₃) δ 2.36 (s, 3H), 2.56 (s, 4H), 2.72 (s, 4H), 3.07 (t, 4H), 3.22 (s, 2H), 3.50 (t, 4H), 5.49 (s, 1H), 7.43 (dd, 1H), 7.47 - 7.52 (m, 2H), 7.58 (t, 1H), 7.72 - 7.77 (m, 2H), 8.25 (dd, 1H), 8.28 (dd, 1H), 8.73 (d, 1H), 9.33 (s, 1H); <i>m/z</i>: 570 (MH⁺).
23		<i>2-(2,5-Dimethylmorpholino)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide</i> ¹H NMR (400 MHz, CDCl₃) δ 1.05 (d, 3H), 1.20 (d, 3H), 2.31 (dd, 1H), 2.54 - 2.62 (m, 1H), 2.84 - 2.88 (m, 1H), 2.99 (d, 1H), 3.07 (t, 4H), 3.37 (dd, 1H), 3.50 (t, 4H), 3.53 (d, 1H), 3.72 - 3.80 (m, 1H), 3.84 (dd, 1H), 5.49 (s, 1H), 7.41 - 7.50 (m, 3H), 7.58 (t, 1H), 7.73 - 7.77 (m, 2H), 8.25 (dd, 1H), 8.28 (dd, 1H), 8.71 (d, 1H), 9.40 (s, 1H); <i>m/z</i>: 585 (MH⁺).

24		<i>2-(2-Methylmorpholino)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide</i> ¹H NMR (400 MHz, CDCl₃) δ 1.21 (d, 3H), 2.18 (dd, 1H), 2.46 - 2.52 (m, 1H), 2.78 - 2.86 (m, 2H), 3.07 (t, 4H), 3.21 (d, 2H), 3.50 (t, 4H), 3.71 - 3.81 (m, 2H), 3.95 - 3.99 (m, 1H), 5.49 (s, 1H), 7.43 (dd, 1H), 7.46 - 7.52 (m, 2H), 7.58 (t, 1H), 7.73 - 7.78 (m, 2H), 8.25 (dd, 1H), 8.28 (dd, 1H), 8.72 (d, 1H), 9.26 (s, 1H); <i>m/z</i>: 570 (MH⁺).
25		<i>2-(3-Ethylmorpholino)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide</i> ¹H NMR (400 MHz, CDCl₃) δ 0.95 (t, 3H), 1.44 - 1.53 (m, 1H), 1.61 - 1.70 (m, 1H), 2.48 - 2.54 (m, 1H), 2.61 - 2.69 (m, 1H), 2.87 - 2.92 (m, 1H), 3.07 (m, 5H), 3.46 - 3.53 (m, 6H), 3.72 - 3.79 (m, 1H), 3.84 - 3.95 (m, 2H), 5.49 (s, 1H), 7.41 - 7.51 (m, 3H), 7.58 (t, 1H), 7.72 - 7.81 (m, 2H), 8.23 - 8.33 (m, 2H), 8.71 (d, 1H), 9.44 (s, 1H); <i>m/z</i>: 585 (MH⁺).
26		<i>2-(2-Ethylmorpholino)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide</i> ¹H NMR (400 MHz, CDCl₃) δ 0.99 (t, 3H), 1.44 - 1.60 (m, 2H), 2.19 (t, 1H), 2.46 - 2.52 (m, 1H), 2.83 (dd, 2H), 3.07 (t, 4H), 3.22 (s, 2H), 3.50 (t, 5H), 3.72 - 3.80 (m, 1H), 3.96 - 4.02 (m, 1H), 5.49 (s, 1H), 7.42 - 7.51 (m, 3H), 7.58 (t, 1H), 7.73 - 7.77 (m, 2H), 8.24 - 8.29 (m, 2H), 8.72 (d, 1H), 9.29 (s, 1H); <i>m/z</i>: 585 (MH⁺).

Example 13

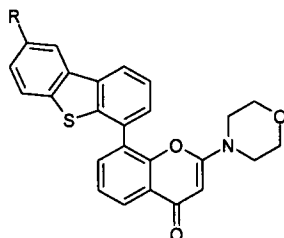
N-methyl-2-morpholino-*N*-(6-(2-morpholino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl)dibenzo[*b,d*]thiophen-2-yl)acetamide (27)

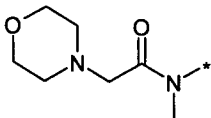
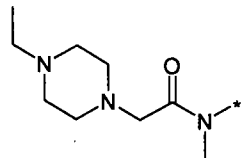
- 5 Sodium hydride, 60% dispersion in mineral oil (26.8 mg, 0.67 mmol) was added portionwise to 2-morpholino-*N*-(6-(2-morpholino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl)dibenzo[*b,d*]thiophen-2-yl)acetamide (17, 318 mg, 0.57 mmol) in anhydrous DMF (6 ml) at 0°C. After stirring under nitrogen at 0°C for 30 minutes the reaction mixture was treated with methyl iodide (0.037 ml, 0.60 mmol). The reaction mixture was allowed to warm to room
- 10 temperature and stirred for 1 hour. The reaction mixture was diluted with methanol (10ml). The crude reaction mixture was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and fractions were evaporated to dryness to afford crude product. The crude product was
- 15 fractions were evaporated to dryness to afford *N*-methyl-2-morpholino-*N*-(6-(2-morpholino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl)dibenzo[*b,d*]thiophen-2-yl)acetamide (198 mg, 60%) as a cream solid; ¹H NMR (400 MHz, CDCl₃) δ 2.38 (4H, s), 2.88- 2.90 (2H, m), 3.30 - 3.32 (7H, m), 3.51 (4H, t), 3.61 (4H, s), 5.57 (1H, s), 6.96 (1H, t), 7.24 (1H, dd), 7.51 - 7.57 (2H, m), 7.75 - 7.82 (2H, m), 7.98 (1H, d), 8.11 (1H, dd), 8.99 (1H, dd); *m/z* 570.31 (MH⁺).

Example 14

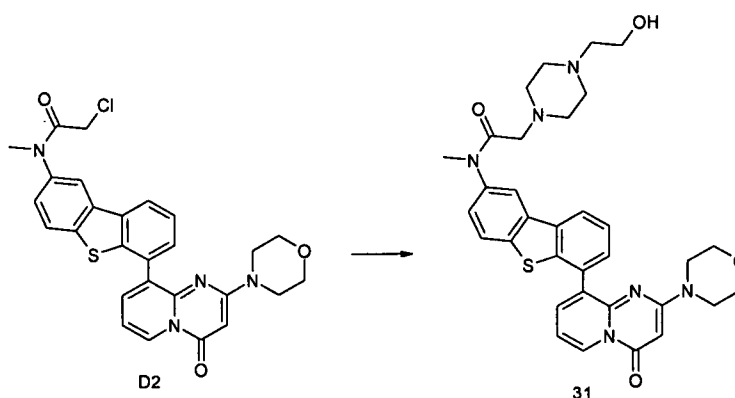
2-(4-(2-hydroxyethyl)piperazin-1-yl)-N-methyl-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (28)

- 5 2-(piperazin-1-yl)ethanol (50.2 mg, 0.39 mmol) was added to 2-chloro-N-methyl-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (C2, 100 mg, 0.19 mmol) and triethylamine (39.0 mg, 0.39 mmol) in DMA (2 mL) at room temperature. After stirring for 5 hours at room temperature the reaction was left standing for 3 days. The crude product was purified by ion exchange chromatography, using an SCX column. The desired
- 10 product was eluted from the column using 7M NH₃/MeOH and fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-(4-(2-hydroxyethyl)piperazin-1-yl)-N-methyl-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (103 mg, 87 %) as
- 15 a white solid; ¹H NMR (400 MHz, CDCl₃) δ 2.53 (10H, s), 2.93 - 2.98 (2H, m), 3.09 - 3.13 (4H, m), 3.38 (3H, s), 3.50 - 3.58 (6H, m), 5.51 (1H, s), 7.33 (1H, dd), 7.48 - 7.64 (3H, m), 7.78 (1H, dd), 7.85 (1H, d), 8.04 (1H, s), 8.19 (1H, d), 8.29 - 8.31 (1H, m) OH signal not seen; *m/z* 613.23(MH⁺).
- 20 The procedure described above was repeated using the appropriate amine and 2-chloro-N-methyl-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (C2). The compounds described below were thus obtained:



Compound	R	Name and Analytical Data
29		<i>N</i> -methyl-2-morpholino- <i>N</i> -(6-(2-morpholino-4-oxo-4 <i>H</i> -chromen-8-yl)dibenzo[<i>b</i> , <i>d</i>]thiophen-2-yl)acetamide ¹ H NMR (400 MHz, CDCl ₃) δ 2.37 (4H, s), 2.89 (2H, s), 3.05 (4H, t), 3.32 (3H, s), 3.47 (4H, t), 3.61 (4H, s), 5.44 (1H, s), 7.27 (1H, dd), 7.43 (1H, t), 7.49 (1H, d), 7.56 (1H, t), 7.71 (1H, dd), 7.78 (1H, d), 8.00 (1H, d), 8.12 (1H, d), 8.23 (1H, dd); <i>m/z</i> : 570.17 (MH ⁺).
30		2-(4-ethylpiperazin-1-yl)- <i>N</i> -methyl- <i>N</i> -(6-(2-morpholino-4-oxo-4 <i>H</i> -chromen-8-yl)dibenzo[<i>b</i> , <i>d</i>]thiophen-2-yl)acetamide ¹ H NMR (400 MHz, CDCl ₃) δ 0.97 (3H, t), 2.29 - 2.47 (10H, m), 2.89 (2H, s), 3.05 (4H, t), 3.31 (3H, s), 3.46 (4H, t), 5.44 (1H, s), 7.26 (1H, dd), 7.41 - 7.57 (3H, m), 7.71 (1H, dd), 7.77 (1H, d), 7.99 (1H, d), 8.12 (1H, dd), 8.23 (1H, dd); <i>m/z</i> : 598.08 (MH ⁺).

Example 15

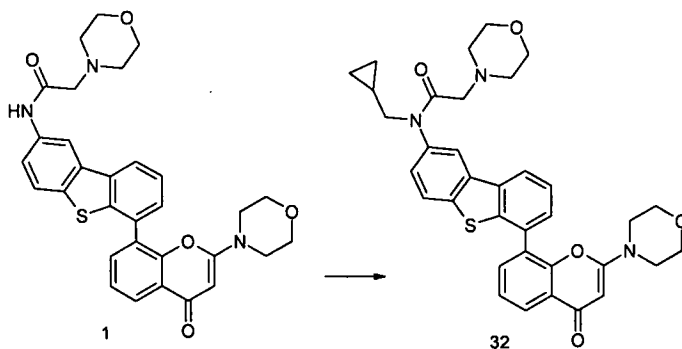


2-(4-(2-hydroxyethyl)piperazin-1-yl)-*N*-methyl-*N*-(6-(2-morpholino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl)dibenzo[*b*,*d*]thiophen-2-yl)acetamide (31)

2-(piperazin-1-yl)ethanol (72.7 mg, 0.56 mmol) was added to 2-chloro-*N*-methyl-*N*-(6-(2-morpholino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl)dibenzo[*b*,*d*]thiophen-2-yl)acetamide (D2,

145 mg, 0.28 mmol), and triethylamine (56.5 mg, 0.56 mmol) in DMA (2 mL) at room temperature. After stirring for 16 hours at room temperature the reaction was heated to 70°C for 3 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-(4-(2-hydroxyethyl)piperazin-1-yl)-N-methyl-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (159 mg, 93 %) as a yellow solid; ¹H NMR(400 MHz, CDCl₃) δ 2.43 - 2.46 (10H, m), 2.91 (2H, s), 3.29 - 3.32 (7H, m), 3.50 (6H, t), 5.57 (1H, s), 6.96 (1H, t), 7.23 (1H, dd), 7.51 - 7.57 (2H, m), 7.75 (1H, d), 7.80 (1H, dd), 7.96 (1H, d), 8.11 (1H, dd), 8.99 (1H, dd) OH signal not seen; *m/z* 612.74(M⁺).

Example 16

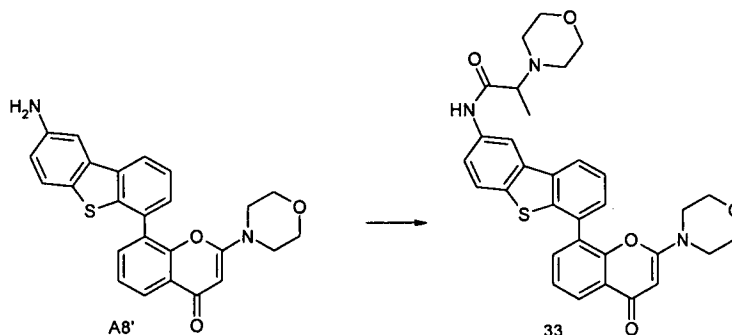


N-(cyclopropylmethyl)-2-morpholino-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (32)

Sodium hydride, 60% dispersion in mineral oil (8.6 mg, 0.22 mmol) was added in one portion to 2-morpholino-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (1, 100 mg, 0.18 mmol) in anhydrous DMF (1.80 ml) cooled to 0°C. The resulting solution was stirred under nitrogen at 0°C for 15 minutes then cyclopropyl methyl bromide (26.7 mg, 0.20 mmol) was added and the reaction mixture allowed to warm to ambient temperature and stirred for a further 18 hours. The reaction mixture was quenched with methanol (10 mL) and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford *N*-(cyclopropylmethyl)-2-morpholino-N-(6-(2-morpholino-4-oxo-4H-

chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (35 mg, 32%) as a cream solid; ^1H NMR (400 MHz, CDCl_3) δ 0.18 (2H, q), 0.45 - 0.50 (2H, m), 0.99 - 1.05 (1H, m), 2.46 (4H, br s), 2.94 (2H, s), 3.13 (4H, t), 3.54 (4H, t), 3.68 - 3.70 (6H, m), 5.51 (1H, s), 7.35 - 7.38 (1H, m), 7.49 - 7.52 (1H, m), 7.57 (1H, d), 7.63 (1H, t), 7.78 - 7.80 (1H, m), 7.86 (1H, d), 8.07 (1H, d), 8.19 - 8.21 (1H, m), 8.29 - 8.32 (1H, m); m/z : 610.12 (MH^+).

Example 17



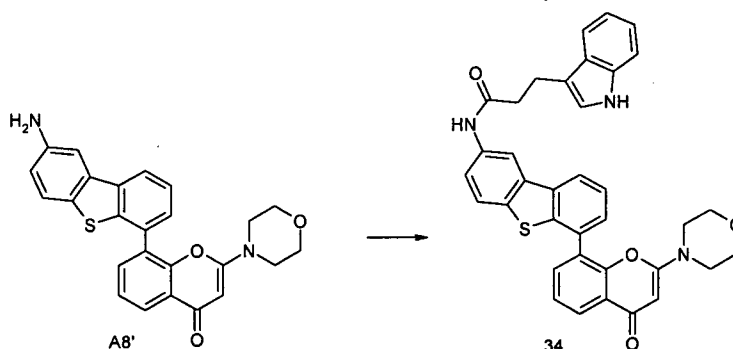
2-morpholino-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)propanamide (33)

2-Chloropropionyl chloride (27 μL , 0.28 mmol) was added to 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8' , 100 mg, 0.23 mmol) and triethylamine (98 μL , 0.70 mmol) in anhydrous DMA (2.00 mL) at ambient temperature. The resulting solution was stirred under nitrogen at ambient temperature for 30 minutes.

Morpholine (61 μL , 0.70 mmol) was then added and the reaction mixture stirred at ambient temperature for 2 hours. The reaction was incomplete so the temperature was increased to 100°C and the reaction mixture was stirred for a further 18 hours. The reaction mixture was diluted with methanol (20 mL) and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3/MeOH and evaporated to dryness to afford impure product. The impure product was purified by flash silica chromatography, elution gradient 0 to 7% 7M NH_3/MeOH in DCM. Fractions containing the desired product were evaporated to dryness to afford impure material. The residue was then purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 2-morpholino-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)propanamide (78 mg, 59 %) as a yellow solid; ^1H NMR (400 MHz, CDCl_3) δ 1.40 (3H, d), 2.64 (2H, m), 2.70 (2H, m), 3.07 (4H, t), 3.27 (1H, q), 3.49 (4H, t), 3.80 - 3.89 (4H, m), 5.49 (1H, s), 7.41 (1H, d), 7.46 - 7.50 (2H, m),

7.57 (1H, t), 7.72 - 7.77 (2H, m), 8.23 - 8.25 (1H, m), 8.27 - 8.29 (1H, m), 8.75 (1H, d), 9.41 (1H, s); m/z : 570.92 (MH^+).

Example 18



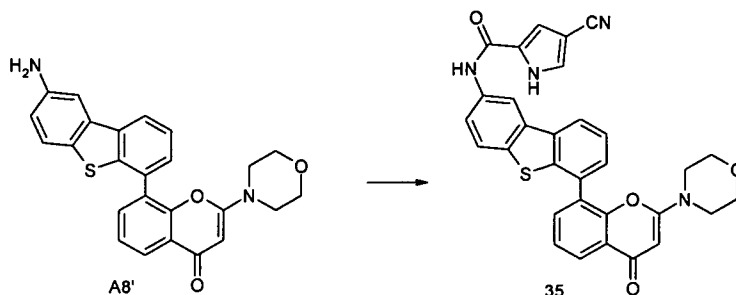
3-(1H-indol-3-yl)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)propanamide (34)

4-(4,6-Dimethoxy[1.3.5]triazin-2-yl)-4-methylmorpholinium chloride hydrate (71.0 mg, 0.26 mmol) was added to 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8', 100 mg, 0.23 mmol) and 3-(1H-indol-3-yl)propanoic acid (48.6 mg, 0.26 mmol) in anhydrous THF (1 mL) and anhydrous DMA (1 mL). The formed mixture was then stirred under nitrogen at ambient temperature for 18 hours. The reaction was incomplete and further 3-(1H-indol-3-yl)propanoic acid (48.6 mg, 0.26 mmol) and 4-(4,6-

dimethoxy[1.3.5]triazin-2-yl)-4-methylmorpholinium chloride hydrate (71.0 mg, 0.26 mmol) were added and the solution was stirred under nitrogen at 60°C for a further 6 hours. The reaction mixture was poured into water (10 mL) and the solution extracted with EtOAc (3 x 10 mL) and DCM (1 x 10 mL), some methanol was required to aid full solubilisation of material. The combined organics were purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3 /MeOH and evaporated to dryness to afford impure product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 3-(1H-indol-3-yl)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-

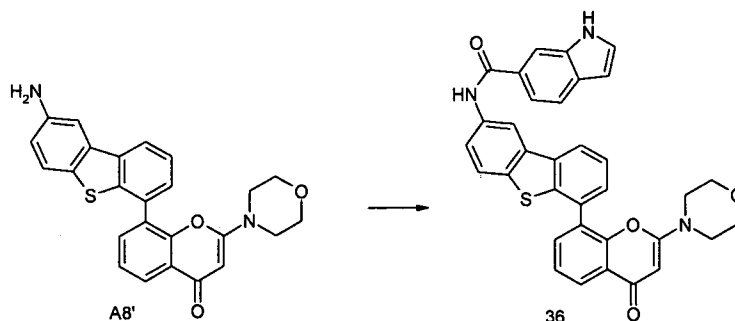
yl)propanamide (56 mg, 40%) as a white solid; 1H NMR (400 MHz, $DMSO-d_6$) δ 2.76 - 2.80 (2H, t), 3.08 - 3.13 (4H, m), 3.43 (4H, t), 5.57 (1H, s), 6.99 - 7.03 (1H, m), 7.07 - 7.11 (1H, m), 7.18 (1H, d), 7.35 (1H, d), 7.57 (1H, t), 7.62 (1H, d), 7.64 - 7.70 (3H, m), 7.90 (2H, m), 8.07 - 8.09 (1H, m), 8.27 - 8.29 (1H, m), 8.71 (1H, d), 10.19 (1H, s), 10.78 (1H, s). One x (2H, t) not observed - obscured by residual solvent; m/z : 600.03 (MH^+).

Example 19



5 *4-cyano-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)-1H-pyrrole-2-carboxamide (35)*

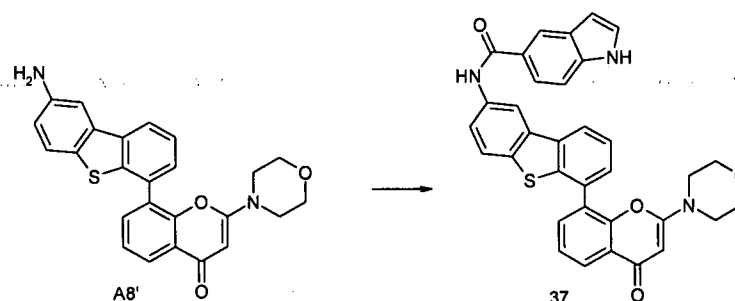
O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (106 mg, 0.28 mmol) was added in one portion to 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8', 100 mg, 0.23 mmol), 4-cyano-1H-pyrrole-2-carboxylic acid (31.8 mg, 0.23 mmol) and N,N-diisopropylethylamine (0.10 mL, 0.58 mmol) in DMA (1.5 mL) at ambient temperature. The resulting solution was stirred at ambient temperature for 18 hours. The reaction was incomplete and further 4-cyano-1H-pyrrole-2-carboxylic acid (31.8 mg, 0.23 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (106 mg, 0.28 mmol) were added and the solution was stirred at ambient temperature for a further 3 days. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure product. This was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford 4-cyano-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)-1H-pyrrole-2-carboxamide (44.6 mg, 35 %) as a yellow solid; ¹H NMR (400 MHz, DMSO-d₆) δ 3.13 (4H, t), 3.44 (4H, t), 5.58 (1H, s), 7.51 (1H, d), 7.58 (1H, t), 7.68 - 7.71 (2H, m), 7.83 - 7.85 (2H, m), 7.89 - 7.92 (1H, m), 7.99 (1H, d), 8.08 - 8.10 (1H, m), 8.30 - 8.35 (1H, m), 8.73 (1H, d), 10.29 (1H, s), 12.71 (1H, br s); *m/z*: 547.06 (MH⁺).

Example 20

N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)-1H-indole-6-carboxamide (36)

- 5 O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (106 mg, 0.28 mmol) was added in one portion to 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8', 100 mg, 0.23 mmol), 1H-indole-6-carboxylic acid (39.5 mg, 0.25 mmol) and N,N-diisopropylethylamine (0.102 mL, 0.58 mmol) in DMA (1.5 mL) at ambient temperature. The resulting solution was stirred at ambient temperature for 18 hours. The
- 10 crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure product. This was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford
- 15 *N*-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)-1H-indole-6-carboxamide (55 mg, 41%) as a cream solid; ¹H NMR (400 MHz, DMSO-d₆) δ 3.13 (4H, t), 3.45 (4H, t), 5.59 (1H, s), 6.56 - 6.57 (1H, m), 7.56 - 7.60 (2H, m), 7.69 (3H, t), 7.73 - 7.75 (1H, m), 7.90 - 7.94 (2H, m), 7.98 (1H, d), 8.08 - 8.10 (1H, m), 8.16 (1H, s), 8.33 - 8.35 (1H, m), 8.89 - 8.91 (1H, m), 10.43 (1H, s), 11.49 (1H, s); *m/z*: 572.08 (MH⁺).

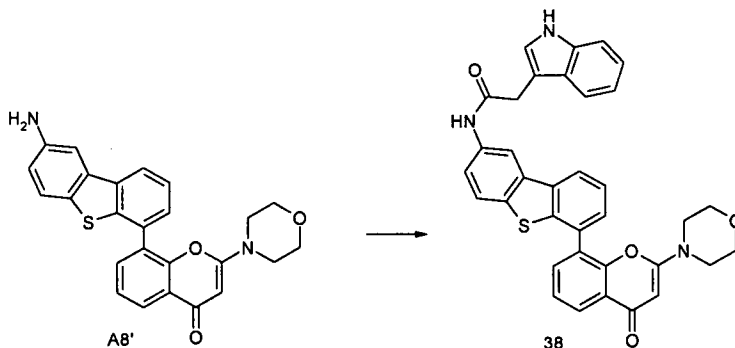
20 **Example 21**



N-(6-(2-morpholino-4-oxo-4*H*-chromen-8-yl)dibenzo[*b,d*]thiophen-2-yl)-1*H*-indole-5-carboxamide (37)

O-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (106 mg, 0.28 mmol) was added in one portion to 8-(8-aminodibenzo[*b,d*]thiophen-4-yl)-2-morpholino-4*H*-chromen-4-one (A8', 100 mg, 0.23 mmol), 1*H*-indole-5-carboxylic acid (39.5 mg, 0.25 mmol) and *N,N*-diisopropylethylamine (0.102 mL, 0.58 mmol) in DMA (1.5 mL) at ambient temperature. The resulting solution was stirred at ambient temperature for 18 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure product. This was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford *N*-(6-(2-morpholino-4-oxo-4*H*-chromen-8-yl)dibenzo[*b,d*]thiophen-2-yl)-1*H*-indole-5-carboxamide (90 mg, 68%) as a yellow solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.13 (4H, br s), 3.44 (4H, t), 5.58 (1H, s), 6.63 (1H, s), 7.50 (1H, t), 7.55 (1H, d), 7.58 (1H, d), 7.66 - 7.71 (2H, m), 7.82 - 7.85 (1H, m), 7.89 - 7.91 (1H, m), 7.92 - 7.98 (2H, m), 8.08 - 8.11 (1H, m), 8.32 - 8.34 (1H, m), 8.37 (1H, s), 8.91 (1H, s), 10.39 (1H, s), 11.42 (1H, s); *m/z*: 572.11 MH⁺.

Example 22

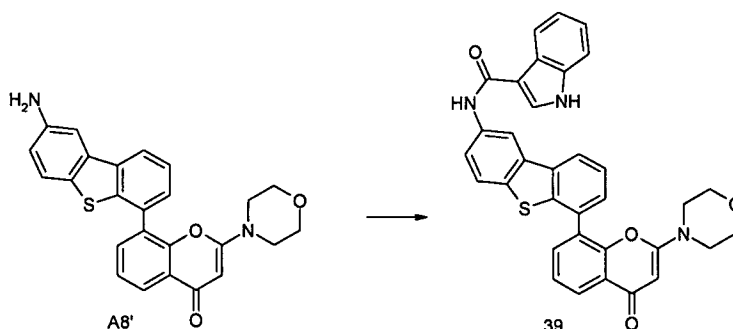


2-(1*H*-indol-3-yl)-*N*-(6-(2-morpholino-4-oxo-4*H*-chromen-8-yl)dibenzo[*b,d*]thiophen-2-yl)acetamide (38)

O-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (106 mg, 0.28 mmol) was added in one portion to 8-(8-aminodibenzo[*b,d*]thiophen-4-yl)-2-morpholino-4*H*-chromen-4-one (A8', 100 mg, 0.23 mmol), 2-(1*H*-indol-3-yl)acetic acid (42.9 mg, 0.25 mmol) and *N,N*-diisopropylethylamine (0.102 mL, 0.58 mmol) in DMA (1.5 mL) at ambient temperature. The resulting solution was stirred at ambient temperature for 18 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure product. This was purified by flash silica chromatography, elution

gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-(1H-indol-3-yl)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (90 mg, 66 %) as a cream solid; ¹H NMR (400 MHz, DMSO-d₆) δ 3.11 (4H, t), 3.42 (4H, t), 3.82 (2H, s), 5.57 (1H, s), 7.00 - 7.04 (1H, m), 7.08 - 7.12 (1H, m), 7.33 (1H, d), 7.38 (1H, d), 7.56 (1H, t), 7.65 - 7.70 (4H, m), 7.87 - 7.90 (1H, m), 7.92 (1H, d), 8.06 - 8.09 (1H, m), 8.25 - 8.27 (1H, m), 8.71 (1H, d), 10.35 (1H, s), 10.93 (1H, s); *m/z*: 586.06 (MH⁺).

Example 23

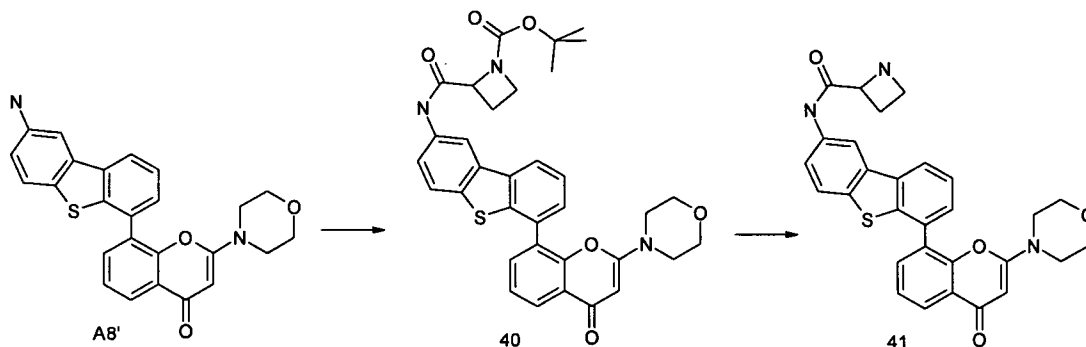


N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)-1H-indole-3-carboxamide (39)

O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (104 mg, 0.27 mmol) was added in one portion to 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8', 98 mg, 0.23 mmol), indole-3-carboxylic acid (40.5 mg, 0.25 mmol) and N,N-diisopropylethylamine (0.100 mL, 0.57 mmol) in DMA (1.5 mL) at ambient temperature. The resulting solution was stirred at ambient temperature for 3 hours. The reaction was incomplete and further N,N-diisopropylethylamine (0.200 mL, 1.14 mmol), indole-3-carboxylic acid (81 mg, 0.50 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (208 mg, 0.54 mmol) were added and the solution was stirred at ambient temperature for a further 18 hours. The reaction was still incomplete and further N,N-diisopropylethylamine (0.400 mL, 2.28 mmol), indole-3-carboxylic acid (162 mg, 1.00 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (416 mg, 1.08 mmol) was added and the solution was stirred at ambient temperature for a further 18 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure product. This was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford *N*-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)-1H-indole-3-carboxamide (70 mg, 54 %) as a yellow solid; ¹H NMR (400 MHz, DMSO-d₆) δ 3.13 (4H, t), 3.45 (4H, t), 5.58 (1H, s), 7.17 - 7.24 (2H, m), 7.51

(1H, d), 7.58 (1H, t), 7.69 (2H, q), 7.85 - 7.88 (1H, m), 7.90 - 7.92 (1H, m), 7.96 (1H, d), 8.08 - 8.10 (1H, m), 8.27 (1H, d), 8.33 - 8.36 (1H, m), 8.37 (1H, d), 8.86 (1H, d), 9.98 (1H, s), 11.77 (1H, s); m/z : 572.10 (MH^+).

5 Example 24



(a) (2S)-tert-butyl 2-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylcarbamoyl)azetidine-1-carboxylate (40)

O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (106 mg, 0.28 mmol) was added in one portion to 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8', 100 mg, 0.23 mmol), (S)-1-(tert-butoxycarbonyl)azetidine-2-carboxylic acid (51.7 mg, 0.26 mmol) and N,N-diisopropylethylamine (0.102 mL, 0.58 mmol) in DMA (1.5 mL) at ambient temperature. The resulting solution was stirred at ambient temperature for 18 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M $NH_3/MeOH$ and evaporated to dryness to afford impure product. This was purified by flash silica chromatography, elution gradient 0 to 5% 7M $NH_3/MeOH$ in DCM. Pure fractions were evaporated to dryness to afford (2S)-tert-butyl 2-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylcarbamoyl)azetidine-1-carboxylate (36.5 mg, 26 %) as a white solid; 1H NMR (400 MHz, $CDCl_3$) δ 1.53 (9H, s), 2.51 (1H, br s), 2.69 (1H, br s), 3.08 (4H, t), 3.50 (4H, t), 3.85 - 3.91 (1H, m), 4.00 (1H, q), 4.91 (1H, t), 5.51 (1H, s), 7.44 - 7.52 (3H, m), 7.57 (1H, t), 7.72 (1H, d), 7.75 - 7.77 (1H, m), 8.23 (1H, s), 8.27 - 8.29 (1H, m), 8.71 (1H, d), 9.80 (1H, br s); m/z : 612.07 (MH^+).

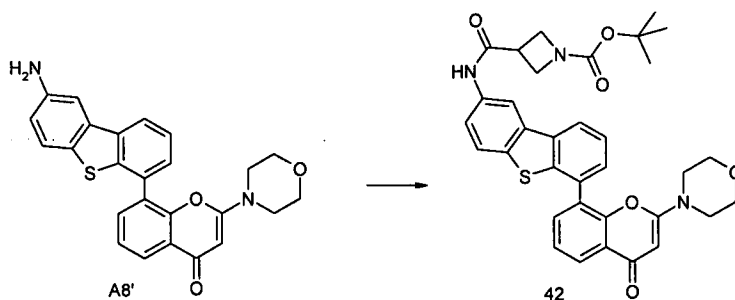
(b) (2S)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)azetidine-2-carboxamide (41)

A solution of 10% TFA in DCM (3 mL) was added to (2S)-tert-butyl 2-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylcarbamoyl)azetidine-1-carboxylate (40, 110 mg, 0.18 mmol) at ambient temperature. The resulting solution was stirred at ambient

temperature for 2 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure product. The crude product was purified by flash silica chromatography, elution gradient 0 to 6% 7M NH₃/MeOH in DCM.

Pure fractions were evaporated to dryness to afford (2S)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)azetidine-2-carboxamide (60 mg, 65 %) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 2.49 - 2.58 (1H, m), 2.74 - 2.82 (1H, m), 3.07 (4H, t), 3.42 - 3.47 (1H, m), 3.50 (4H, t), 3.87 - 3.93 (1H, m), 4.52 - 4.57 (1H, m), 5.50 (1H, s), 7.46 - 7.52 (2H, m), 7.53 - 7.56 (1H, m), 7.57 (1H, t), 7.73 - 7.77 (2H, m), 8.23 - 8.25 (1H, m), 8.27 - 8.29 (1H, m), 8.77 (1H, d), 9.82 (1H, s). NH not observed; *m/z*: 512.14 (MH⁺).

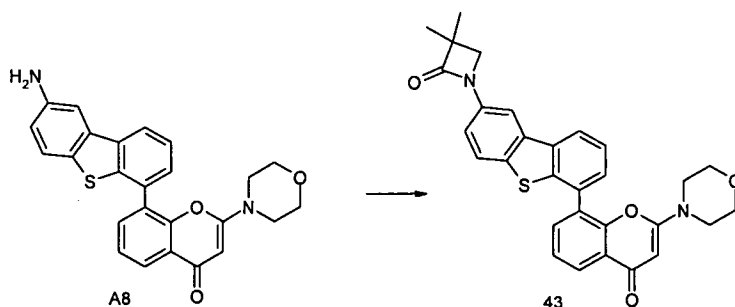
Example 25



Tert-butyl 3-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylcarbamoyl)azetidine-1-carboxylate (42)

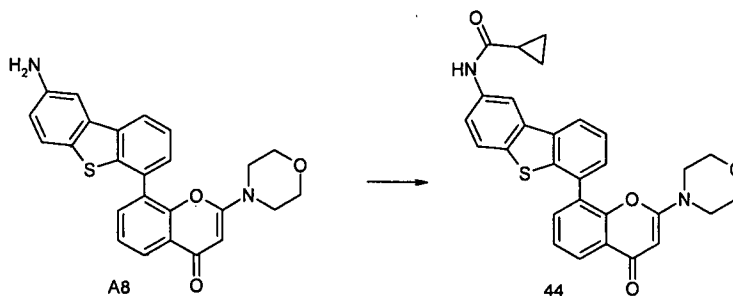
O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (106 mg, 0.28 mmol) was added in one portion to 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8', 100 mg, 0.23 mmol), 1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid (51.7 mg, 0.26 mmol) and N,N-diisopropylethylamine (0.102 mL, 0.58 mmol) in DMA (1.5 mL) at ambient temperature. The resulting solution was stirred at ambient temperature for 18 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure product. This was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford tert-butyl 3-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylcarbamoyl)azetidine-1-carboxylate (43 mg, 30%) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.47 (9H, s), 3.07 (4H, t), 3.41 - 3.47 (1H, m), 3.49 (4H, t), 4.18 (2H, t), 4.27 - 4.30 (2H, m), 5.51 (1H, s), 7.38 - 7.40 (1H, m), 7.47 - 7.52 (2H, m), 7.58 (2H, t), 7.73 (1H, d), 7.75 - 7.77 (1H, m), 8.20 - 8.22 (1H, m), 8.27 - 8.29 (1H, m), 8.72 (1H, d); *m/z*: 612.14 (MH⁺).

Example 26



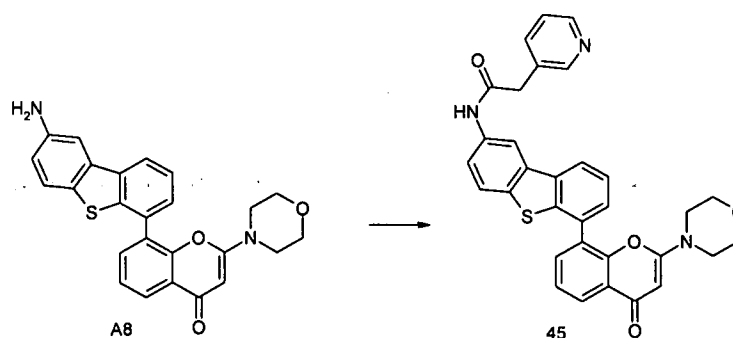
3,3-dimethyl-1-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)azetidin-
2-one (43)

3-bromo-2,2-dimethylpropanoyl chloride (51.2 mg, 0.26 mmol) was added to a stirred solution of 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8, 100 mg, 0.23 mmol), and triethylamine (47.2 mg, 0.47 mmol) in DMA (2 mL) at room temperature. After stirring for 4 hours, the reaction mixture was then treated with morpholine (61.0 mg, 0.70 mmol) and stirred at room temperature for a further 2 hours. After stirring for a further 2 hours the reaction mixture was treated with morpholine (61.0 mg, 0.70 mmol) and stirred at room temperature for a further 4 hours. After a further 4 hours at room temperature the reaction was heated to 50°C overnight. The crude reaction mixture was purified by ion exchange chromatography, using an SCX column. The product was eluted from the column using 7M NH₃/MeOH and fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford 3,3-dimethyl-1-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)azetidin-2-one (72.0 mg, 60 %) as a white solid; ¹H NMR (400 MHz, DMSO-d₆) δ 1.38 (6H, s), 3.10 (4H, t), 3.42 (4H, t), 3.67 (2H, s), 5.57 (1H, s), 7.57 (1H, t), 7.68 - 7.72 (3H, m), 7.89 (1H, dd), 8.00 (1H, d), 8.08 (1H, dd), 8.23 (1H, d), 8.44 (1H, dd); *m/z*: 511.07 (MH⁺).

Example 27

N-(6-(2-Morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)cyclopropanecarboxamide (44)

- 5 Cyclopropanecarbonyl chloride (0.021 mL, 0.23 mmol) was added to 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8, 100 mg, 0.23 mmol) in DMA (1 mL). The resulting solution was stirred at room temperature for 1 hour. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents. Fractions containing the desired compound
- 10 were evaporated to dryness to afford *N*-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)cyclopropanecarboxamide (42mg, 36%); ¹H NMR (400 MHz, CDCl₃) δ 0.86 - 0.94 (m, 2H), 1.14 - 1.19 (m, 2H), 1.57 - 1.62 (m, 1H), 3.07 (t, 4H), 3.50 (t, 4H), 5.49 (s, 1H), 7.37 (dd, 1H), 7.48 (t, 2H), 7.54 - 7.61 (m, 2H), 7.71 (d, 1H), 7.75 (dd, 1H),
- 15 8.20 (dd, 1H), 8.28 (dd, 1H), 8.71 (s, 1H); *m/z*: 497.80 (MH⁺).

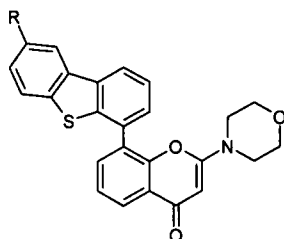
Example 28

(a) *N*-(6-(2-Morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)-2-(pyridin-3-yl)acetamide (45)

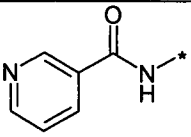
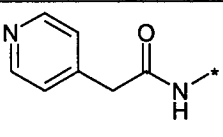
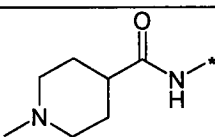
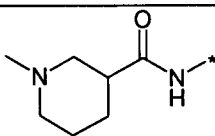
- 20 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholin-4-ium chloride hydrate (76 mg, 0.26 mmol) was added to 2-(pyridin-3-yl)acetic acid hydrochloride (40 mg, 0.26 mmol), 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8, 100 mg, 0.23 mmol) and *N,N*-diisopropylethylamine (0.122 mL, 0.70 mmol) in THF (2 mL) and DMA (1 mL) at

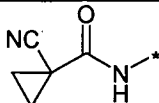
room temperature. The resulting suspension was stirred at room temperature for 18 hours. The reaction mixture was evaporated to dryness and re-dissolved in DCM (20 mL) and washed with water (10 mL). The organic layer was separated and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)-2-(pyridin-3-yl)acetamide (45 mg, 34%) as a white solid; ¹H NMR (400 MHz, CDCl₃ + d₄acetic acid) δ 3.11 (t, J = 4.7 Hz, 4H), 3.48 (t, 4H), 3.97 (s, 2H), 5.89 (s, 1H), 7.44 - 7.56 (m, 4H), 7.62 (q, 1H), 7.67 (d, 1H), 7.76 (dd, 1H), 8.17 (dd, 1H), 8.27 (dd, 1H), 8.30 (d, 1H), 8.62 (d, 1H), 8.67 (d, 1H), 9.09 (s, 1H); m/z: 548.07 (MH⁺).

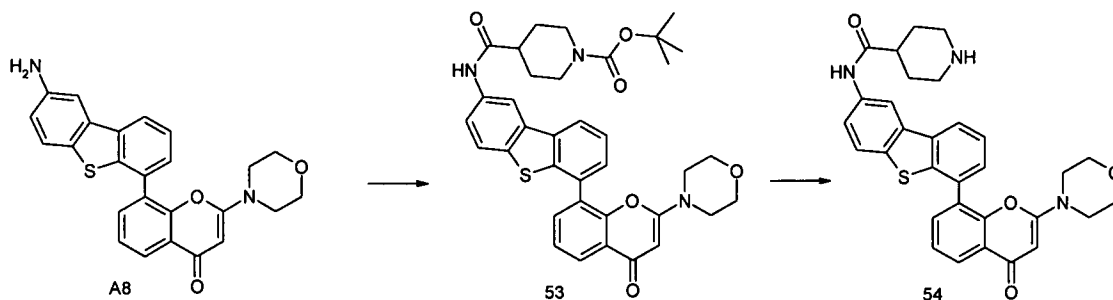
The following compounds were prepared in an analogous fashion:



Compound	R	Name and Analytical Data
46		<i>N</i> -(6-(2-Morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)oxazole-4-carboxamide ¹ H NMR (400 MHz, CDCl ₃) δ 3.09 (t, 4H), 3.51 (t, 4H), 5.51 (s, 1H), 7.48 (t, 2H), 7.57 - 7.61 (m, 2H), 7.75 - 7.78 (m, 2H), 7.97 (d, 1H), 8.24 (dd, 1H), 8.29 (dd, 1H), 8.39 (d, 1H), 8.80 (d, 1H), 8.93 (s, 1H); m/z: 524.04 (MH ⁺).
47		<i>N</i> -(6-(2-Morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)isonicotinamide ¹ H NMR (400 MHz, CDCl ₃) δ 3.04 (t, 4H), 3.47 (t, 4H), 5.42 (s, 1H), 7.48 (t, 2H), 7.58 (t, 2H), 7.76 (d, 2H), 7.86 (d, 2H), 8.22 (dd, 1H), 8.27 (dd, 1H), 8.80 - 8.84 (m, 4H); m/z: 534.04 (MH ⁺).

48		<i>N</i> -(6-(2-Morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)nicotinamide ¹ H NMR (400 MHz, CDCl ₃) δ 3.05 (t, 4H), 3.48 (t, 4H), 5.47 (s, 1H), 7.47 (t, 3H), 7.56 (d, 1H), 7.59 - 7.62 (dd, 1H), 7.76 (d, 2H), 8.22 (d, 1H), 8.27 (dd, 1H), 8.34 (dt, 1H), 8.79 - 8.82 (m, 3H), 9.25 (s, 1H); <i>m/z</i> : 534.04 (MH ⁺).
49		<i>N</i> -(6-(2-Morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)-2-(pyridin-4-yl)acetamide ¹ H NMR (400 MHz, CDCl ₃) δ 3.04 (t, 4H), 3.46 (t, 4H), 3.83 (s, 2H), 5.46 (s, 1H), 7.36 - 7.39 (m, 3H), 7.48 (t, 2H), 7.55 (t, 1H), 7.68 (d, 1H), 7.75 (dd, 1H), 8.17 (d, 1H), 8.25 - 8.29 (m, 2H), 8.63 (d, 2H), 8.68 (d, 1H); <i>m/z</i> : 548.08 (MH ⁺).
50		1-Methyl- <i>N</i> -(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)piperidine-4-carboxamide ¹ H NMR (400 MHz, CDCl ₃) δ 1.91 - 2.08 (m, 6H), 2.29 - 2.38 (m, 4H), 2.96 - 3.02 (m, 2H), 3.05 (t, 4H), 3.48 (t, 4H), 5.48 (s, 1H), 7.39 (dd, 1H), 7.48 (t, 2H), 7.55 (t, 1H), 7.69 (d, 1H), 7.75 (dd, 1H), 7.84 (s, 1H), 8.20 (d, 1H), 8.28 (dd, 1H), 8.75 (s, 1H); <i>m/z</i> : 554.13 (MH ⁺).
51		1-Methyl- <i>N</i> -(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)piperidine-3-carboxamide ¹ H NMR (400 MHz, CDCl ₃) δ 1.77 (s, 2H), 1.85 - 1.92 (m, 2H), 1.99 - 2.09 (m, 1H), 2.29 - 2.64 (m, 3H), 2.48 (s, 3H), 2.87 (s, 2H), 3.07 (t, 4H), 3.49 (t, 4H), 5.50 (s, 1H), 7.41 - 7.50 (m, 3H), 7.55 (t, 1H), 7.69 (d, 1H), 7.75

		(d, 1H), 8.23 (d, 1H), 8.28 (d, 1H), 8.75 (s, 1H); <i>m/z</i> : 554.20 (MH ⁺).
52		1-Cyano-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)cyclopropanecarboxamide ¹H NMR (400 MHz, CDCl₃) δ 1.67 (q, 2H), 1.87 (q, 2H), 3.08 (t, 4H), 3.50 (t, 4H), 5.52 (s, 1H), 7.47 - 7.52 (m, 3H), 7.58 (t, 1H), 7.75 - 7.79 (m, 2H), 8.20 (dd, 1H), 8.26 - 8.30 (m, 2H), 8.54 (d, 1H); <i>m/z</i>: 522.08 (MH⁺).

Example 29

(a) *tert*-Butyl 4-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylcarbamoyl)piperidine-1-carboxylate (53)

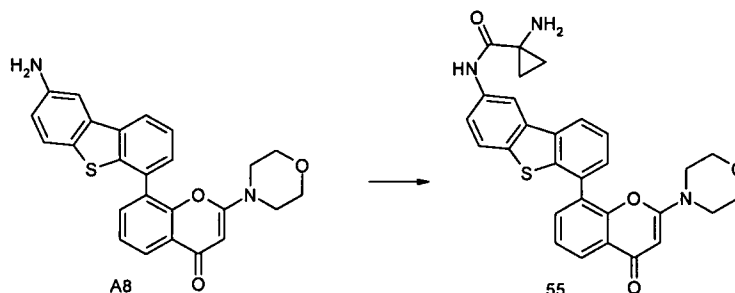
4-(4,6-Dimethoxy[1.3.5]triazin-2-yl)-4-methylmorpholinium chloride hydrate (73.3 mg, 0.26 mmol) was added to 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8, 103 mg, 0.24 mmol) and 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (60.7 mg, 0.26 mmol) in THF (1 mL) and DMA (1 mL) under nitrogen. The reaction mixture was evaporated to dryness and redissolved in DCM (20 mL), and washed with water (15 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford *tert*-butyl 4-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylcarbamoyl)piperidine-1-carboxylate (116 mg, 75 %) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.49 (s, 9H), 1.76 - 1.87 (m, 2H), 1.97 (d, 2H), 2.45 - 2.52 (m, 1H), 2.84 (t, 2H), 3.06 (t, 4H), 3.49 (t, 4H), 4.23 (d, 2H), 5.49 (s, 1H), 7.37 (dd, 1H), 7.46 - 7.51 (m, 2H), 7.54 - 7.60 (m, 2H), 7.71 (d, 1H), 7.75 (dd, 1H), 8.21 (dd, 1H), 8.28 (dd, 1H), 8.72 (d, 1H); *m/z*: 640.13 (MH⁺).

(b) *N*-(6-(2-Morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)piperidine-4-carboxamide (54)

tert-Butyl 4-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylcarbamoyl)piperidine-1-carboxylate (53, 116 mg, 0.18 mmol) was treated with TFA (5.00 mL) in DCM (5 mL). The resulting solution was stirred at room temperature for 1 hour. The reaction mixture was evaporated to dryness and redissolved in MeOH (2 mL). The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford *N*-(6-(2-morpholino-4-oxo-4H-chromen-8-

yl)dibenzo[b,d]thiophen-2-yl)piperidine-4-carboxamide (86 mg, 88 %) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.76 - 1.85 (m, 2H), 1.98 (d, 2H), 2.46 - 2.54 (m, 1H), 2.71 (t, 2H), 3.05 (t, 4H), 3.22 (d, 2H), 3.48 (t, 4H), 5.28 - 5.69 (br s, 1H), 5.49 (s, 1H), 7.41 (dd, 1H), 7.45 - 7.50 (m, 2H), 7.55 (t, 1H), 7.69 (d, 1H), 7.75 (dd, 1H), 7.94 (s, 1H), 8.20 (dd, 1H), 8.27 (dd, 1H), 8.76 (s, 1H); *m/z*: 540.13 (MH⁺).

Example 30

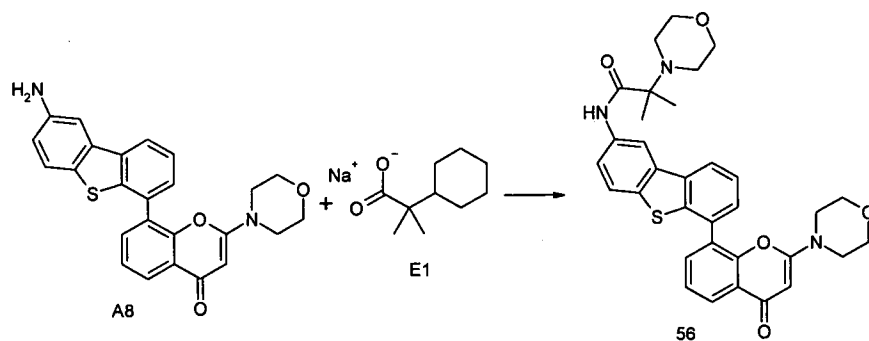


1-Amino-*N*-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)cyclopropanecarboxamide (55)

4-(4,6-Dimethoxy[1.3.5]triazin-2-yl)-4-methylmorpholinium chloride hydrate (135 mg, 0.49 mmol) was added to 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8, 190.5 mg, 0.44 mmol) and 1-(tert-butoxycarbonylamino)cyclopropanecarboxylic acid (98 mg, 0.49 mmol) in THF (25 mL) under nitrogen. The resulting suspension was stirred at 44 °C for 3 hours. DMA (25 mL) was added. The reaction mixture was evaporated to dryness and redissolved in MeOH (5 mL). The crude product was absorbed onto an SCX ion exchange column then left for 3 hours. The product was eluted using 7M NH₃/MeOH and the solvent removed *in vacuo*. Trifluoroacetic acid (2 mL, 25.96 mmol) and DCM (25.00 mL) were added and the mixture stirred at room temperature for 1 hour. The reaction mixture was evaporated to dryness and redissolved in MeOH (10 mL). The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was

eluted from the column using 7M NH₃/MeOH and product-containing fractions were evaporated onto silica gel (5 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Product containing fractions were evaporated to dryness to afford semi-pure 1-amino-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)cyclopropanecarboxamide (230 mg, 101 %) as a white solid. 110 mg of this material was purified by preparative LCMS (Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 1-amino-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)cyclopropanecarboxamide (70 mg, 30.7%); ¹H NMR (400 MHz, CDCl₃) δ 0.99 (q, 2H), 1.65 (q, 2H), 1.85 (s, 2H), 3.07 (t, 4H), 3.49 (t, 4H), 5.49 (s, 1H), 7.44 - 7.50 (m, 3H), 7.55 (t, 1H), 7.72 (d, 1H), 7.76 (dd, 1H), 8.22 (dd, 1H), 8.28 (dd, 1H), 8.80 (d, 1H), 10.09 (s, 1H); *m/z*: 512.12 (MH⁺).

Example 31

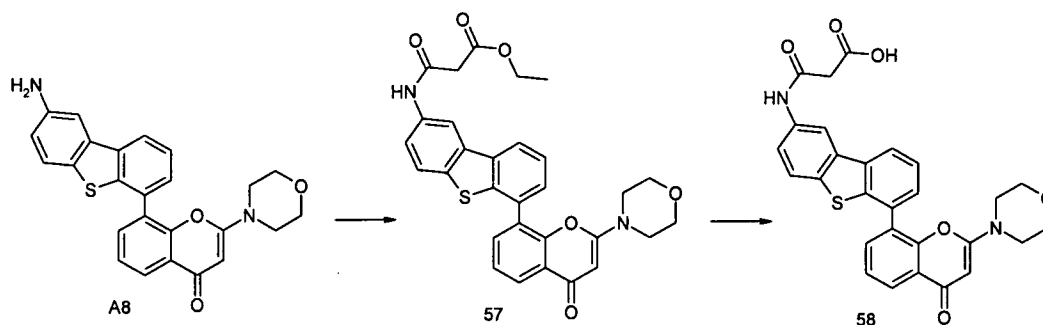


2-Methyl-2-morpholino-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)propanamide (56)

O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (81 mg, 0.21 mmol) was added to sodium 2-methyl-2-morpholinopropanoate (E1, 207 mg, 0.53 mmol), 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8, 101mg, 0.21 mmol) and N,N-Diisopropylethylamine (0.111 mL, 0.64 mmol) in DMA (4 mL). The resulting solution was stirred at room temperature for 18 hours. The reaction mixture was evaporated to dryness and redissolved in EtOAc (50 mL), and washed with water (50 mL). The organic layer was dried over MgSO₄, filtered and evaporated onto silica gel (5 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-methyl-2-morpholino-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)propanamide (86 mg, 69%) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.36 (s, 6H), 2.64 (t, 4H), 3.07 (t, 4H), 3.49 (t,

4H), 3.84 (t, 4H), 5.50 (s, 1H), 7.37 (dd, 1H), 7.46 - 7.50 (m, 2H), 7.57 (t, 1H), 7.73 (d, 1H), 7.75 (dd, 1H), 8.24 (dd, 1H), 8.28 (dd, 1H), 8.77 (d, 1H), 9.52 (s, 1H); m/z : 584.14 (MH^+).

Example 32



(a) *Ethyl 3-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylamino)-3-oxopropionate (57)*

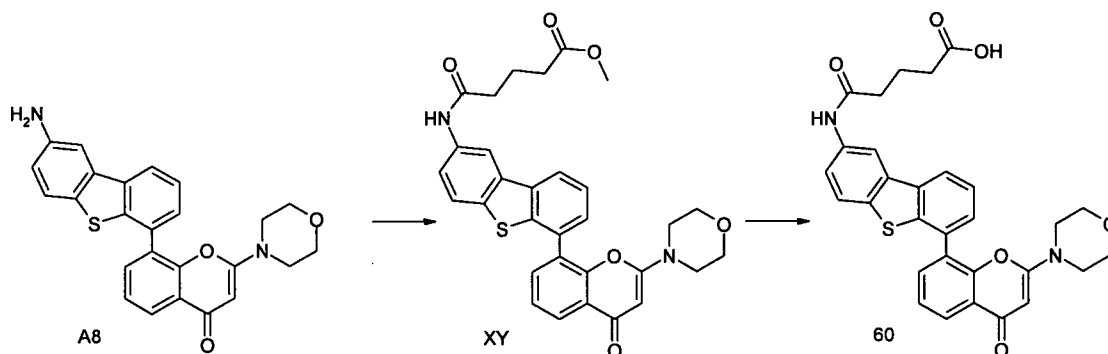
4-(4,6-Dimethoxy[1.3.5]triazin-2-yl)-4-methylmorpholinium chloride hydrate (71.7 mg, 0.26 mmol) was added to 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8, 101 mg, 0.24 mmol) and 3-ethoxy-3-oxopropionic acid (34.3 mg, 0.26 mmol) in THF (1 mL) and DMA (1 mL) under nitrogen. The reaction mixture was evaporated to dryness and redissolved in DCM (20 mL), and washed with water (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated onto silica gel (2 g). The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford ethyl 3-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylamino)-3-oxopropionate (98 mg, 77 %) as a white solid; m/z : 543.07 (MH^+).

(b) *3-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylamino)-3-oxopropionic acid (58)*

Sodium hydroxide (0.099 mL, 0.20 mmol) was added to ethyl 3-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylamino)-3-oxopropionate (57, 98 mg, 0.18 mmol) in dioxane (10 mL). The resulting suspension was stirred at room temperature for 18 hours. The reaction mixture was acidified with 2M HCl then filtered and the filtrate was purified by preparative HPLC (Waters SunFire column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 3-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylamino)-3-oxopropionic acid (11.00 mg, 11.84 %); 1H NMR (400 MHz, $DMSO-d_6$) δ 3.12 (t, 4H), 3.43 (t, 6H), 5.57 (s,

1H), 7.57 (t, 1H), 7.63 - 7.69 (m, 3H), 7.90 (d, 1H), 7.94 (dd, 1H), 8.08 (d, 1H), 8.30 (dd, 1H), 8.68 (d, 1H), 10.45 (s, 1H), 12.67 (s, 1H); m/z : 515.76 (MH^+).

Example 33



a) Methyl 5-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylamino)-5-oxopentanoate (XY)

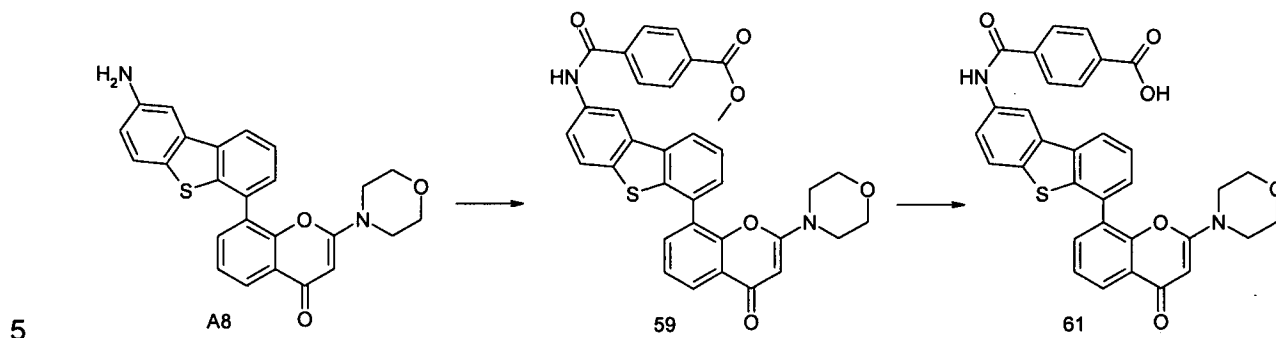
4-(4,6-Dimethoxy[1.3.5]triazin-2-yl)-4-methylmorpholinium chloride hydrate (71.0 mg, 0.26 mmol) was added to 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8, 100 mg, 0.23 mmol) and 5-methoxy-5-oxopentanoic acid (37.5 mg, 0.26 mmol) in THF (1 mL) and DMA (1 mL) under nitrogen. The reaction mixture was evaporated to dryness and redissolved in DCM (20 mL), and washed with water (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated onto silica gel (2 g). The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford methyl 5-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylamino)-5-oxopentanoate (77 mg, 59.3 %) as a white solid; m/z : 557.14 (MH^+).

(b) 5-(6-(2-Morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylamino)-5-oxopentanoic acid (60)

Sodium hydroxide (0.076 mL, 0.15 mmol) was added to methyl 5-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylamino)-5-oxopentanoate (XY), 77 mg, 0.14 mmol) in dioxane (10 mL). The resulting suspension was stirred at room temperature for 18 hours. The reaction mixture was acidified with 2M HCl then filtered and the filtrate was purified by preparative HPLC (Waters SunFire column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 5-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylamino)-5-oxopentanoic acid (9.00 mg, 11.99 %); 1H NMR (400 MHz, $CDCl_3$ + d_4 acetic acid) δ 2.09 (t, 2H), 2.51 (q,

4H), 3.11 (t, 4H), 3.48 (t, 4H), 5.93 (s, 1H), 7.36 (dd, 1H), 7.44 - 7.50 (m, 2H), 7.55 (t, 1H), 7.68 (d, 1H), 7.76 (dd, 1H), 8.20 (dd, 1H), 8.25 (dd, 1H), 8.67 (d, 1H); m/z : 543.42 (MH^+).

Example 34



(a) Methyl 4-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylcarbamoyl)benzoate (59)

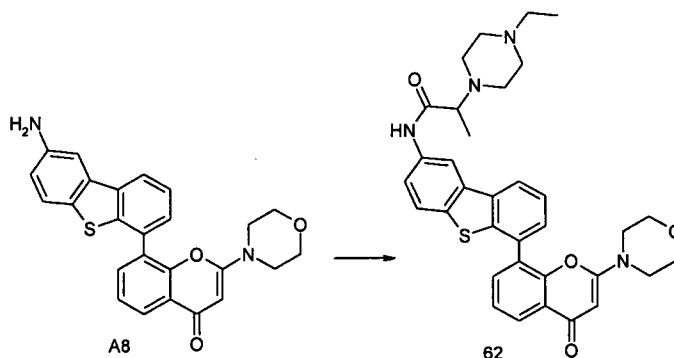
4-(4,6-Dimethoxy[1.3.5]triazin-2-yl)-4-methylmorpholinium chloride hydrate (71.0 mg, 0.26 mmol) was added to 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8, 100 mg, 0.23 mmol) and 4-(methoxycarbonyl)benzoic acid (46.2 mg, 0.26 mmol) in THF (1 mL) and DMA (1 mL) under nitrogen. The reaction mixture was evaporated to dryness and redissolved in DCM (75 mL), and washed with water (25 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated onto silica gel (2 g). The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford methyl 4-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylcarbamoyl)benzoate (66.0 mg, 48%) as a white solid; m/z : 591.08 (MH^+).

b) 4-(6-(2-Morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylcarbamoyl)benzoic acid (61)

Sodium hydroxide (0.061 mL, 0.12 mmol) was added to methyl 4-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylcarbamoyl)benzoate (59, 66 mg, 0.11 mmol) in dioxane (10 mL). The resulting suspension was stirred at room temperature for 18 hours. The reaction mixture was acidified with 2M HCl and the filtrate was purified by preparative HPLC (Waters SunFire column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 4-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylcarbamoyl)benzoic acid (7.00 mg, 11%); 1H NMR (400 MHz, $DMSO-d_6$) δ 3.13 (t, 4H), 3.44 (t, 4H), 5.58 (s, 1H), 7.58 (t,

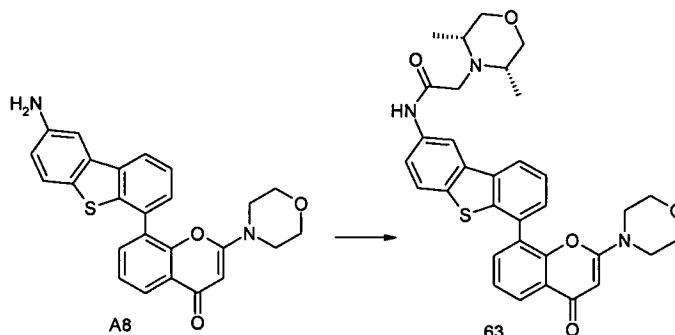
1H), 7.68 - 7.73 (m, 2H), 7.87 - 7.92 (m, 2H), 8.01 (d, 1H), 8.08 - 8.16 (m, 5H), 8.34 (dd, 1H), 8.86 - 8.87 (m, 1H), 10.68 (s, 1H), 13.25 (s, 1H); m/z : 575.82 (MH^+).

Example 35



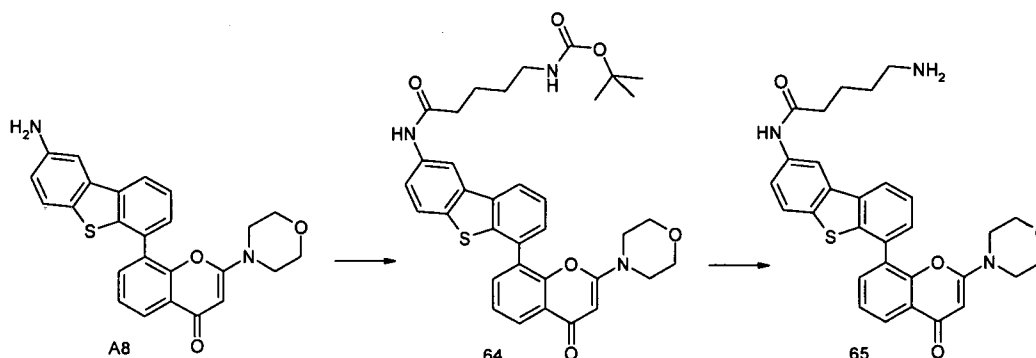
2-(4-ethylpiperazin-1-yl)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)propanamide (62)

2-Bromopropionic acid (0.020 mL, 0.26 mmol) was added to 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8, 100 mg, 0.23 mmol) and N,N-Diisopropylethylamine (0.041 mL, 0.23 mmol) in DCM (3 mL). The resulting suspension was stirred at room temperature for 1 hour. 1-Ethylpiperazine (0.019 mL, 0.15 mmol) was added to 2-chloro-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)propanamide (26 mg, 0.05 mmol) in DMA (0.25 mL). The resulting solution was stirred at room temperature for 18 hours. The reaction was incomplete and further 1-ethylpiperazine (0.019 mL, 0.15 mmol) was added and the solution was stirred at room temperature for a further 45 hours. The reaction mixture was sealed into a microwave tube. The reaction was heated to 100°C for 30 minutes in the microwave reactor and cooled to RT. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 2-(4-ethylpiperazin-1-yl)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)propanamide (21.00 mg, 70.2 %); 1H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, 3H), 1.38 (d, 3H), 2.49 (q, 2H), 2.53 - 2.70 (m, 3H), 2.72 - 2.77 (m, 1H), 3.07 (t, 4H), 3.30 (q, 1H), 3.48 - 3.51 (m, 8H), 5.49 (s, 1H), 7.38 (dd, 1H), 7.46 - 7.52 (m, 2H), 7.57 (t, 1H), 7.72 (d, 1H), 7.76 (dd, 1H), 8.25 (dd, 1H), 8.28 (dd, 1H), 8.78 (d, 1H), 9.54 (s, 1H); m/z : 597.16 (MH^+).

Example 36

2-((3S,5R)-3,5-Dimethylmorpholino)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (63)

- 5 Chloroacetyl chloride (0.020 mL, 0.25 mmol) was added to 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8, 97 mg, 0.23 mmol) in DMA (2 mL). The resulting solution was stirred at room temperature for 1 hour. (3R,5S)-3,5-dimethylmorpholine (103 mg, 0.68 mmol), Sodium iodide (3.39 mg, 0.02 mmol) and N,N-Diisopropylethylamine (0.158 mL, 0.91 mmol) were added and the reaction mixture sealed into a microwave tube. The
- 10 reaction was heated to 120 °C for 1 hour in the microwave reactor and cooled to RT. The reaction mixture was diluted with EtOAc (50 mL), and washed with water (50 mL). The organic layer was dried over MgSO₄, filtered and evaporated onto silica gel (5 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-((3S,5R)-3,5-
- 15 dimethylmorpholino)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (86 mg, 65.1 %) as a brown solid. The crude product was purified by preparative HPLC (Waters SunFire column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 2-
- 20 ((3S,5R)-3,5-dimethylmorpholino)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (55 mg, 42%); ¹H NMR (400 MHz, CDCl₃) δ 1.05 (d, 4H), 1.20 (d, 2H), 2.31 (q, 1H), 2.54 - 2.63 (m, 1H), 2.72 - 2.80 (m, 1H), 3.07 (t, 4H), 3.30 - 3.40 (m, 3H), 3.50 (t, 4H), 3.72 - 3.80 (m, 1H), 3.84 (dt, 1H), 5.50 (s, 1H), 7.42 - 7.52 (m, 3H), 7.58 (t, 1H), 7.73 - 7.77 (m, 2H), 8.24 - 8.30 (m, 2H), 8.70 (dd, 1H), 9.40 & 9.52 (2 s,
- 25 1H); *m/z*: 584.36 (MH⁺).

Example 37

(a) *tert*-Butyl 5-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylamino)-5-oxopentylcarbamate (64)

- 5 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8, 100 mg, 0.23 mmol) was added to 5-(*tert*-butoxycarbonylamino)pentanoic acid (57.6 mg, 0.27 mmol), N,N-Diisopropylethylamine (0.098 mL, 0.56 mmol) and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (98 mg, 0.26 mmol) in DMA (1 mL). The reaction mixture was diluted with EtOAc (25 mL), and washed sequentially with water (25 mL) and
- 10 saturated brine (5 mL). The organic layer was dried over MgSO₄, filtered and evaporated onto silica gel (2 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford *tert*-butyl 5-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylamino)-5-oxopentylcarbamate (115 mg, 78 %) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.46 (s, 9H), 1.59 - 1.66 (m, 2H), 1.80 - 1.87 (m, 2H), 2.50 (t, 2H), 3.06 (t, 4H), 3.22 (q, 2H), 3.49 (t, 4H), 4.71 (s, 1H), 5.50 (s, 1H), 7.43 - 7.50 (m, 3H), 7.55 (t, 1H), 7.69 (dd, 1H), 7.75 (dd, 1H), 8.02 (s, 1H), 8.20 (dd, 1H), 8.28 (dd, 1H), 8.71 (d, 1H); *m/z*: 628.17 (MH⁺).
- 15

(b) 5-Amino-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)pentanamide (65)

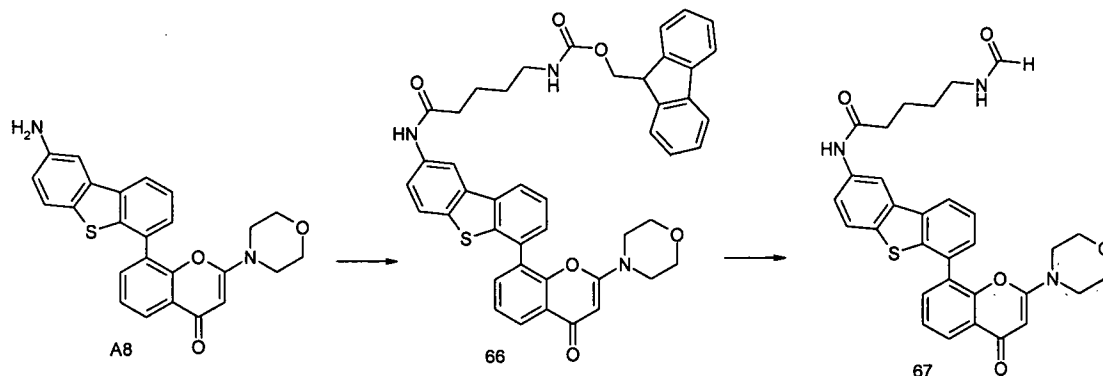
20

- Hydrogen chloride in 1,4-dioxane (0.434 mL, 1.74 mmol) was added to *tert*-butyl 5-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylamino)-5-oxopentylcarbamate (64, 109 mg, 0.17 mmol) in dioxane (1 mL). The resulting suspension was stirred at room temperature for 1 hour. The reaction mixture was diluted with MeOH (10 mL), then purified
- 25 by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and product containing fractions were evaporated onto silica gel (5 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 20% methanolic ammonia in DCM. Pure fractions were evaporated to dryness to afford 5-amino-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-

2-yl)pentanamide (83 mg, 91 %) as a white solid; ^1H NMR (400 MHz, DMSO- d_6) δ 1.62 - 1.76 (m, 4H), 2.44 (t, 2H), 2.85 (t, 2H), 3.11 (t, 4H), 3.27 (s, 2H), 3.43 (t, 4H), 5.55 (s, 1H), 7.54 (t, 1H), 7.62 - 7.70 (m, 3H), 7.84 - 7.88 (m, 2H), 8.08 (dd, 1H), 8.23 (dd, 1H), 8.70 (d, 1H), 10.26 (s, 1H); m/z : 528.10 (MH^+).

5

Example 38



(a) (9H-fluoren-9-yl)methyl 5-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylamino)-5-oxopentylcarbamate (66)

10 8-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one (A8, 100 mg, 0.23 mmol) was added to 5-(9H-fluoren-9-ylmethoxycarbonylamino)pentanoic acid (87 mg, 0.26 mmol), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (0.137 mL, 0.26 mmol) and N,N-Diisopropylethylamine (0.089 mL, 0.51 mmol) in DMA (1 mL). The resulting solution was stirred at room temperature for 24 hours. The reaction

15 mixture was diluted with EtOAc (150 mL), and washed sequentially with water (50 mL) and saturated brine (10 mL). The organic layer was dried over MgSO_4 , filtered and evaporated onto silica gel (5 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford

20 (9H-fluoren-9-yl)methyl 5-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylamino)-5-oxopentylcarbamate (220 mg, 126 %) as a white solid; ^1H NMR (400 MHz, DMSO) δ 1.47 - 1.55 (m, 2H), 1.62 - 1.70 (m, 2H), 2.39 (t, 2H), 3.06 (q, 2H), 3.11 (t, 4H), 3.43 (t, 4H), 4.21 (t, 1H), 4.30 (d, 2H), 5.54 (s, 1H), 7.27 (t, 1H), 7.31 (t, 2H), 7.39 (t, 2H), 7.54 (t, 1H), 7.60 - 7.69 (m, 5H), 7.84 (s, 1H), 7.86 (d, 1H), 8.08 (dd, 1H), 8.24 (dd, 1H), 8.70 (d, 1H), 10.09 (s, 1H); m/z : 750.13 (MH^+).

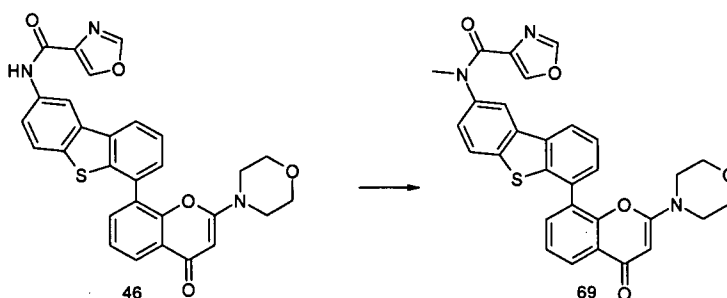
25

(b) 5-Formamido-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)pentanamide (67)

4-Dimethylaminopyridine (1000 mg, 8.19 mmol) was added to (9H-fluoren-9-yl)methyl 5-(6-

(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-ylamino)-5-oxopentylcarbamate (65, 220 mg, 0.29 mmol) in DMF (20 mL). The resulting solution was stirred at room temperature for 24 hours. The reaction mixture was evaporated to dryness and redissolved in EtOAc (125 mL), and washed with water (75 mL). The organic layer was dried over MgSO_4 , filtered and evaporated onto silica gel (5 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Product containing fractions were evaporated to dryness. The crude product was purified by preparative LCMS (Waters XBridge Prep C18 OBD column, 5 μ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and 3:1 MeOH:MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 5-formamido-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)pentanamide (10 mg, 6%) as a white solid; ^1H NMR (400 MHz, CDCl_3) δ 1.65 - 1.72 (m, 2H), 1.82 - 1.89 (m, 2H), 2.52 (t, 2H), 3.07 (t, 4H), 3.43 (q, 2H), 3.50 (t, 4H), 5.49 (s, 1H), 5.78 (s, 1H), 7.42 - 7.52 (m, 3H), 7.56 (t, 1H), 7.71 (d, 1H), 7.75 (dd, 1H), 7.86 (s, 1H), 8.22 (dd, 1H), 8.26 (s, 1H), 8.28 (dd, 1H), 8.71 (d, 1H); m/z : 556.72 (MH^+).

Example 39

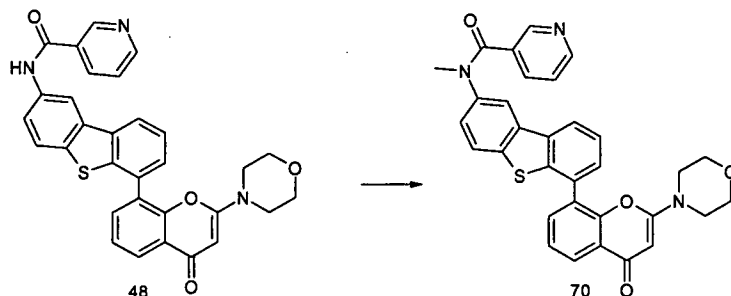


N-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzo[thiophen-2-yl]-1,3-oxazole-4-carboxamide (69)

Sodium hydride, 60% dispersion in mineral oil (13.10 mg, 0.33 mmol) was added in one portion to N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzo[thiophen-2-yl]-1,3-oxazole-4-carboxamide (46, 135 mg, 0.26 mmol) in anhydrous DMF (2.5 mL) cooled to 0°C. The resulting mixture was stirred under nitrogen at 0°C for 30 minutes then methyl iodide (10% solution in anhydrous DMF, 0.17 mL, 0.27 mmol) was added and the reaction mixture allowed to warm to ambient temperature and stirred for a further 1 hour. The reaction mixture was diluted with methanol (20 mL) and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3 /MeOH and evaporated to dryness to afford impure material. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH_3 /MeOH

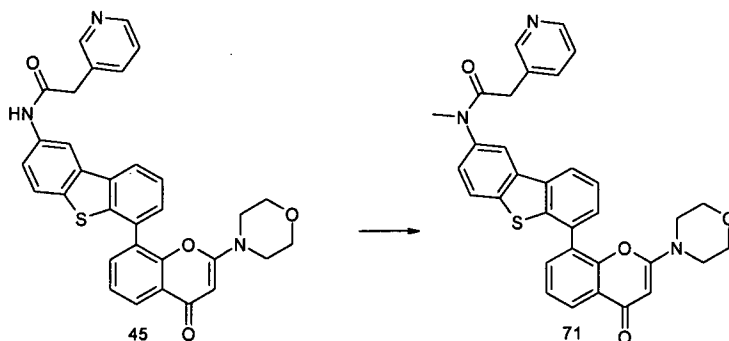
in DCM. Pure fractions were evaporated to dryness to afford N-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]-1,3-oxazole-4-carboxamide (122 mg, 88 %) as a white solid.; ¹H NMR (400 MHz, CDCl₃) δ 3.08 (4H, t), 3.50 (4H, t), 3.58 (3H, s), 5.49 (1H, s), 7.28 - 7.31 (1H, m), 7.43 - 7.54 (3H, m), 7.59 (2H, t), 7.74 - 7.77 (1H, m), 7.80 (1H, d), 8.03 (1H, d), 8.13 - 8.15 (1H, m), 8.26 - 8.29 (1H, m); m/z: 538.073 (MH⁺).

Example 40



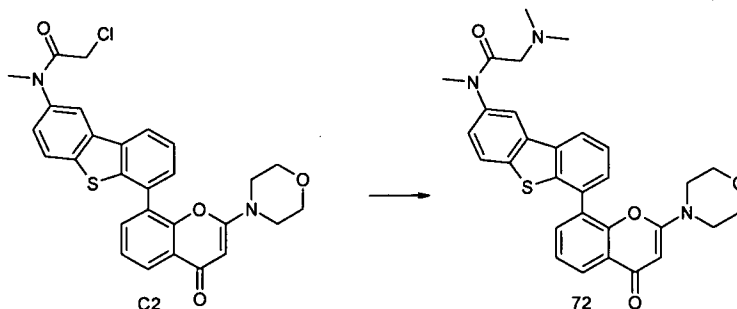
N-methyl-*N*-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]pyridine-3-carboxamide (70)

Sodium hydride, 60% dispersion in mineral oil (12.12 mg, 0.30 mmol) was added in one portion to N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]pyridine-3-carboxamide (48, 147 mg, 0.28 mmol) in anhydrous DMF (2737 μL) cooled to 0°C. The resulting mixture was stirred under nitrogen at 0°C for 20 minutes then methyl iodide (10% solution in anhydrous DMF, 0.18 mL, 0.29 mmol) was added and the reaction mixture allowed to warm to ambient temperature and stirred for a further 1 hour. The reaction mixture was diluted with methanol (20 mL) and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure material. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford *N*-methyl-*N*-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]pyridine-3-carboxamide (101 mg, 67%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 3.08 (4H, t), 3.49 - 3.52 (4H, m), 3.63 (3H, s), 5.51 (1H, s), 7.11 - 7.21 (2H, m), 7.46 - 7.53 (2H, m), 7.58 (1H, t), 7.68 - 7.75 (3H, m), 7.90 (1H, d), 8.06 - 8.08 (1H, m), 8.27 - 8.29 (1H, m), 8.41 - 8.42 (1H, m), 8.54 (1H, s); m/z: 548.11 (MH⁺).

Example 41

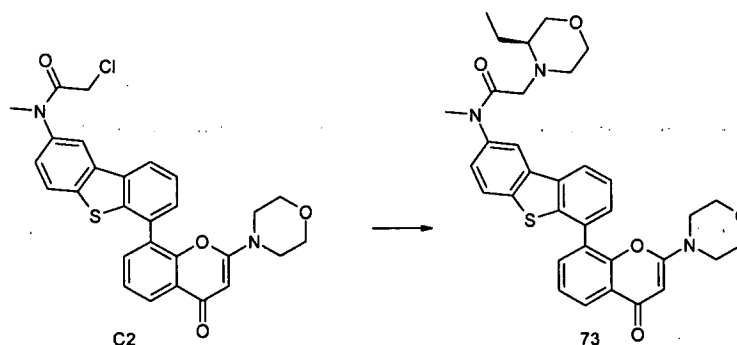
N-methyl-*N*-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]-2-pyridin-3-ylacetamide (71)

- 5 Sodium hydride, 60% dispersion in mineral oil (11.25 mg, 0.28 mmol) was added in one portion to *N*-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]-2-pyridin-3-ylacetamide (45, 140 mg, 0.26 mmol) in anhydrous DMF (2.5 mL) cooled to 0°C. The resulting mixture was stirred under nitrogen at 0°C for 20 minutes then methyl iodide (10% solution in anhydrous DMF, 0.17 mL, 0.27 mmol) was added and the reaction mixture allowed
- 10 to warm to ambient temperature and stirred for a further 1 hour. The reaction mixture was diluted with methanol (20 mL) and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure material. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH
- 15 in DCM. Pure fractions were evaporated to dryness to afford impure product. This was then purified by preparative HPLC (Waters SunFire column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and 3:1 MeOH/MeCN as eluents. Fractions containing the desired compound were free-based by ion exchange chromatography, using an SCX column. The desired product was eluted from the
- 20 column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford *N*-methyl-*N*-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]-2-pyridin-3-ylacetamide (8.50 mg, 5.92 %) as a cream solid; ¹H NMR (400 MHz, CDCl₃) δ 3.13 (4H, t), 3.40 (3H, s), 3.51 (2H, s), 3.55 (4H, t), 5.52 (1H, s), 7.20 - 7.23 (1H, m), 7.27 - 7.31 (1H, m), 7.49 - 7.53 (1H, m), 7.56 - 7.65 (3H, m), 7.78 - 7.80 (1H, m), 7.88 (1H, d), 7.93 (1H, s), 8.12 -
- 25 8.14 (1H, m), 8.16 (1H, s), 8.29 - 8.32 (1H, m), 8.46 (1H, d); *m/z*: 562.07 (MH⁺).

Example 42

2-(dimethylamino)-N-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (72)

- 5 Dimethylamine, 2M solution in THF (0.347 mL, 0.69 mmol) was added to 2-chloro-N-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (C2, 90 mg, 0.17 mmol) in anhydrous DMA (1.5 mL). The resulting solution was stirred at ambient temperature for 18 hours. The crude product was diluted with methanol and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and the crude product was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-(dimethylamino)-N-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (81 mg, 88 %) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 2.28 (6H, s), 2.95 (2H, s), 3.12 (4H, t), 3.39 (3H, s), 3.53 (4H, t), 5.51 (1H, s), 7.31 - 7.34 (1H, m), 7.50 (1H, t), 7.55 (1H, d), 7.62 (1H, t), 7.76 - 7.79 (1H, m), 7.85 (1H, d), 8.05 (1H, d), 8.20 (1H, d), 8.29 - 8.31 (1H, m); m/z: 528.10 (MH⁺).

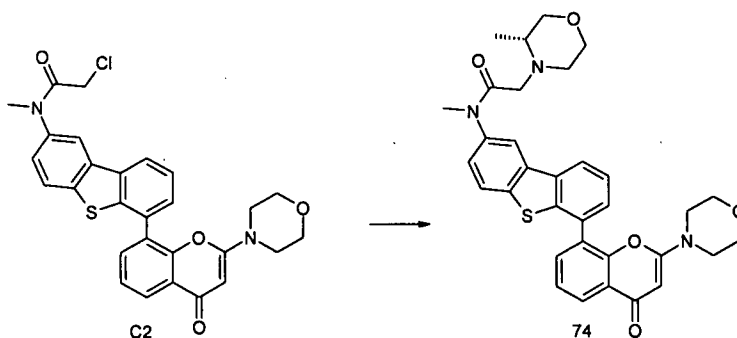
Example 43

- 20 *2-[(3S)-3-ethylmorpholin-4-yl]-N-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (73)*

(S)-3-ethylmorpholine (DD3, 55.6 mg, 0.35 mmol) as the 0.5 eq oxalate salt was dissolved in methanol and free based by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and carefully evaporated

to afford the free base. To the flask containing this material was added anhydrous DMA (1.5 mL), triethylamine (0.096 mL, 0.69 mmol) and 2-chloro-N-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (C2, 90 mg, 0.17 mmol) and the solution stirred at ambient temperature for 2 hours. The reaction was incomplete so the temperature was increased to 60°C and the reaction mixture was stirred for a further 3 days. The crude product was diluted with methanol and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and the crude product was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-[(3S)-3-ethylmorpholin-4-yl]-N-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (72.6 mg, 70%) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 0.71 (3H, br s), 1.16 - 1.32 (2H, m), 2.32 (1H, br s), 2.54 (1H, br s), 2.74 (1H, d), 2.98 (1H, d), 3.12 (4H, t), 3.27 - 3.34 (2H, m), 3.38 (3H, s), 3.54 (4H, t), 3.59 - 3.68 (3H, m), 5.51 (1H, s), 7.32 (1H, d), 7.50 (1H, t), 7.56 (1H, d), 7.63 (1H, t), 7.78 (1H, d), 7.85 (1H, d), 8.04 (1H, s), 8.19 (1H, d), 8.30 (1H, d); m/z: 598.15 (MH⁺).

Example 44

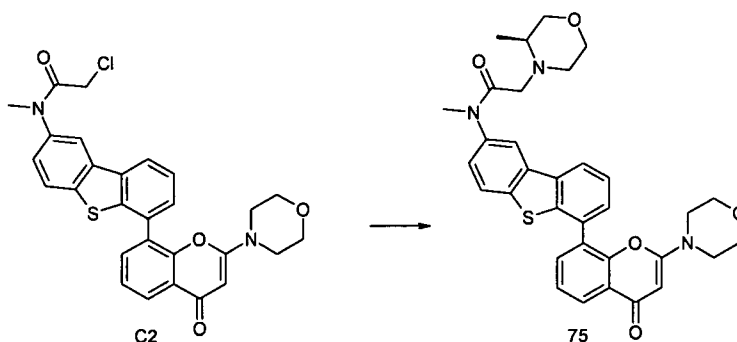


N-methyl-2-[(3R)-3-methylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (74)

A suspension of 2-chloro-N-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (C2, 55 mg, 0.11 mmol) in anhydrous DMA (1.5 mL) and DCM (1 mL) was added to (3R)-3-methylmorpholine (CC3, 42.1 mg, 0.23 mmol) and triethylamine (59 mL, 0.42 mmol). The resulting solution was stirred at 60°C for 2 hours. The crude product was diluted with methanol and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and the crude product was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford *N*-methyl-2-[(3R)-3-methylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxochromen-8-

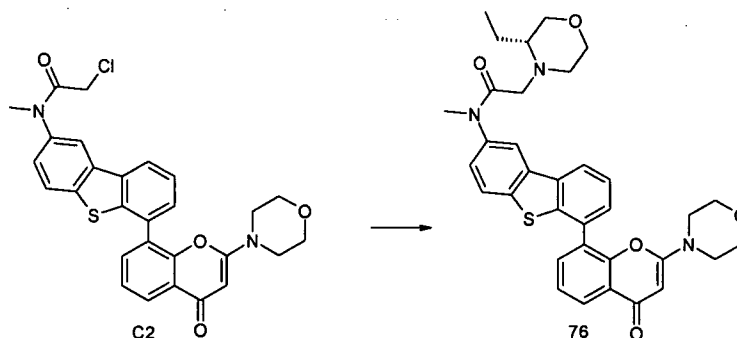
yl)dibenzothiophen-2-yl]acetamide (63.8 mg, 95 %) as a white solid; ^1H NMR (400 MHz, CDCl_3) δ 1.08 (3H, d), 1.84 (1H, s), 2.16 (1H, s), 2.66 (1H, d), 2.77 (1H, d), 2.96 (2H, s), 3.12 (4H, t), 3.39 (3H, s), 3.54 (4H, t), 3.66 - 3.78 (3H, m), 5.51 (1H, s), 7.32 - 7.34 (1H, m), 7.50 (1H, t), 7.56 (1H, d), 7.62 (1H, t), 7.77 - 7.79 (1H, m), 7.85 (1H, d), 8.07 (1H, d), 8.18 - 8.20 (1H, m), 8.29 - 8.31 (1H, m); m/z : 584.12 (MH^+).

Example 45



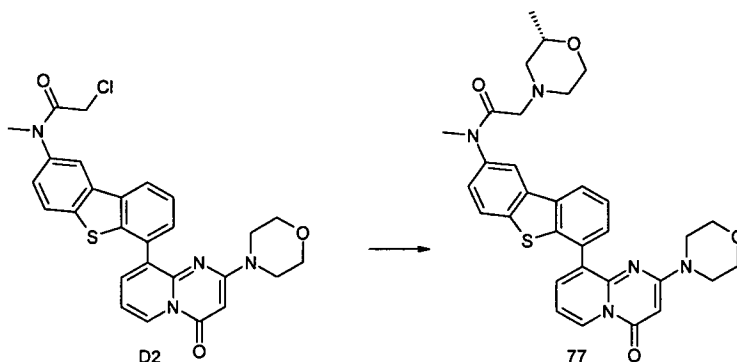
N-methyl-2-[(3*S*)-3-methylmorpholin-4-yl]-*N*-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (75)

A suspension of 2-chloro-*N*-methyl-*N*-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (C2, 55 mg, 0.11 mmol) in anhydrous DMA (1.5 mL) and DCM (1 mL) was added to (3*S*)-3-methylmorpholine (38.6 mg, 0.21 mmol) and triethylamine (0.059 mL, 0.42 mmol). The resulting solution was stirred at 60°C for 2 hours. The crude product was diluted with methanol and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3/MeOH and the crude product was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH_3/MeOH in DCM. Pure fractions were evaporated to dryness to afford *N*-methyl-2-[(3*S*)-3-methylmorpholin-4-yl]-*N*-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (59.0 mg, 95 %) as a white solid; ^1H NMR (400 MHz, CDCl_3) δ 1.08 (3H, d), 1.85 (1H, br s), 2.17 (1H, br s), 2.66 - 2.79 (2H, m), 2.97 (2H, s), 3.12 (4H, t), 3.39 (3H, s), 3.54 (4H, t), 3.69 - 3.78 (3H, m), 5.51 (1H, s), 7.32 - 7.34 (1H, m), 7.50 (1H, t), 7.56 (1H, d), 7.62 (1H, t), 7.77 - 7.79 (1H, m), 7.85 (1H, d), 8.07 (1H, d), 8.19 (1H, d), 8.29 - 8.31 (1H, m); m/z : 584.14 (MH^+).

Example 46

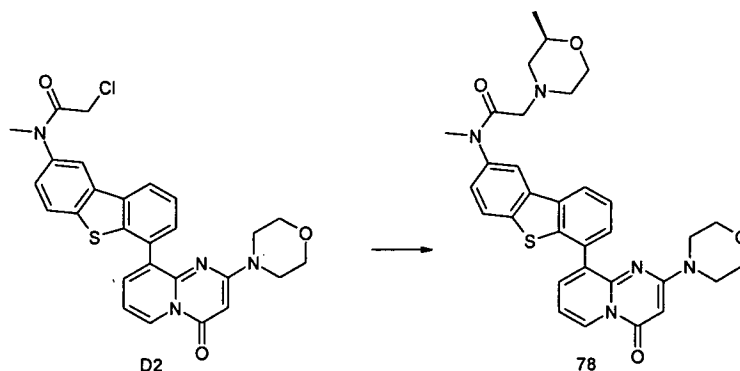
2-[(3R)-3-ethylmorpholin-4-yl]-N-methyl-N-[6-(2-morpholin-4-yl)-4-oxochromen-8-yl]dibenzothiophen-2-ylacetamide (76)

- 5 (R)-3-ethylmorpholine (DD3, 55.6 mg, 0.35 mmol) as the 0.5 eq oxalate salt was dissolved in methanol and free based by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and carefully evaporated to afford the free base. To the flask containing this material was added anhydrous DMA (1.5 mL), triethylamine (96 µL, 0.69 mmol) and 2-chloro-N-methyl-N-[6-(2-morpholin-4-yl)-4-oxochromen-8-yl]dibenzothiophen-2-ylacetamide (90 mg, 0.17 mmol) and the solution
- 10 stirred at ambient temperature for 2 hours. The reaction was incomplete so the temperature was increased to 60°C and the reaction mixture was stirred for a further 3 days. The crude product was diluted with methanol and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and the crude product was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-[(3R)-3-ethylmorpholin-4-yl]-N-methyl-N-[6-(2-morpholin-4-yl)-4-oxochromen-8-yl]dibenzothiophen-2-ylacetamide (72 mg, 69%) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 0.71 (3H, br s), 1.16 - 1.32 (2H, m), 2.32 (1H, br s), 2.54 (1H, br s), 2.74 (1H, d), 2.98 (1H, d), 3.12 (4H, t), 3.27 - 3.34 (2H, m), 3.38 (3H, s), 3.54 (4H, t), 3.59 - 3.68 (3H, m), 5.51 (1H, s), 7.32 (1H, d), 7.50 (1H, t), 7.56 (1H, d), 7.63 (1H, t), 7.78 (1H, d), 7.85 (1H, d), 8.04 (1H, s), 8.19 (1H, d), 8.30 (1H, d); m/z: 598.15 (MH⁺).
- 20

Example 47

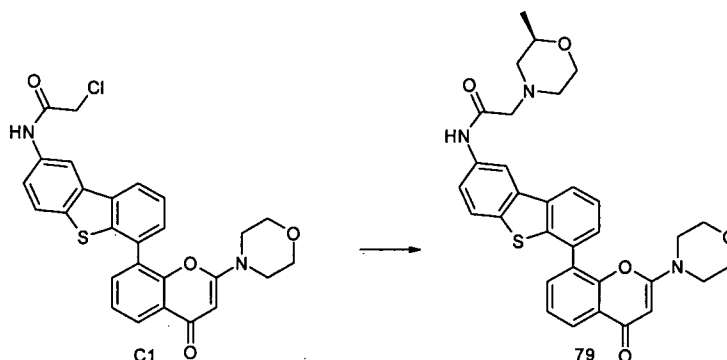
N-methyl-2-[(2*S*)-2-methylmorpholin-4-yl]-*N*-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-*a*]pyrimidin-9-yl)dibenzothiophen-2-yl]acetamide (77)

- 5 *N*-ethyl-*N*-isopropylpropan-2-amine (0.413 mL, 2.37 mmol) was added to a suspension of 2-chloro-*N*-methyl-*N*-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-*a*]pyrimidin-9-yl)dibenzothiophen-2-yl]acetamide (D2, 410 mg, 0.79 mmol) and (2*S*)-2-methylmorpholine hydrobromide (EE3, 216 mg, 1.18 mmol) in anhydrous DMA (7 mL). The resulting suspension was stirred under nitrogen at ambient temperature for 3 days. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford (*S*)-*N*-methyl-2-(2-methylmorpholino)-*N*-[6-(2-morpholino-4-oxo-4H-pyrido[1,2-*a*]pyrimidin-9-yl)dibenzo[*b,d*]thiophen-2-yl]acetamide (369 mg, 80 %) as a pale yellow foam. This was slurried in diethyl ether and the precipitate was collected by filtration, washed with Et₂O (10 mL) and dried under vacuum to afford (*N*-methyl-2-[(2*S*)-2-methylmorpholin-4-yl]-*N*-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-*a*]pyrimidin-9-yl)dibenzothiophen-2-yl]acetamide (322 mg, 69.8 %) as a cream solid, which was used without further purification; ¹H NMR (400 MHz, CDCl₃) δ 1.07 (3H, d), 1.81 (1H, t), 2.13 (1H, t), 2.65 (1H, d), 2.75 (1H, d), 2.91 - 3.00 (2H, m), 3.37 - 3.38 (7H, m), 3.58 (4H, t), 3.65 - 3.77 (3H, m), 5.64 (1H, s), 7.03 (1H, t), 7.29 - 7.32 (1H, m), 7.58 - 7.65 (2H, m), 7.83 (1H, d), 7.86 - 7.89 (1H, m), 8.05 (1H, d), 8.17 - 8.19 (1H, m), 9.05 - 9.07 (1H, m); *m/z*: 584.50 (MH⁺).

Example 48

N-methyl-2-[(2*R*)-2-methylmorpholin-4-yl]-*N*-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-*a*]pyrimidin-9-yl)dibenzothiophen-2-yl]acetamide (78)

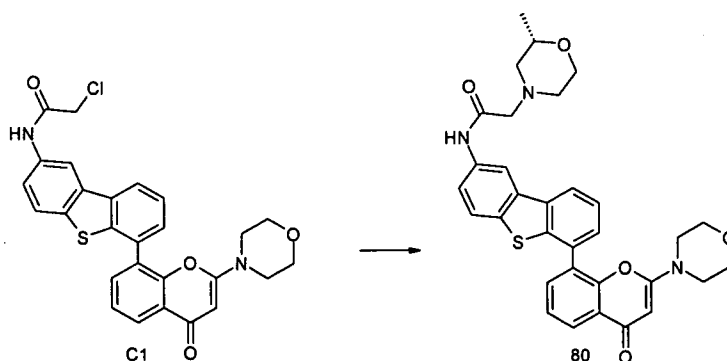
- 5 *N*-ethyl-*N*-isopropylpropan-2-amine (0.393 mL, 2.25 mmol) was added to a suspension of 2-chloro-*N*-methyl-*N*-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-*a*]pyrimidin-9-yl)dibenzothiophen-2-yl]acetamide (D2, 390 mg, 0.75 mmol) and (2*R*)-2-methylmorpholine hydrobromide (FF3, 205 mg, 1.13 mmol) in anhydrous DMA (7 mL). The resulting suspension was stirred under nitrogen at 60°C for 18 hours. The crude product was purified by ion exchange
- 10 chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford *N*-methyl-2-[(2*R*)-2-methylmorpholin-4-yl]-*N*-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-*a*]pyrimidin-9-yl)dibenzothiophen-2-yl]acetamide
- 15 (419 mg, 96 %) as a pale yellow foam. This was slurried in diethyl ether and the precipitate was collected by filtration, washed with Et₂O (10 mL) and dried under vacuum to afford (*R*)-*N*-methyl-2-(2-methylmorpholino)-*N*-(6-(2-morpholino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl)dibenzo[*b,d*]thiophen-2-yl)acetamide (366 mg, 83 %) as a cream solid, which was used without further purification; ¹H NMR (400 MHz, CDCl₃) δ 1.07 (3H, d), 1.81 (1H, t), 2.13 (1H, t), 2.65 (1H, d), 2.75 (1H, d), 2.91 - 3.00 (2H, m), 3.37 - 3.38 (7H, m), 3.58 (4H, t), 3.65 - 3.77 (3H, m), 5.64 (1H, s), 7.03 (1H, t), 7.29 - 7.32 (1H, m), 7.58 - 7.65 (2H, m), 7.83 (1H, d), 7.86 - 7.89 (1H, m), 8.05 (1H, d), 8.17 - 8.19 (1H, m), 9.05 - 9.07 (1H, m); *m/z*: 584.49 (MH⁺).
- 20

Example 49

2-[(2R)-2-methylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzo[b,d]thiophen-2-yl]acetamide (79)

- 5 A suspension of 2-chloro-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (C1, 119 mg, 0.235 mmol) in anhydrous DMA (1044 μ L) and DCM (1 mL) was added to (2R)-2-methylmorpholine hydrobromide (FF3, 86 mg, 0.47 mmol) and triethylamine (131 μ L, 0.94 mmol). The resulting solution was stirred at 60°C for 2 hours. The crude product was diluted with methanol and purified by ion exchange chromatography,
- 10 using an SCX column. The desired product was eluted from the column using 7M NH_3/MeOH and the crude product was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH_3/MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-[(2R)-2-methylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxochromen-8-
- 15 yl)dibenzo[b,d]thiophen-2-yl]acetamide (125 mg, 93 %) as a white solid; ^1H NMR (400 MHz, CDCl_3) δ 1.22 (3H, d), 2.18 (1H, t), 2.47 - 2.53 (1H, m), 2.79 - 2.86 (2H, m), 3.07 (4H, t), 3.22 (2H, s), 3.50 (4H, t), 3.74 - 3.82 (2H, m), 3.95 - 3.99 (1H, m), 5.49 (1H, s), 7.43 - 7.45 (1H, m), 7.47 - 7.50 (2H, m), 7.58 (1H, t), 7.73 - 7.77 (2H, m), 8.25 (1H, s), 8.27 - 8.29 (1H, m), 8.71 (1H, d), 9.27 (1H, s); m/z : 570.08 (MH^+).

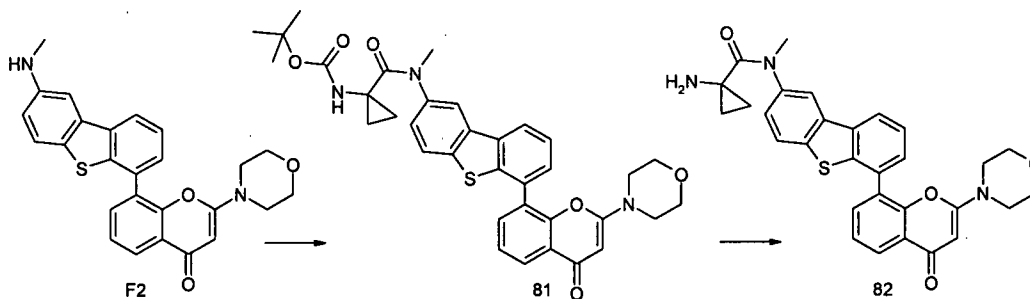
20 **Example 50**



2-[(2S)-2-methylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (80)

A suspension of 2-chloro-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)acetamide (C1, 55 mg, 0.11 mmol) in anhydrous DMA (1.5 mL) and DCM (1 mL) was added to (2S)-2-methylmorpholine hydrobromide (EE3, 86 mg, 0.47 mmol) and triethylamine (0.059 mL, 0.42 mmol). The resulting solution was stirred at 60°C for 2 hours. The crude product was diluted with methanol and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and the crude product was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-[(2S)-2-methylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (108 mg, 81 %) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.22 (3H, d), 2.18 (1H, t), 2.47 - 2.53 (1H, m), 2.79 - 2.86 (2H, m), 3.07 (4H, t), 3.22 (2H, s), 3.50 (4H, t), 3.74 - 3.82 (2H, m), 3.95 - 3.99 (1H, m), 5.49 (1H, s), 7.43 - 7.45 (1H, m), 7.47 - 7.50 (2H, m), 7.58 (1H, t), 7.73 - 7.77 (2H, m), 8.25 (1H, s), 8.27 - 8.29 (1H, m), 8.71 (1H, d), 9.27 (1H, s); m/z: 570.08 (MH⁺).

Example 51



1-amino-N-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (82)

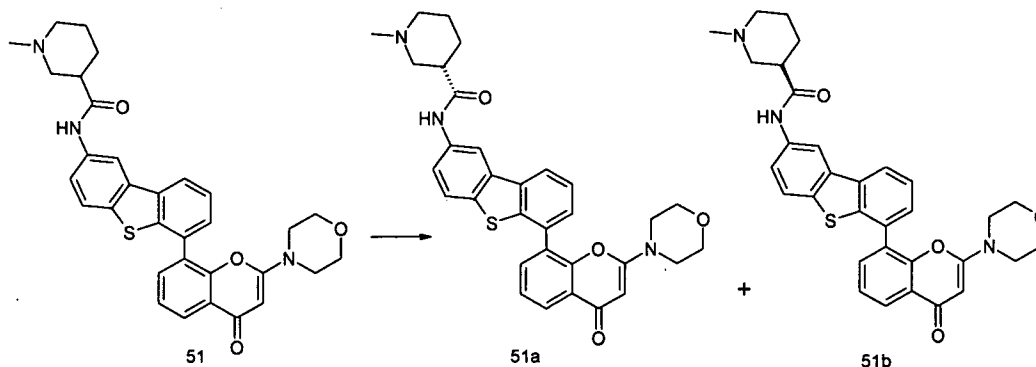
(a) tert-butyl N-[1-[methyl-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]carbamoyl]cyclopropyl]carbamate (81)

O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (138 mg, 0.36 mmol) was added in one portion to 8-[8-(methylamino)dibenzothiophen-4-yl]-2-morpholin-4-ylchromen-4-one (F2, 146 mg, 0.33 mmol), 1-(tert-butoxycarbonylamino)cyclopropanecarboxylic acid (69.7 mg, 0.35 mmol) and N,N-diisopropylethylamine (144 µL, 0.82 mmol) in anhydrous DMA (3156 µL). The resulting solution was stirred under nitrogen at ambient temperature for 3 days. The reaction was incomplete and further 1-(tert-butoxycarbonylamino)cyclopropanecarboxylic acid (69.7 mg,

0.35 mmol) and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (138 mg, 0.36 mmol) were added and the solution was stirred at 60°C for a further 24 hours. The cooled reaction mixture was diluted with methanol and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure tert-butyl N-[1-[methyl-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]carbamoyl]cyclopropyl]carbamate as a beige solid. This was taken through to de-boc with no further purification; m/z: 626.40 (MH⁺).

(b) *1-amino-N-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (82)*

A solution of trifluoroacetic acid (0.4 mL, 5.19 mmol) in DCM (4 mL) was added to tert-butyl N-[1-[methyl-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]carbamoyl]cyclopropyl]carbamate (81, 206 mg, 0.33 mmol). The resulting solution was stirred under nitrogen at ambient temperature for 1 hour. The reaction was incomplete and further trifluoroacetic acid (0.4 mL, 5.19 mmol) and a drop of water was added and the solution was stirred at ambient temperature for a further 18 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford still slightly impure product. The crude product was repurified by flash silica chromatography, elution gradient 0 to 4% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford 1-amino-N-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (128 mg, 74.0 %) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 0.71 - 0.74 (2H, m), 1.30 (2H, br s), 1.32 - 1.35 (2H, m), 3.12 (4H, t), 3.42 (3H, s), 3.54 (4H, t), 5.51 (1H, s), 7.41 - 7.43 (1H, m), 7.50 (1H, t), 7.54 - 7.56 (1H, m), 7.62 (1H, t), 7.77 - 7.79 (1H, m), 7.87 (1H, d), 8.11 (1H, d), 8.17 - 8.19 (1H, m), 8.29 - 8.31 (1H, m); m/z: 526.14 (MH⁺).

Example 52

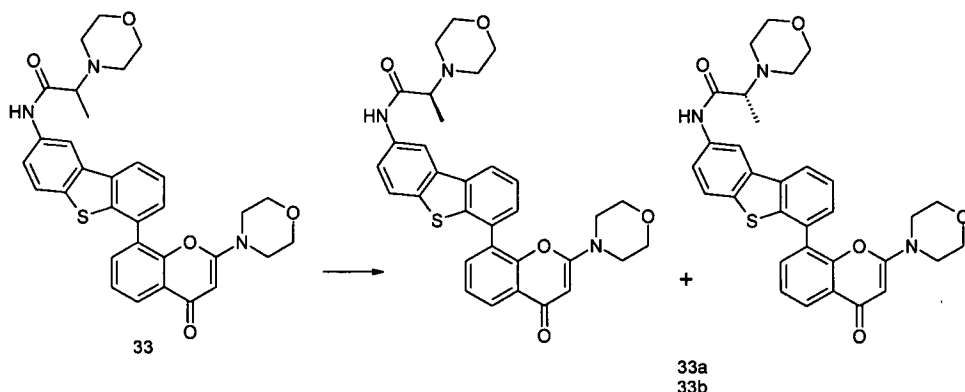
(3R)-1-methyl-N-[6-(2-morpholino-4-oxo-chromen-8-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (51a) and (3S)-1-methyl-N-[6-(2-morpholino-4-oxo-chromen-8-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (51b)

A sample of racemic 1-methyl-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)piperidine-3-carboxamide (51) was taken and the two enantiomers separated by preparative chiral-HPLC on a Merck Chiralcel OD column, eluting isocratically with 50% EtOH in MeOH as eluent. The fractions containing the desired compound were evaporated to dryness to afford the two separated isomers. These compounds were insoluble in DCM and seemed to retain solvent. The first eluted enantiomer was then purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford (3R)-1-methyl-N-[6-(2-morpholino-4-oxo-chromen-8-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide as a white solid. NMR analysis of both enantiomers showed impurities, so were further purified by flash silica chromatography. The first eluted "R" isomer was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford (3R)-1-methyl-N-[6-(2-morpholino-4-oxo-chromen-8-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (36.4 mg), EN02414-53-1 (36.4 mg, 0.066 mmol) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.41 - 1.60 (2H, m), 1.71 - 1.75 (1H, m), 1.86 - 1.92 (2H, m), 2.10 (1H, t), 2.23 (3H, s), 2.45 - 2.47 (1H, m), 2.61 - 2.70 (1H, m), 2.73 (1H, d), 3.11 (4H, t), 3.43 (4H, t), 5.57 (1H, s), 7.57 (1H, t), 7.64 - 7.70 (3H, m), 7.89 (2H, t), 8.07 - 8.09 (1H, m), 8.27 - 8.29 (1H, m), 8.70 (1H, d), 10.23 (1H, s) m/z: 554.42 (MH⁺).

The second eluted "S" isomer was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford (3S)-1-methyl-N-[6-(2-morpholino-4-oxo-chromen-8-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (21.90 mg) EN02414-53-2 (21.9 mg, 0.040 mmol) as a white solid; ¹H NMR

(400 MHz, CDCl₃) δ 1.41 - 1.60 (2H, m), 1.71 - 1.75 (1H, m), 1.86 - 1.92 (2H, m), 2.10 (1H, t), 2.23 (3H, s), 2.45 - 2.47 (1H, m), 2.61 - 2.70 (1H, m), 2.73 (1H, d), 3.11 (4H, t), 3.43 (4H, t), 5.57 (1H, s), 7.57 (1H, t), 7.64 - 7.70 (3H, m), 7.89 (2H, t), 8.07 - 8.09 (1H, m), 8.27 - 8.29 (1H, m), 8.70 (1H, d), 10.23 (1H, s); m/z: 554.42 (MH⁺).

5

Example 53

(2S)-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide and (2R)-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-

10 yl)dibenzothiophen-2-yl]propanamide, (33a) & (33b) - absolute stereochemistry not defined

A sample of racemic 2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide (33) was taken and the two enantiomers separated by preparative chiral-HPLC on a Merck Chiralpak AS column, eluting isocratically with 90% MeCN in MeOH as eluent. The fractions containing the desired compounds were evaporated to dryness to afford the first eluted enantiomer of 2-morpholino-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)propanamide, EN02414-54-1 (113.2 mg) as a tan solid and the other enantiomer of 2-morpholino-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)propanamide EN02414-54-2 (116.7 mg, 0.205 mmol, 37.6 %) also as a tan solid.

20

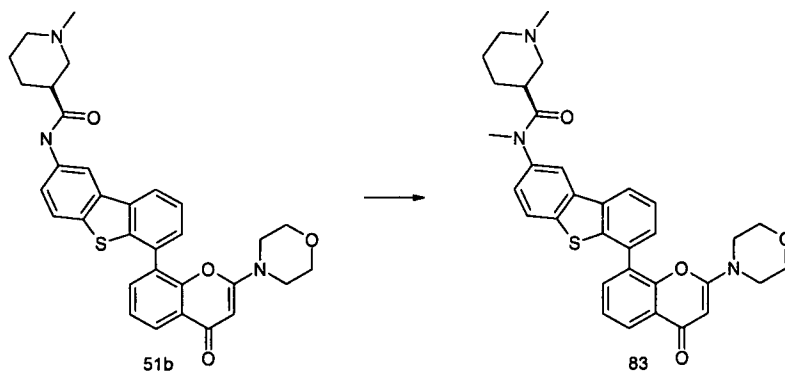
Both had slight impurities, so were further purified by flash silica chromatography.

The first eluted isomer was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to 2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide (81 mg) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.40 (3H, d), 2.64 (2H, m), 2.70 (2H, m), 3.07 (4H, t), 3.27 (1H, q), 3.49 (4H, t), 3.80 - 3.89 (4H, m), 5.49 (1H, s), 7.41 (1H, d), 7.46 - 7.50 (2H, m), 7.57 (1H, t), 7.72 - 7.77 (2H, m), 8.23 - 8.25 (1H, m), 8.27 - 8.29 (1H, m), 8.75 (1H, d), 9.41 (1H, s); m/z: 570.38 (MH⁺).

25

The second eluted isomer was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide (87 mg) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 1.40 (3H, d), 2.64 (2H, m), 2.70 (2H, m), 3.07 (4H, t), 3.27 (1H, q), 3.49 (4H, t), 3.80 - 3.89 (4H, m), 5.49 (1H, s), 7.41 (1H, d), 7.46 - 7.50 (2H, m), 7.57 (1H, t), 7.72 - 7.77 (2H, m), 8.23 - 8.25 (1H, m), 8.27 - 8.29 (1H, m), 8.75 (1H, d), 9.41 (1H, s); m/z: 570.39 (MH⁺).

Example 54



(3S)-1-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (83)

Sodium hydride, 60% dispersion in mineral oil (8.74 mg, 0.22 mmol) was added in one portion to *(3S)*-1-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (51b, 110 mg, 0.20 mmol) in anhydrous DMF (1974 μL) cooled to 0°C. The resulting mixture was stirred under nitrogen at 0°C for 20 minutes then methyl iodide (10% solution in anhydrous DMF, 0.18 mL, 0.29 mmol) was added and the reaction mixture allowed to warm to ambient temperature and stirred for a further 1 hour.

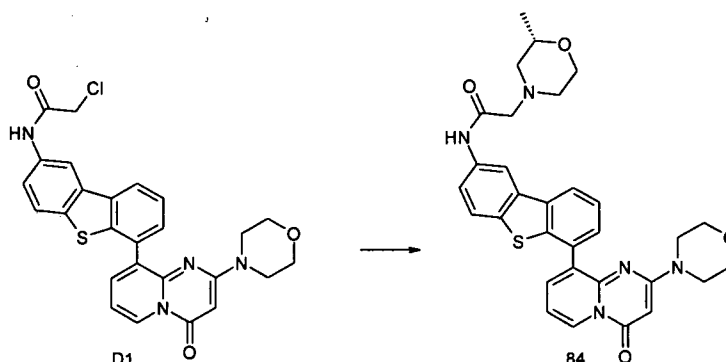
The reaction mixture was diluted with methanol (20 mL) and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure material. The crude product was purified by flash silica chromatography, elution gradient 0 to 8% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to afford a white solid.

The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing [AP-HPLC Buffer]) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford *((3S)*-1-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (18.10 mg, 16%) as a

cream solid; ^1H NMR (400 MHz, DMSO) δ 1.03 - 1.10 (2H, m), 1.24 - 1.37 (2H, m), 1.49 (2H, d), 1.64 - 1.73 (2H, m), 2.03 (3H, s), 2.40 - 2.49 (1H, m), 3.08 - 3.15 (4H, m), 3.29 (3H, s), 3.40 - 3.46 (4H, m), 5.57 (1H, s), 7.52 (1H, d), 7.58 (1H, t), 7.69 - 7.74 (2H, m), 7.91 (1H, d), 8.06 - 8.13 (2H, m), 8.49 (1H, s), 8.52 - 8.57 (1H, m); m/z : 569 (MH^+).

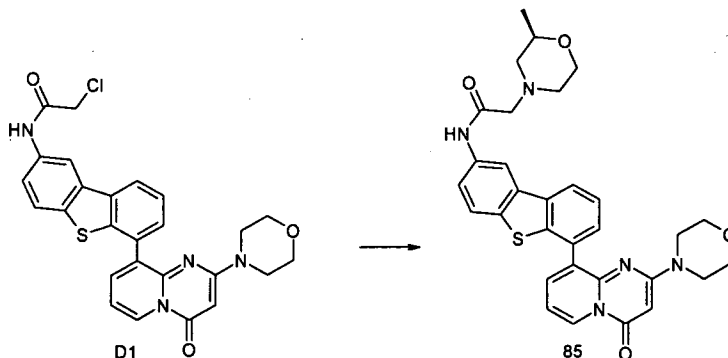
5

Example 55



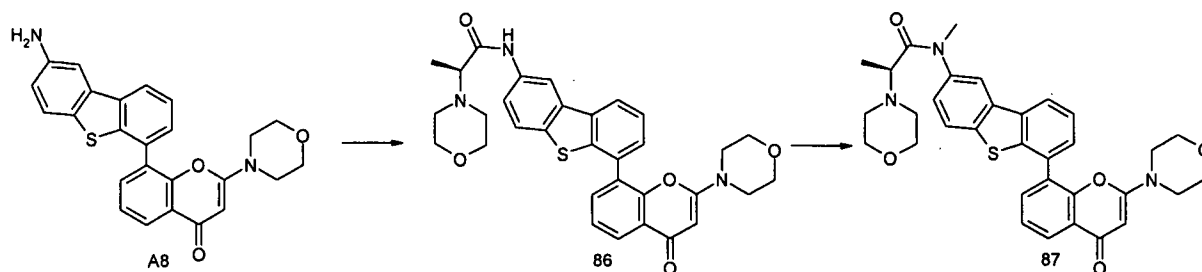
2-[(2S)-2-methylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl]acetamide (84)

- 10 A suspension of 2-chloro-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (D1, 55 mg, 0.11 mmol) in anhydrous DMA (2 mL) and DCM (1 mL) was added to (2S)-2-methylmorpholine hydrobromide (EE3, 72.1 mg, 0.40 mmol) and triethylamine (0.059 mL, 0.42 mmol). The resulting solution was stirred at 60°C for 1.5 hours. The crude product was diluted with methanol and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3 /MeOH and the crude product was purified by flash silica chromatography, elution gradient 0 to 7% 7M NH_3 /MeOH in DCM. Fractions were evaporated to dryness to afford a liquid. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford (2-[(2S)-2-methylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl]acetamide (50.8 mg, 45%) as a beige solid; ^1H NMR (400 MHz, DMSO) δ 1.08 (3H, d), 1.99 (1H, t), 2.25 - 2.35 (2H, m), 2.77 (1H, d), 2.84 (1H, d), 3.29 - 3.34 (6H, m), 3.43 - 3.48 (4H, m), 3.67 - 3.70 (1H, m), 3.78 (1H, d), 5.67 (1H, s), 7.23 (1H, t), 7.62 - 7.66 (2H, m), 7.74 (1H, d), 7.90 (1H, d), 8.06 (1H, d), 8.24 - 8.30 (1H, m), 8.67 (1H, s), 8.93 (1H, d), 9.94 (1H, s); m/z : 570 (MH^+).
- 25

Example 56

2-[(2R)-2-methylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl]acetamide (85)

- 5 A suspension 2-chloro-N-(6-(2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl)acetamide (D1, 55 mg, 0.11 mmol) in anhydrous DMA (2 mL) and DCM (1 mL) was added to (2R)-2-methylmorpholine (FF3, 40.1 mg, 0.40 mmol) and triethylamine (0.059 mL, 0.42 mmol). The resulting solution was stirred at 60°C for 1.5
- 10 hours. The crude product was diluted with methanol and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and the crude product was purified by flash silica chromatography, elution gradient 0 to 5% 7M NH₃/MeOH in DCM. The crude product was purified by
- 15 preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 2-[(2R)-2-methylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzo[b,d]thiophen-2-yl]acetamide (37.6 mg, 33%) as a cream solid; ¹H NMR (400 MHz, DMSO) δ 1.08 (3H, d), 1.99 (1H, t), 2.25 - 2.35 (2H, m), 2.77 (1H, d), 2.84 (1H, d), 3.29 - 3.34 (6H, m), 3.43 - 3.48 (4H, m), 3.67 - 3.70 (1H, m), 3.78 (1H, d), 5.67 (1H, s), 7.23 (1H, t),
- 20 7.62 - 7.66 (2H, m), 7.74 (1H, d), 7.90 (1H, d), 8.06 (1H, d), 8.24 - 8.30 (1H, m), 8.67 (1H, s), 8.93 (1H, d), 9.94 (1H, s); m/z: 570 (MH⁺).

Example 57

(2S)-N-methyl-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide (87)

(a) (2S)-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide (86)

- 5 8-(8-aminodibenzothiophen-4-yl)-2-morpholin-4-ylchromen-4-one (A8, 166 mg, 0.39 mmol) was added to (S)-2-morpholinopropanoic acid (G2, 67.8 mg, 0.43 mmol), N,N-diisopropylethylamine (0.162 mL, 0.93 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (177 mg, 0.46 mmol) in DMA (4 mL). The reaction was stirred at ambient temperature for 1 hour. A further 25mg acid and 50mg HATU were
- 10 added and the reaction left heating at 50°C for a further hour. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford a gum. The resulting gum was purified by flash silica chromatography, elution gradient 0 to 7% 7M NH₃MeOH in DCM. Fractions were evaporated to dryness to afford a yellow
- 15 gum. The gum was sonicated in ether until solid formed. Hexane was then added and the resulting solid filtered. The residue was washed with hexane to give the product (2S)-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide as a solid (164mg, 74%); ¹H NMR (400 MHz, DMSO) δ 1.26 (3H, d), 2.60 - 2.65 (1H, m), 3.08 - 3.16 (4H, m), 3.27 - 3.33 (4H, m), 3.39 - 3.45 (4H, m), 3.65 - 3.70 (4H, m), 5.57 (1H, s), 7.56 (1H, t), 7.65 - 7.70 (2H, m), 7.76 (1H, d), 7.88 (1H, d), 7.94 (1H, d), 8.08 (1H, d),
- 20 8.32 (1H, d), 8.71 (1H, d), 10.03 (1H, s); m/z: 570 (MH⁺).

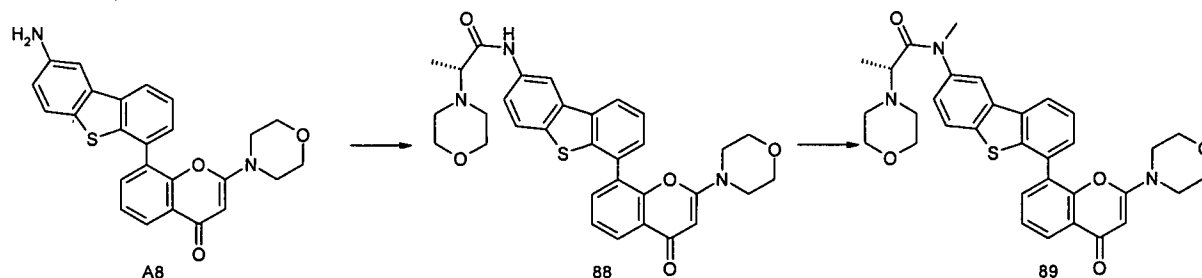
(b) (2S)-N-methyl-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide (87)

- 25 Sodium hydride, 60% dispersion in mineral oil (11.97 mg, 0.30 mmol) was added in one portion to ((2S)-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide (86, 155 mg, 0.27 mmol) in anhydrous DMF (5 mL) cooled to 0°C. The resulting mixture was stirred under nitrogen at 0°C for 20 minutes then Methyl iodide (42.5 mg) was added and the reaction mixture allowed to warm to ambient temperature and stirred
- 30 for a further 1 hour. The reaction mixture was diluted with methanol and a few drops water and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure material. The crude product was purified by flash silica chromatography, elution gradient 0 to 7% 7M NH₃/MeOH in DCM. fractions were evaporated
- 35 to dryness to afford (2S)-N-methyl-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-

yl)dibenzothiophen-2-yl]propanamide as a cream solid (100mg, 63%); ^1H NMR (400 MHz, DMSO) δ 1.07 (3H, d), 2.14 - 2.22 (1H, m), 3.09 - 3.16 (3H, m), 3.25 - 3.32 (8H, m), 3.40 - 3.48 (8H, m), 5.57 (1H, s), 7.52 - 7.62 (2H, m), 7.67 - 7.74 (2H, m), 7.90 (1H, d), 8.05 - 8.11 (2H, m), 8.45 - 8.49 (1H, m), 8.50 - 8.55 (1H, m); m/z : 584 (MH^+).

5

Example 58



(2R)-N-methyl-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide (89)

10 (a) (2R)-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide (88)

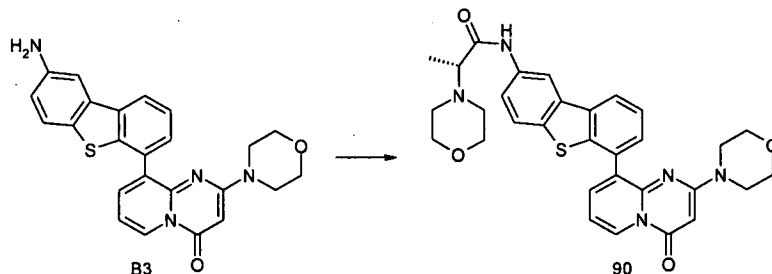
8-(8-aminodibenzothiophen-4-yl)-2-morpholin-4-ylchromen-4-one (A8, 206 mg, 0.48 mmol) was added to (R)-2-morpholinopropanoic acid (H2, 92 mg, 0.58 mmol), N,N-diisopropylethylamine (0.201 mL, 1.15 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (219 mg, 0.58 mmol) in DMA (4 mL). The reaction was stirred at 50°C for 45 minutes. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3/MeOH and pure fractions were evaporated to dryness to afford a gum. The resulting gum was purified by flash silica chromatography, elution gradient 0 to 7% 7M NH_3/MeOH in DCM. Fractions were evaporated to dryness to afford a yellow gummy solid. The gum was sonicated in ether until solid formed. Hexane added and the resulting solid filtered. The solid material was washed with hexane to give (2R)-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide as a pale yellow solid (220mg, 80%); ^1H NMR (400 MHz, DMSO) δ 1.26 (3H, d), 2.60 - 2.65 (1H, m), 3.08 - 3.16 (4H, m), 3.27 - 3.33 (4H, m), 3.39 - 3.45 (4H, m), 3.65 - 3.70 (4H, m), 5.57 (1H, s), 7.56 (1H, t), 7.65 - 7.70 (2H, m), 7.76 (1H, d), 7.88 (1H, d), 7.94 (1H, d), 8.08 (1H, d), 8.32 (1H, d), 8.71 (1H, d), 10.03 (1H, s); m/z : 570 (MH^+).

25

(b) (2R)-N-methyl-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide (89)

Sodium hydride, 60% dispersion in mineral oil (16.99 mg, 0.42 mmol) was added in one portion to (2R)-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide (88, 220mg) in anhydrous DMF (5 mL) cooled to 0°C. The resulting mixture was stirred under nitrogen at 0°C for 20 minutes then methyl iodide (10% solution in anhydrous DMF) (0.026 mL, 0.42 mmol) was added and the reaction mixture allowed to warm to ambient temperature and stirred for a further 1 hour. The reaction mixture was diluted with methanol and water and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure material. The crude product was purified by flash silica chromatography, elution gradient 0 to 8% 7M NH₃/MeOH in DCM. Fractions were evaporated to dryness to afford a cream solid (55mg, 24%); ¹H NMR (400 MHz, DMSO) δ 1.07 (3H, d), 2.14 - 2.22 (1H, m), 3.09 - 3.16 (3H, m), 3.25 - 3.32 (8H, m), 3.40 - 3.48 (8H, m), 5.57 (1H, s), 7.52 - 7.62 (2H, m), 7.67 - 7.74 (2H, m), 7.90 (1H, d), 8.05 - 8.11 (2H, m), 8.45 - 8.49 (1H, m), 8.50 - 8.55 (1H, m); m/z: 584 (MH⁺).

Example 59

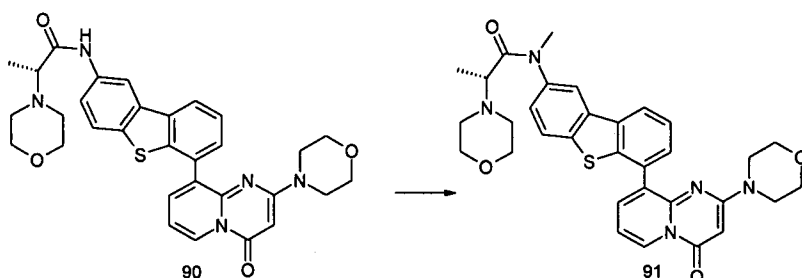


(2R)-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]propanamide (90)

9-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (B3, 100 mg, 0.23 mmol) was added to (R)-2-morpholinopropanoic acid (H2, 40.9 mg, 0.26 mmol), N,N-Diisopropylethylamine (0.098 mL, 0.56 mmol) and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (111 mg, 0.29 mmol) in DMA (4 mL). The reaction was stirred at ambient temperature for 2 hours. The reaction mixture was diluted with EtOAc (150 mL), and washed with water (50 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated onto silica. The resulting powder was purified by flash silica chromatography, elution gradient 0 to 7% MeOH in DCM. Fractions were evaporated to dryness to afford a yellow gum, and LCMS showed 5% starting material remaining. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column,

5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford (2R)-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]propanamide (55.6 mg, 41%) as a beige solid; ^1H NMR (400 MHz, DMSO) δ 1.26 (3H, d), 2.59 - 2.70 (1H, m), 3.24 - 3.37 (8H, m), 3.40 - 3.50 (4H, m), 3.65 - 3.73 (4H, m), 5.67 (1H, s), 7.22 (1H, t), 7.61 - 7.67 (2H, m), 7.74 (1H, d), 7.90 (1H, d), 8.06 (1H, d), 8.25 - 8.30 (1H, m), 8.68 (1H, s), 8.93 (1H, d), 10.01 (1H, s); m/z: 570 (MH^+).

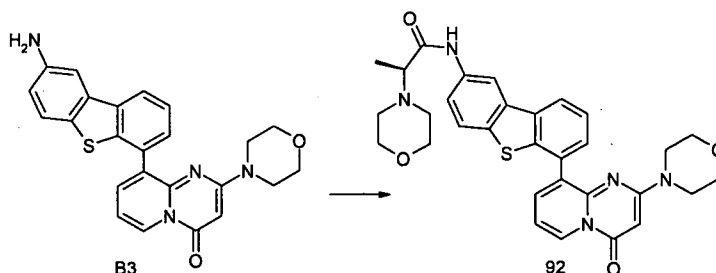
Example 60



(2R)-N-methyl-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]propanamide (91)

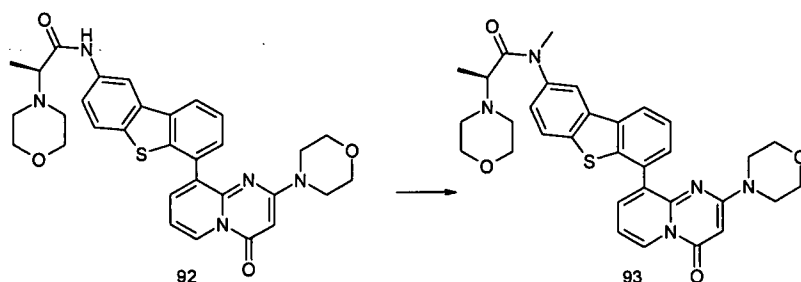
Sodium hydride, 60% dispersion in mineral oil (15.14 mg, 0.38 mmol) was added in one portion to (2R)-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]propanamide (90, 196mg) in anhydrous DMF (5 mL) cooled to 0°C. The resulting mixture was stirred under nitrogen at 0°C for 20 minutes then methyl iodide 10% solution in anhydrous DMF (0.024 mL, 0.38 mmol) in anhydrous DMF (8 mL) was added and the reaction mixture allowed to warm to ambient temperature and stirred for a further 1 hour. The reaction was then quenched with methanol and left to stand for 48 hours.

The reaction mixture was diluted with methanol and water and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3 /MeOH and evaporated to dryness to afford semi-pure material. (120mg, 60%); ^1H NMR (400 MHz, DMSO) δ 1.10 (3H, d), 2.21(2H,m), 3.28-3.32(8H,m), 3.35-3.40 (1H,t), 3.40-3.50(9H,m), 5.55 (1H,s), 7.18 (1H,t), 7.42 (1H,d), 7.60-7.65 (2H,d), 7.92-8.10 (2H,m), 8.30 (1H,s), 8.39 (1H,d), 8.91 (1H,d); m/z: 584 (MH^+).

Example 61

(2S)-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]propanamide (92)

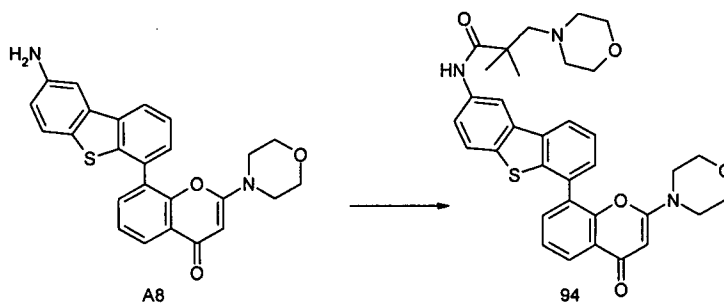
- 5 9-(8-aminodibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (B3, 100 mg, 0.23 mmol) was added to (S)-2-morpholinopropanoic acid (G2, 44.6 mg, 0.28 mmol), N,N-diisopropylethylamine (0.098 mL, 0.56 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (106 mg, 0.28 mmol) in DMA (4 mL). The reaction was then stirred at 60°C for 2 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford a gum. The gum was diluted with EtOAc (150 mL), and washed sequentially with 2M NaOH (50 mL), water (50 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated onto silica. The resulting powder was purified by flash silica chromatography, elution gradient 0 to 7% MeOH in DCM. Fractions were evaporated to dryness to afford a yellow solid. This was triturated with ether/hexane and filtered to give *(2S)*-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]propanamide as a pale yellow solid (51mg, 38%); ¹H NMR (400 MHz, DMSO) δ 1.26 (3H, d), 2.59 - 2.70 (1H, m), 3.24 - 3.37 (8H, m), 3.40 - 3.50 (4H, m), 3.65 - 3.73 (4H, m), 5.67 (1H, s), 7.22 (1H, t), 7.61 - 7.67 (2H, m), 7.74 (1H, d), 7.90 (1H, d), 8.06 (1H, d), 8.25 - 8.30 (1H, m), 8.68 (1H, s), 8.93 (1H, d), 10.01 (1H, s); m/z: 570 (MH⁺).

Example 62

(2S)-N-methyl-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]propanamide (93)

Sodium hydride, 60% dispersion in mineral oil (17.30 mg, 0.43 mmol) was added in one portion to (2S)-2-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]propanamide (92, 224 mg, 0.39 mmol) in anhydrous DMF (8 mL) cooled to 0°C. The resulting mixture was stirred under nitrogen at 0°C for 20 minutes then Methyl iodide (62mg) was added and the reaction mixture allowed to warm to ambient temperature and stirred for a further 1 hour. The reaction was then quenched with methanol and left to stand at room temperature for 48 hours. The reaction mixture was diluted with methanol and water and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure material. The crude product was purified by flash silica chromatography, elution gradient 0 to 7% 7M NH₃/MeOH in DCM. fractions were evaporated to dryness to afford a yellow solid (160mg, 70%); ¹H NMR (400 MHz, DMSO) δ 1.10 (3H, d), 2.21(2H,m), 3.28-3.32(8H,m), 3.35-3.40 (1H,t), 3.40-3.50(9H,m), 5.55 (1H,s), 7.18 (1H,t), 7.42 (1H,d), 7.60-7.65 (2H,d), 7.92-8.10 (2H,m), 8.30 (1H,s), 8.39 (1H,d), 8.91 (1H,d); m/z: 584 (MH⁺).

Example 63

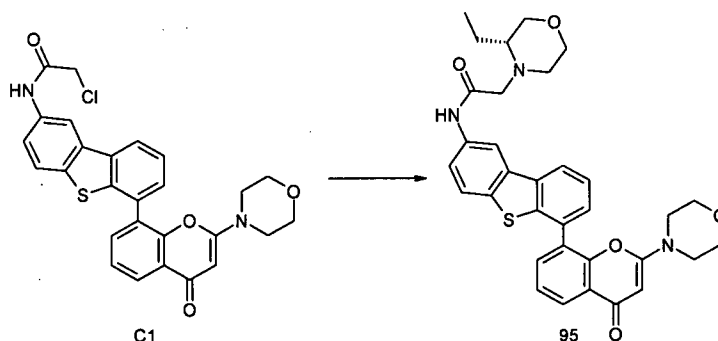


2,2-dimethyl-3-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide (94)

8-(8-aminodibenzothiophen-4-yl)-2-morpholin-4-ylchromen-4-one (A8, 250 mg, 0.58 mmol) was added in one portion to 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (710 mg, 1.87 mmol), potassium 2,2-dimethyl-3-morpholinopropanoate (J1, 603 mg, 1.75 mmol) and N-ethyl-N-isopropylpropan-2-amine (241 mg, 1.87 mmol) under nitrogen atmosphere. The resulting suspension was stirred at room temperature for 2 hours and heated to 50°C for 1 hour. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford product as a yellow oil. This was purified by

crystallisation from Et₂O to afford product as a cream solid. The solid was dissolved in DCM and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford product. The product was diluted with DCM (50 mL), and washed sequentially with water (50 mL), and saturated brine (20 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated to afford desired product. The crude product was purified by flash silica chromatography, eluting with ethyl acetate and then elution gradient 5 to 100% MeOH in DCM. Pure fractions were evaporated to dryness to afford 2,2-dimethyl-3-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide (126 mg, 36%) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.25 (6H, s), 2.52 (2H, s), 2.70 (4H, t), 3.00 (4H, t), 3.41 - 3.44 (4H, m), 3.80 (4H, t), 5.42 (1H, s), 7.27 (1H, dd), 7.39 - 7.43 (2H, m), 7.49 (1H, t), 7.64 (1H, d), 7.69 (1H, dd), 8.15 (1H, dd), 8.21 (1H, dd), 8.78 (1H, d), 10.79 (1H, s) trace methanol; m/z: 598.54 (MH⁺).

Example 64

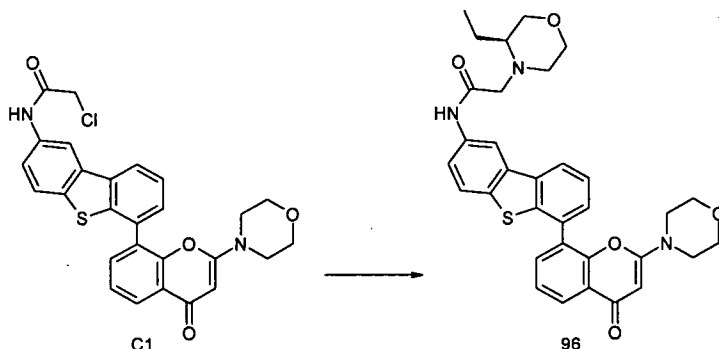


2-[(3R)-3-ethylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (95)

(3R)-3-ethylmorpholine hemioxalate salt (DD3, 123 mg, 0.77 mmol) was added in one portion to 2-chloro-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (C1; 194 mg, 0.38 mmol), in DMA (3.25 mL). The resulting suspension was stirred at room temperature for 3 days. The reaction was then heated at 50°C for 18 hours whereupon product had formed. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 2% MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-[(3R)-3-ethylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (55.0 mg, 24%) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 0.88 (3H, t), 2.44

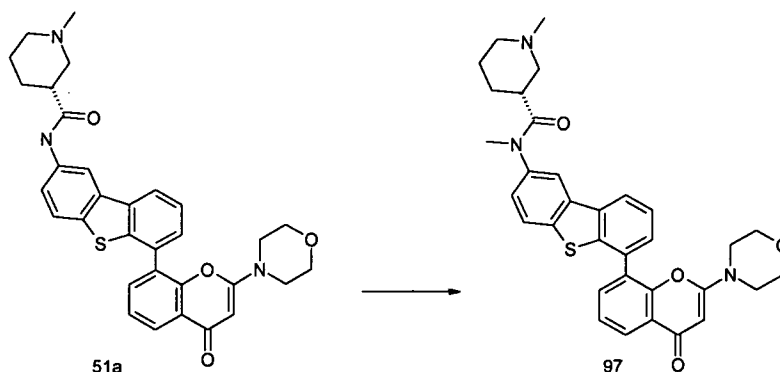
(1H, m), 2.59 (1H, t), 2.83 (1H, d), 2.99 - 3.06 (5H, m), 3.44 (6H, t), 3.66 - 3.71 (1H, m), 3.78 - 3.87 (2H, m), 5.43 (1H, s), 7.35 - 7.45 (3H, m), 7.51 (1H, t), 7.66 - 7.70 (2H, m), 8.17 - 8.23 (2H, m), 8.64 (1H, d), 9.37 (1H, s) 2 protons under water; m/z : 584.48 (MH^+).

5 Example 65



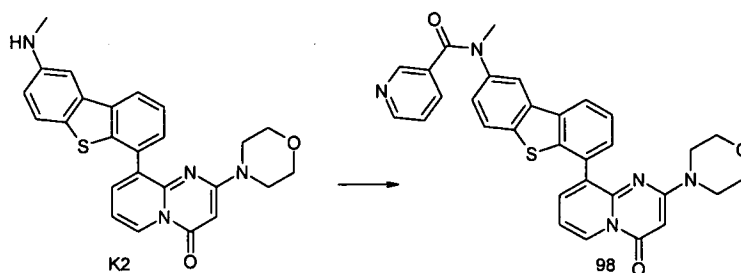
2-[(3S)-3-ethylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (96)

(3S)-3-ethylmorpholine hemi oxalate salt (CC3, 123 mg, 0.77 mmol) was added in one portion to 2-chloro-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (C1, 194 mg, 0.38 mmol) in DMA (3.25 mL). The resulting suspension was stirred at room temperature for 6 hours. The reaction was then heated to 50°C for 1 hour. The reaction was allowed to cool to room temperature and stirred at room temperature overnight. The reaction was then heated to 50°C for 18 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3 /MeOH and pure fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 2% MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-[(3S)-3-ethylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (65.0 mg, 29%) as a cream solid; 1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t), 1.40 - 1.45 (1H, m), 1.53 - 1.61 (1H, m), 2.41 - 2.47 (1H, m), 2.55 - 2.61 (1H, m), 2.81 - 2.85 (1H, m), 2.99 - 3.06 (5H, m), 3.39 - 3.46 (6H, m), 3.65 - 3.71 (1H, m), 3.77 - 3.87 (2H, m), 5.42 (1H, s), 7.35 - 7.44 (3H, m), 7.51 (1H, t), 7.66 - 7.70 (2H, m), 8.17 - 8.23 (2H, m), 8.64 (1H, d), 9.37 (1H, s); m/z : 584.50 (MH^+).

Example 66

(3R)-N,1-dimethyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (97)

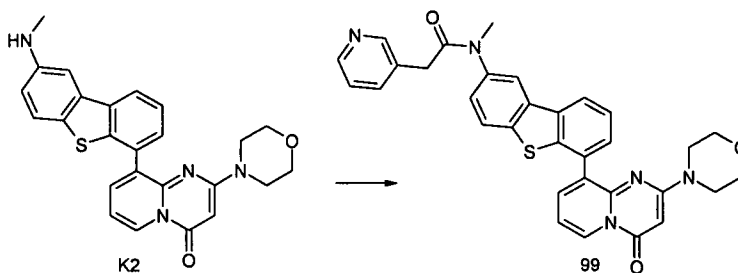
- 5 Sodium hydride, 60% dispersion in mineral oil (6.38 mg, 0.16 mmol) was added portionwise to (3R)-1-methyl-N-[6-(2-morpholino-4-oxo-chromen-8-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (51a, 75 mg, 0.14 mmol) in anhydrous DMF (2 mL) cooled to 0°C. The resulting mixture was stirred under nitrogen at 0°C for 30 minutes then methyl iodide (8.86 μ l, 0.14 mmol) was added and the reaction mixture allowed to warm to ambient temperature and stirred for a further 1 hour. The reaction mixture was diluted with methanol (10mL). This
- 10 diluted reaction mixture was then purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3 /MeOH and fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% 7M NH_3 /MeOH in DCM. Pure fractions
- 15 were evaporated to dryness to afford (3R)-N,1-dimethyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (59.0 mg, 77 %) as a white solid; ^1H NMR (400 MHz, DMSO) δ 1.04 - 1.10 (2H, m), 1.24 - 1.36 (2H, m), 1.47 - 1.51 (1H, m), 1.64 - 1.72 (2H, m), 1.93 (1H, t), 2.04 (3H, s), 2.41 - 2.43 (1H, m), 3.09 - 3.13 (4H, m), 3.26 (3H, s), 3.43 (4H, t), 5.58 (1H, s), 7.52 (1H, d), 7.59 (1H, t), 7.70 - 7.73 (2H, m), 7.91
- 20 (1H, dd), 8.08 - 8.12 (2H, m), 8.50 (1H, s), 8.53 - 8.56 (1H, m); m/z : 568.19 (MH^+).

Example 67

N-methyl-*N*-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-*a*]pyrimidin-9-yl)dibenzothiophen-2-yl]pyridine-3-carboxamide (98)

9-[8-(methylamino)dibenzothiophen-4-yl]-2-morpholin-4-ylpyrido[1,2-*a*]pyrimidin-4-one (K2, 150 mg, 0.34 mmol) was added in one portion to O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (193 mg, 0.51 mmol), nicotinic acid (62.6 mg, 0.51 mmol) and *N,N*-diisopropylethylamine (0.177 mL, 1.02 mmol) in anhydrous DMA (3 mL). The resulting solution was stirred at ambient temperature for 4 hours and then left to stand at room temperature for 3 days. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3/MeOH and pure fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford product which was crystallised from ether and filtered to give *N*-methyl-*N*-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-*a*]pyrimidin-9-yl)dibenzothiophen-2-yl]pyridine-3-carboxamide (110 mg, 59.3 %); ^1H NMR (400 MHz, CDCl_3) δ 3.28 (4H, t), 3.49 (4H, t), 3.56 (3H, s), 5.55 (1H, s), 6.94 (1H, t), 7.02 - 7.09 (2H, m), 7.46 - 7.53 (2H, m), 7.58 - 7.65 (2H, m), 7.77 (1H, dd), 7.81 (1H, d), 7.99 (1H, dd), 8.35 (1H, dd), 8.49 (1H, s), 8.97 (1H, dd); m/z : 548.46 (MH^+).

Example 68

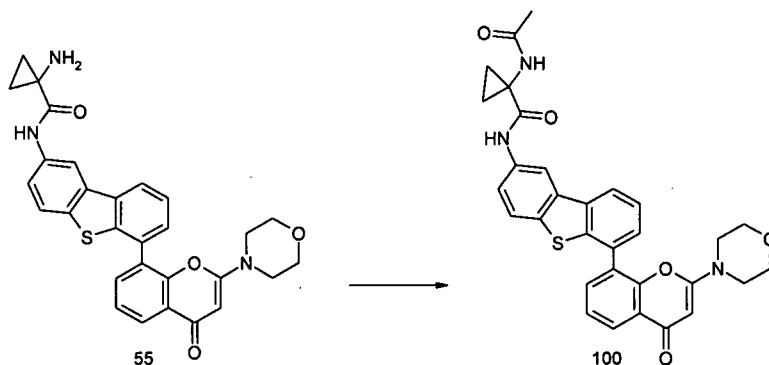


N-methyl-*N*-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-*a*]pyrimidin-9-yl)dibenzothiophen-2-yl]-2-pyridin-3-ylacetamide (99)

9-[8-(Methylamino)dibenzothiophen-4-yl]-2-morpholin-4-ylpyrido[1,2-*a*]pyrimidin-4-one (K2, 249 mg, 0.56 mmol) was added in one portion to O-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (535 mg, 1.41 mmol), 2-(pyridin-3-yl)acetic acid hydrochloride (244 mg, 1.41 mmol) and *N,N*-diisopropylethylamine (0.588 mL, 3.38 mmol) in anhydrous DMA (3 mL). The resulting solution was stirred at ambient temperature for 2 hours and then left to stand at room temperature over the weekend. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3/MeOH and fractions were evaporated to dryness to

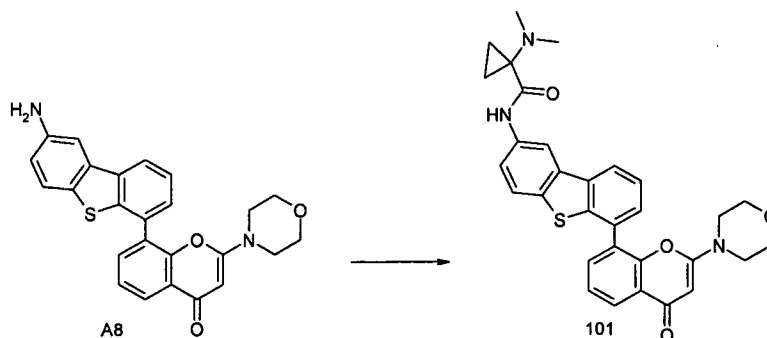
afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Fractions were evaporated to dryness to afford product. LCMS looked fine but NMR indicated a slight impurity in the aromatic region so the compound was purified again as follows: The product was purified by flash silica chromatography, elution gradient 0 to 2% 7M NH₃/MeOH in DCM. Pure fractions were evaporated to dryness to N-methyl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]-2-pyridin-3-ylacetamide (133 mg, 42%) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 2.91 (3H, s), 3.30 (4H, t), 3.50 (4H, t), 5.55 (1H, s), 6.75 (1H, dd), 6.93 (1H, t), 7.28 (1H, d), 7.43 - 7.48 (3H, m), 7.81 (1H, dd), 8.06 (1H, dd), 8.96 (1H, dd); m/z: 443.43 (MH⁺).

Example 69



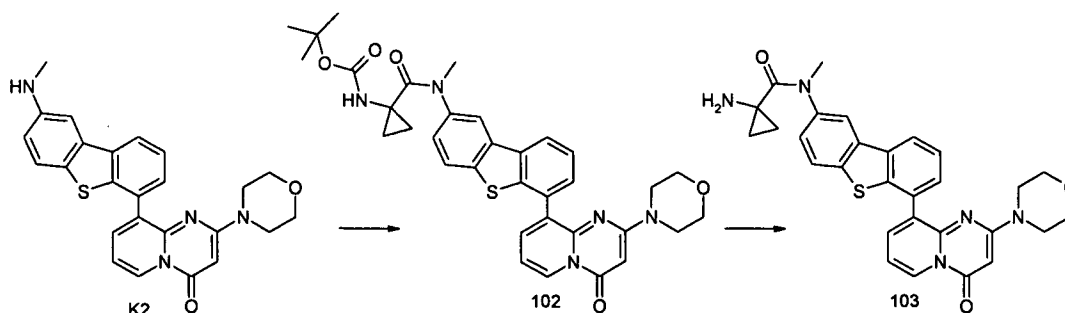
1-acetamido-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (100)

Acetyl chloride (14.52 mg, 0.18 mmol) was added in one portion to 1-amino-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (55, 86 mg, 0.17 mmol) and triethylamine (0.059 mL, 0.42 mmol) in DMA (2 mL) and the reaction was stirred at room temperature for 4 hours. The reaction mixture was left to stand over the weekend. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford crude product. The crude product was very insoluble so the solid was triturated in diethyl ether and filtered and dried to give 1-acetamido-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (53.0 mg, 57%) as a white solid; ¹H NMR (400 MHz, DMSO) δ 1.01 (2H, q), 1.44 (2H, q), 1.95 (3H, s), 3.12 (4H, d), 3.43 (4H, t), 5.57 (1H, s), 7.19 (1H, s), 7.57 (1H, t), 7.67 - 7.75 (2H, m), 7.88 - 7.94 (2H, m), 8.08 (1H, dd), 8.31 (1H, dd), 8.43 (1H, s), 8.61 (1H, d), 9.66 (1H, s); m/z: 554.48 (MH⁺).

Example 70

1-(dimethylamino)-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (101)

- 5 8-(8-Aminodibenzothiophen-4-yl)-2-morpholin-4-ylchromen-4-one (A8, 150 mg, 0.35 mmol) was added to 1-(dimethylamino)cyclopropanecarboxylic acid (L1, 54.3 mg, 0.42 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (160 mg, 0.42 mmol) and N,N-diisopropylethylamine (0.146 mL, 0.84 mmol) in DMA (1 mL). The resulting suspension was stirred at room temperature for 2 hours and then the reaction was heated to
- 10 60°C for 1 hour whereupon all reactants went into solution. The mixture was then stirred at room temperature for 16 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and fractions were evaporated to dryness to afford crude product. The
- 15 crude product was purified by flash silica chromatography, elution gradient 0 to 2% MeOH in DCM. Pure fractions were evaporated to dryness to afford 1-(dimethylamino)-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (150 mg, 79 %) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.06 - 1.08 (2H, m), 1.29 - 1.33 (2H, m), 2.26 (6H, s), 3.00 (4H, t), 3.43 (4H, t), 5.43 (1H, s), 7.38 - 7.51 (4H, m), 7.66 (1H, d), 7.69 (1H, dd), 8.17 (1H, dd), 8.21 (1H, dd), 8.73 (1H, d), 10.01 (1H, s); m/z: 540.48
- 20 (MH⁺).

Example 71

1-amino-N-methyl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (103)

(a) Tert-butyl N-[1-[methyl-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]carbamoyl]cyclopropyl]carbamate (102)

- 5 9-[8-(methylamino)dibenzothiophen-4-yl]-2-morpholin-4-ylpyrido[1,2-a]pyrimidin-4-one (K2, 200 mg, 0.45 mmol) was added in one portion to N,N-diisopropylethylamine (0.394 mL, 2.26 mmol), 1-(tert-butoxycarbonylamino)cyclopropanecarboxylic acid (182 mg, 0.90 mmol) and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (378 mg, 0.99 mmol) in anhydrous DMA (3 mL). The resulting solution was stirred under nitrogen at
10 ambient temperature for 3 hours and then 2 hours at 60°C. The reaction mixture was then stirred at room temp for 3 days. The reaction was incomplete and further 1-(tert-butoxycarbonylamino)cyclopropanecarboxylic acid (182 mg, 0.90 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (378 mg, 0.99 mmol) were added and the solution was stirred at 60°C for a further 24 hours.
15 The cooled reaction mixture was diluted with methanol and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness to afford impure tert-butyl N-[1-[methyl-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]carbamoyl]cyclopropyl]carbamate as a beige solid. This was taken on with no further
20 purification.

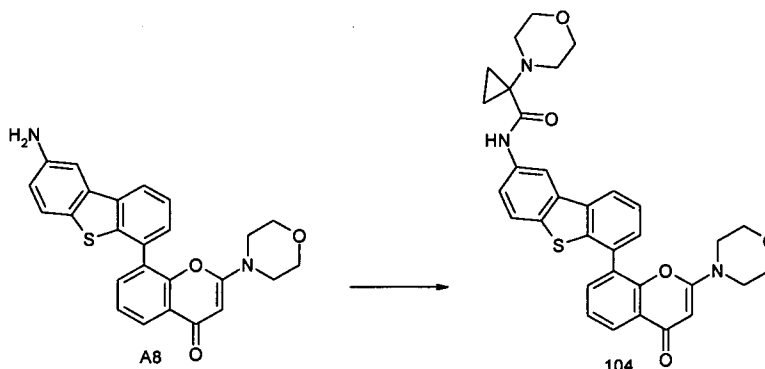
(b) 1-amino-N-methyl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (103)

- A solution of 10% TFA in DCM (2.5 mL) was added to tert-butyl N-[1-[methyl-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]carbamoyl]cyclopropyl]carbamate (102, 69 mg, 0.11 mmol) at 25°C. The resulting solution
25 was stirred at 25 °C for 2 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford crude product.
30 The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 1-amino-N-methyl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]cyclopropane-1-
35

carboxamide (26.0 mg); ^1H NMR (400 MHz, CDCl_3) δ 0.65 - 0.68 (2H, m), 1.26 - 1.28 (2H, m), 3.31 (4H, t), 3.35 (3H, s), 3.51 (4H, t), 5.57 (1H, s), 6.97 (1H, t), 7.33 (1H, dd), 7.53 - 7.58 (2H, m), 7.78 - 7.82 (2H, m), 8.02 (1H, d), 8.11 (1H, dd), 8.99 (1H, dd); m/z : 526.49 (MH^+).

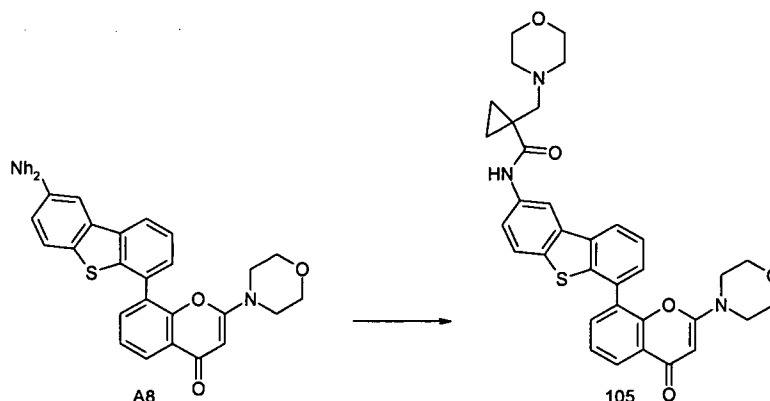
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Example 72



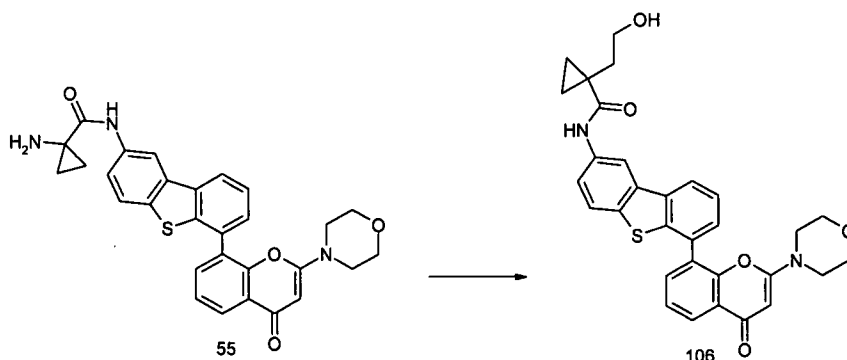
1-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (104)

- 10 8-(8-Aminodibenzothiophen-4-yl)-2-morpholin-4-ylchromen-4-one (A8, 100 mg, 0.23 mmol) was added to 1-morpholin-4-ylcyclopropane-1-carboxylic acid hydrochloride (M2, 80 mg, 0.39 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (147 mg, 0.39 mmol) and N,N-diisopropylethylamine (0.134 mL, 0.77 mmol) in DMA (1 mL). The resulting suspension was stirred at room temperature for 18 hours. The crude product
- 15 was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3/MeOH and fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford
- 20 1-morpholin-4-yl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (105 mg, 77 %) as a white solid; ^1H NMR (400 MHz, CDCl_3) δ 1.12 - 1.16 (2H, m), 1.33 - 1.36 (2H, m), 2.49 (4H, s), 3.00 (4H, t), 3.41 - 3.44 (4H, m), 3.80 - 3.80 (4H, m), 5.43 (1H, s), 7.33 (1H, dd), 7.41 - 7.44 (2H, m), 7.50 (1H, t), 7.66 - 7.71 (2H, m), 8.17 - 8.22 (2H, m), 8.73 (1H, d), 10.05 (1H, s); m/z : 582.39 (MH^+).

Example 73

1-(morpholin-4-ylmethyl)-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (105)

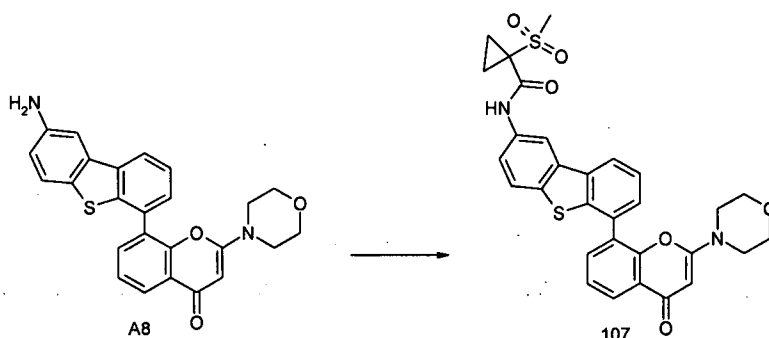
- 5 8-(8-Aminodibenzothiophen-4-yl)-2-morpholin-4-ylchromen-4-one (A8, 100 mg, 0.23 mmol) was added to 1-(morpholinomethyl)cyclopropanecarboxylic acid (N3, 86 mg, 0.47 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (177 mg, 0.47 mmol) and N,N-diisopropylethylamine (0.163 mL, 0.93 mmol) in DMA (1 mL). The resulting suspension was stirred at room temperature for 3 hours. The crude product was purified by
- 10 ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford 1-(morpholin-4-ylmethyl)-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-
- 15 carboxamide (117 mg, 84 %) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 0.59 - 0.62 (2H, m), 1.37 - 1.41 (2H, m), 2.61 - 2.71 (6H, m), 3.00 (4H, t), 3.41 - 3.44 (4H, m), 3.83 - 3.84 (4H, m), 5.43 (1H, s), 7.24 - 7.27 (1H, m), 7.40 - 7.51 (3H, m), 7.64 (1H, d), 7.69 (1H, dd), 8.15 (1H, dd), 8.21 (1H, dd), 8.77 (1H, d), 11.82 (1H, s); m/z: 596.41 (MH⁺).

Example 74

1-(2-hydroxyethyl)-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (106)

1-Amino-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (55, 150 mg, 0.29 mmol) was added to 2-hydroxyacetaldehyde (26.4 mg, 0.44 mmol), sodium cyanotrihydroborate (73.7 mg, 1.17 mmol) and magnesium sulfate (70.6 mg, 0.59 mmol) in methanol (7 mL) under nitrogen. The resulting suspension was stirred at 40°C for 18 hours. More 2-hydroxyacetaldehyde (26.4 mg, 0.44 mmol) was added and the reaction stirred at 50°C for 5 hours. The reaction mixture was filtered, then concentrated in vacuo. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Fractions were evaporated to dryness to afford product which was not pure. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM to give 1-(2-hydroxyethyl)-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (55mg, 34%) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 0.97 - 1.00 (2H, m), 1.47 - 1.50 (2H, m), 2.40 (1H, t), 2.86 (2H, t), 2.96 (4H, t), 3.39 (4H, t), 3.77 (2H, q), 5.39 (1H, s), 7.34 - 7.48 (4H, m), 7.55 (1H, d), 7.68 (1H, dd), 8.13 (1H, dd), 8.21 (1H, dd), 8.79 (1H, d), 10.29 (1H, s); m/z: 556.42 (MH⁺).

Example 75

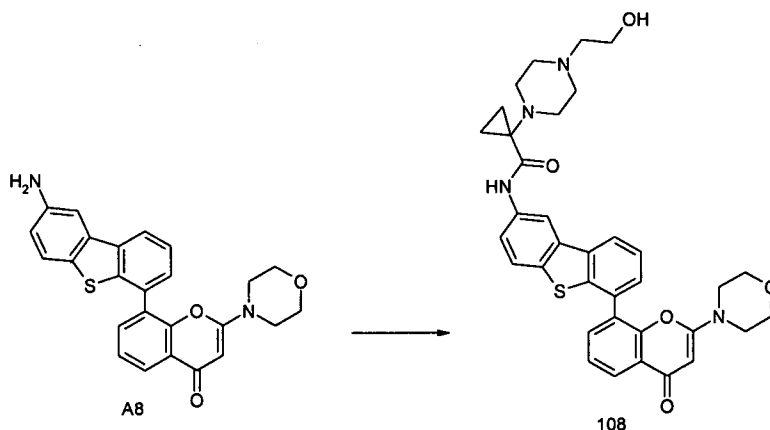


1-methylsulfonyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (107)

8-(8-Aminodibenzothiophen-4-yl)-2-morpholin-4-ylchromen-4-one (A8, 100 mg, 0.23 mmol) was added to 1-methylsulfonylcyclopropane-1-carboxylic acid (O3, 46.0 mg, 0.28 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (106 mg, 0.28 mmol) and N,N-diisopropylethylamine (0.134 mL, 0.77 mmol) in DMA (1 mL). The resulting suspension was stirred at room temperature for 5 hours. LCMS confirmed no reaction so the

reaction mixture was heated at 50°C for a further 3 hours. LCMS confirmed no reaction so 1-methylsulfonylcyclopropane-1-carboxylic acid (46.0 mg, 0.28 mmol) was added and reaction heated at 50°C for a further 18 hours. LCMS confirmed no reaction so O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (106 mg, 0.28 mmol) was added and the reaction was heated for a further 4 hours at 50°C. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford 1-methylsulfonyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (82 mg, 61%) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.74 - 1.76 (2H, m), 1.78 - 1.80 (2H, m), 3.01 (4H, t), 3.10 (3H, s), 3.44 (4H, t), 5.44 (1H, s), 7.41 - 7.54 (4H, m), 7.68 - 7.71 (2H, m), 8.15 (1H, dd), 8.22 (1H, dd), 8.51 (1H, d), 9.72 (1H, s); m/z: 575.35 (MH⁺).

Example 76

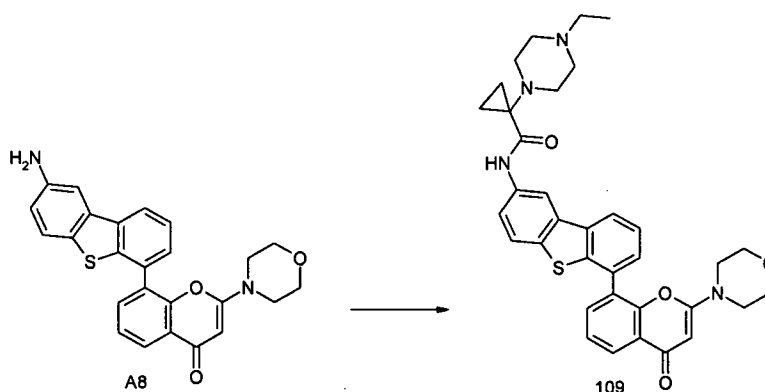


1-[4-(2-hydroxyethyl)piperazin-1-yl]-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (108)

8-(8-Aminodibenzothiophen-4-yl)-2-morpholin-4-ylchromen-4-one (A8, 100 mg, 0.23 mmol) was added to 1-(4-(2-hydroxyethyl)piperazin-1-yl)cyclopropanecarboxylic acid (P6, 70.0 mg, 0.33 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (142 mg, 0.37 mmol) and N,N-diisopropylethylamine (0.163 mL, 0.93 mmol) in DMA (2 mL). The resulting suspension was stirred at room temperature for 5 hours. LCMS confirmed little reaction so the reaction mixture was heated at 50°C for a further 3 hours. LCMS confirmed little reaction so O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (142 mg, 0.37 mmol) was added and reaction stirred at room temperature for a further 3 days. The crude product was purified by ion exchange

chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford 1-[4-(2-hydroxyethyl)piperazin-1-yl]-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (56mg, 38%) as a cream solid; ¹H NMR (400 MHz, CDCl₃) δ 1.11 - 1.13 (2H, m), 1.32 - 1.36 (2H, m), 2.46 - 2.76 (10H, m), 3.00 (4H, t), 3.42 (4H, t), 3.61 (2H, t), 5.43 (1H, s), 7.30 (1H, dd), 7.42 (2H, t), 7.50 (1H, t), 7.65 - 7.70 (2H, m), 8.16 - 8.22 (2H, m), 8.76 (1H, d), 10.04 (1H, s); m/z: 625.51 (MH⁺).

Example 77



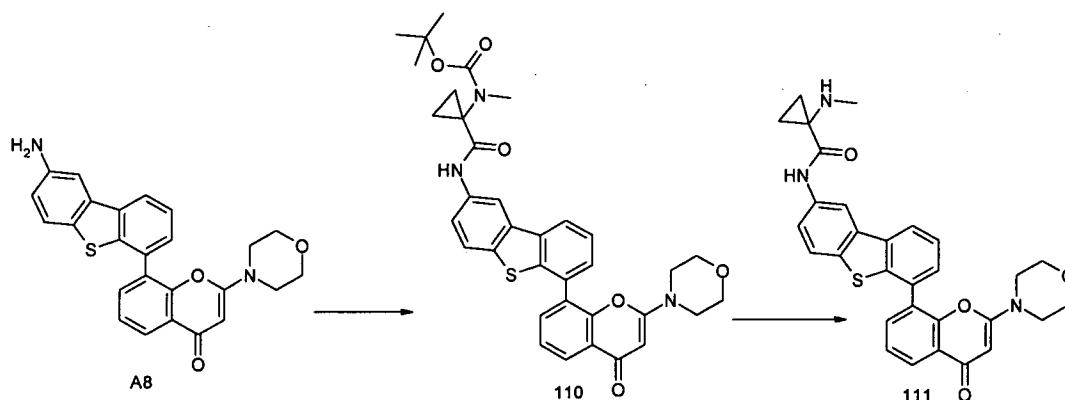
1-(4-ethylpiperazin-1-yl)-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (109)

8-(8-Aminodibenzothiophen-4-yl)-2-morpholin-4-ylchromen-4-one (A8, 100 mg, 0.23 mmol) was added to 1-(4-ethylpiperazin-1-yl)cyclopropanecarboxylic acid (Q2, 55.5 mg, 0.28 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (142 mg, 0.37 mmol) and N,N-diisopropylethylamine (0.122 mL, 0.70 mmol) in DMA (2 mL). The resulting suspension was stirred at room temperature for 5 hours. LCMS confirmed little reaction so the reaction mixture was heated at 50°C for a further 2 hours. LCMS confirmed little reaction so O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (142 mg, 0.37 mmol) was added and reaction stirred at room temperature for a further 1 hour. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford 1-(4-ethylpiperazin-1-yl)-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide

(102 mg, 72%) as a cream solid; ^1H NMR (400 MHz, CDCl_3) δ 1.07 (3H, t), 1.10 - 1.13 (2H, m), 1.30 - 1.34 (2H, m), 2.41 - 2.59 (10H, m), 3.00 (4H, t), 3.42 (4H, t), 5.42 (1H, s), 7.31 (1H, dd), 7.41 (2H, t), 7.49 (1H, t), 7.65 - 7.70 (2H, m), 8.16 - 8.22 (2H, m), 8.75 (1H, d), 10.09 (1H, s); m/z : 607.49 (MH $^+$).

5

Example 78



1-(methlamino)-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (111)

10 (a) Tert-butyl N-methyl-N-[1-[[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]carbamoyl]cyclopropyl]carbamate (110)

8-(8-Aminodibenzothiophen-4-yl)-2-morpholin-4-ylchromen-4-one (A8, 120 mg, 0.28 mmol) was added to 1-[methyl-[(2-methylpropan-2-yl)oxycarbonyl]amino]cyclopropane-1-carboxylic acid (R1, 54.8 mg, 0.25 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (155 mg, 0.41 mmol) and N,N-diisopropylethylamine (0.133 mL, 0.76 mmol) in DMA (2 mL). The resulting mixture was stirred at room temperature for 5 hours. LCMS confirmed some reaction so the reaction mixture was heated at 50°C for a further 18 hours. The reaction mixture was concentrated and diluted with EtOAc (15 mL), and washed sequentially with saturated Na_2CO_3 (10 mL), water (10 mL), and saturated brine (10 mL).

15 The organic layer was dried over Na_2SO_4 , filtered and evaporated to afford crude product.

The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford tert-butyl N-methyl-N-[1-[[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]carbamoyl]cyclopropyl]carbamate (86 mg, 54%) as a white solid; m/z : 626.45 (MH $^+$).

25

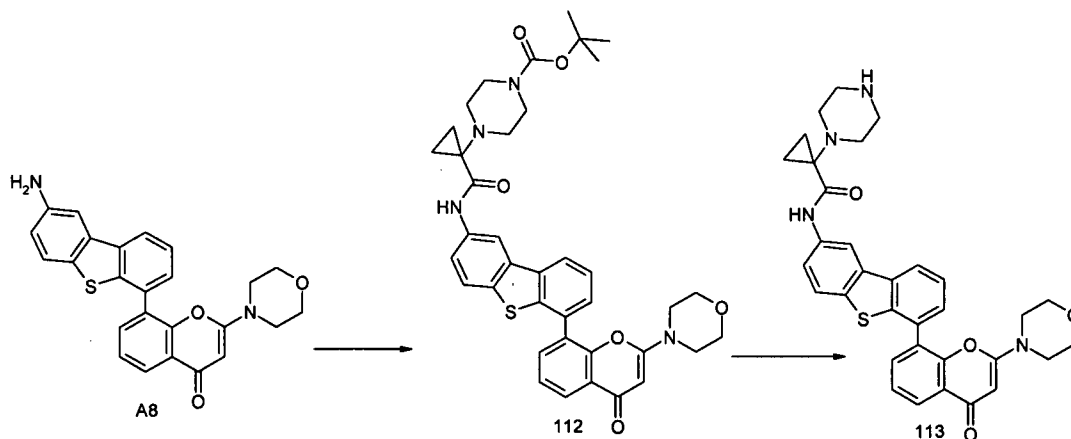
(b) 1-(methylamino)-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (111)

A solution of 10% TFA in DCM (2.5 mL) was added to tert-butyl N-methyl-N-[1-[[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]carbamoyl]cyclopropyl]carbamate (86 mg, 0.14 mmol) at 25°C. The resulting solution was stirred at 25°C for 2 hours.

The crude product was purified by ion exchange chromatography, using an SCX column.

The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford 1-(methylamino)-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (80 mg, 111 %) as a cream solid; ¹H NMR (400 MHz, CDCl₃) δ 0.94 - 0.97 (2H, m), 1.44 - 1.46 (2H, m), 2.42 (3H, s), 3.00 (4H, t), 3.42 (4H, t), 5.43 (1H, s), 7.38 - 7.43 (3H, m), 7.48 (1H, t), 7.64 - 7.70 (2H, m), 8.15 - 8.22 (2H, m), 8.72 (1H, d), 9.91 (1H, s); m/z: 526.49 (MH⁺).

Example 79



N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]-1-piperazin-1-ylcyclopropane-1-carboxamide (113)

(a) Tert-butyl 4-[1-[[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]carbamoyl]cyclopropyl]piperazine-1-carboxylate (112)

8-(8-Aminodibenzothiophen-4-yl)-2-morpholin-4-ylchromen-4-one (A8, 150 mg, 0.35 mmol) was added to 1-[4-[(2-methylpropan-2-yl)oxycarbonyl]piperazin-1-yl]cyclopropane-1-carboxylic acid (S1, 114 mg, 0.42 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (266 mg, 0.70 mmol) and N,N-diisopropylethylamine (0.183 mL, 1.05 mmol) in DMA (2 mL). The resulting suspension was stirred at room temperature for 18 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and fractions were evaporated to dryness to afford crude product. The

crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford tert-butyl 4-[1-[[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]carbamoyl]cyclopropyl]piperazine-1-carboxylate (189 mg, 79 %) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.09 - 1.12 (2H, m), 1.33 - 1.36 (2H, m), 1.41 (9H, s), 2.38 - 2.51 (4H, m), 3.00 (4H, t), 3.33 - 3.73 (8H, m), 5.43 (1H, s), 7.33 (1H, dd), 7.40 - 7.43 (2H, m), 7.49 (1H, t), 7.65 - 7.70 (2H, m), 8.16 - 8.22 (2H, m), 8.70 (1H, d), 10.01 (1H, s); m/z: 681.59 (MH⁺).

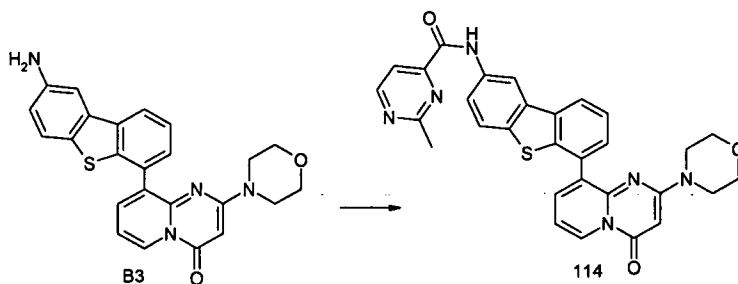
(b) *N*-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]-1-piperazin-1-ylcyclopropane-1-carboxamide (113)

A solution of 10% TFA in DCM (2.5 mL) was added to tert-butyl 4-[1-[[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]carbamoyl]cyclopropyl]piperazine-1-carboxylate (112, 185 mg, 0.27 mmol) at 25°C. The resulting solution was stirred at 25°C for 2 hours.

The crude product was purified by ion exchange chromatography, using an SCX column.

The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford *N*-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]-1-piperazin-1-ylcyclopropane-1-carboxamide (148 mg, 94 %) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.11 - 1.14 (2H, m), 1.31 - 1.34 (2H, m), 2.47 (4H, s), 2.98 - 3.01 (8H, m), 3.42 (4H, t), 5.43 (1H, s), 7.33 (1H, dd), 7.40 - 7.43 (2H, m), 7.49 (1H, t), 7.65 - 7.70 (2H, m), 8.16 - 8.22 (2H, m), 8.73 (1H, d), 10.13 (1H, s); m/z: 579.60 (MH⁺).

Example 80

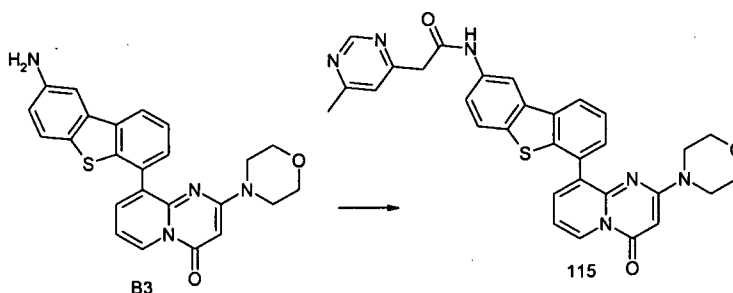


2-methyl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-*a*]pyrimidin-9-yl)dibenzothiophen-2-yl]pyrimidine-4-carboxamide (114)

N,N-Diisopropylethylamine (0.163 mL, 0.93 mmol) was added dropwise to a partial solution of 2-methylpyrimidine-4-carboxylic acid (48.4 mg, 0.35 mmol), 9-(8-aminodibenzothiophen-4-yl)-2-morpholin-4-ylpyrido[1,2-*a*]pyrimidin-4-one (B3, 100mg, 0.23 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (133 mg, 0.35

mmol) in DMA (1 mL), stirred at room temperature under nitrogen. The mixture was stirred at room temperature for 1 hour and then heated to 80°C for 5 minutes to ensure dissolution of all of the starting material. LCMS indicated complete reaction so the mixture was quenched into water (10mL) and the precipitate filtered off, washed with water (5 mL), and dried. The crude product was purified by flash silica chromatography, elution gradient 2 to 5% MeOH in DCM. Pure fractions were evaporated to dryness and the solid produced triturated with acetonitrile (1mL), filtered and dried to afford 2-methyl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]pyrimidine-4-carboxamide (47.4 mg, 37%) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 2.89 (3H, s), 3.35 - 3.38 (4H, m), 3.56 - 3.58 (4H, m), 5.63 (1H, s), 7.02 (1H, t), 7.55 - 7.59 (2H, m), 7.68 - 7.71 (1H, m), 7.79 (1H, d), 7.86 - 7.88 (1H, m), 8.06 - 8.07 (1H, m), 8.25 - 8.29 (1H, m), 8.86 (1H, d), 8.96 (1H, d), 9.04 - 9.06 (1H, m), 10.11 (1H, s); m/z: 549.36 (MH⁺).

Example 81

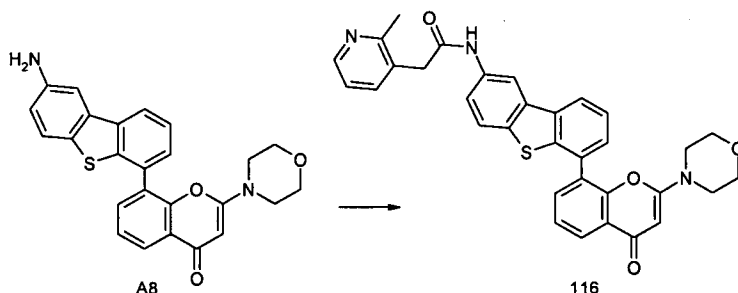


2-(6-methylpyrimidin-4-yl)-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]acetamide (115)

N,N-Diisopropylethylamine (0.163 mL, 0.93 mmol) was added dropwise to a partial solution of 2-(6-methylpyrimidin-4-yl)acetic acid (T1, 55.7 mg, 0.35 mmol), 9-(8-aminodibenzothiophen-4-yl)-2-morpholin-4-ylpyrido[1,2-a]pyrimidin-4-one (B3, 100mg, 0.23 mmol), and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (133 mg, 0.35 mmol) in DMA (1 mL), stirred at room temperature, under nitrogen. The mixture was stirred at room temperature for 1 hour and then heated to 80°C for 5 minutes to ensure dissolution of all of the starting material. LCMS indicated complete reaction so the mixture was quenched into water (10mL) and the precipitate filtered off, washed with water (5 mL), and diethyl ether (5 mL) and dried. The crude product was purified by flash silica chromatography, elution gradient 2 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-(6-methylpyrimidin-4-yl)-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]acetamide (52 mg, 40%) as a cream foam; ¹H NMR (400 MHz, CDCl₃) δ , 2.58 (3H, s), 3.33 - 3.36 (4H, m), 3.54 - 3.56 (4H, m), 3.88 (2H, s),

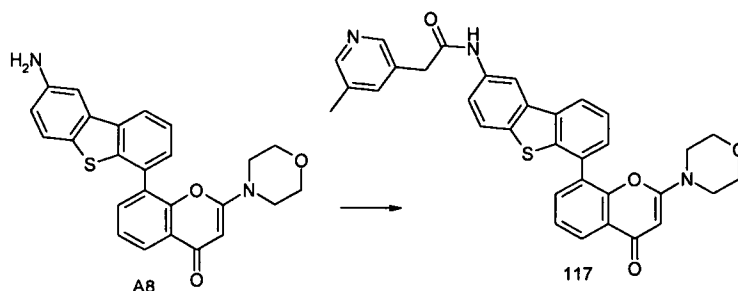
5.62 (1H, s), 7.00 (1H, t), 7.45 - 7.48 (1H, m), 7.52 - 7.56 (1H, m), 7.55 (1H, s), 7.70 (1H, d), 7.84 - 7.87 (1H, m), 8.19 - 8.23 (1H, m), 8.59 (1H, d), 9.02 - 9.05 (1H, m), 9.15 (1H, d), 9.68 (1H, s); m/z: 563.37 (MH⁺).

5 Example 82



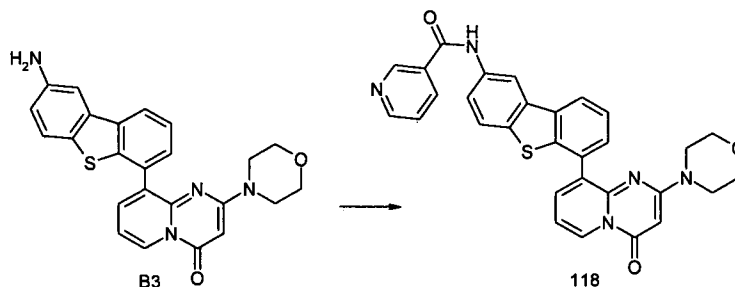
2-(2-methylpyridin-3-yl)-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (116)

8-(8-Aminodibenzothiophen-4-yl)-2-morpholin-4-ylchromen-4-one (A8, 100mg, 0.23 mmol) was added in one portion to a solution of 2-(2-methylpyridin-3-yl)acetic acid hydrochloride (U2, 52.5 mg, 0.28 mmol), HATU (106 mg, 0.28 mmol) and DIPEA (0.122 mL, 0.70 mmol) in dry DMA (1 mL) under nitrogen and stirred at room temperature overnight. The mixture was incomplete by LCMS so further HATU (106 mg, 0.28 mmol) and DIPEA (0.122 mL, 0.70 mmol) were added and the stirring continued for a further 24 hours. The volatiles were removed in vacuo and to the residue water (10mL) was added with stirring to produce a suspension. The crude solid was filtered off and washed with water (2mL), dried in vacuo and purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 18 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 2-(2-methylpyridin-3-yl)-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (66 mg, 50%) as a white foam; ¹H NMR (400 MHz, CDCl₃) δ 2.66 (3H, s), 3.05 (4H, t), 3.48 (4H, t), 3.85 (2H, s), 5.48 (1H, s), 7.21 - 7.24 (1H, m), 7.34 (1H, d), 7.46 - 7.49 (2H, m), 7.55 (1H, t), 7.66 - 7.70 (2H, m), 7.73 - 7.76 (1H, m), 7.81 (1H, s), 8.18 (1H, d), 8.26 - 8.28 (1H, m), 8.51 (1H, s), 8.64 (1H, s); m/z: 562.36 (MH⁺).

Example 83

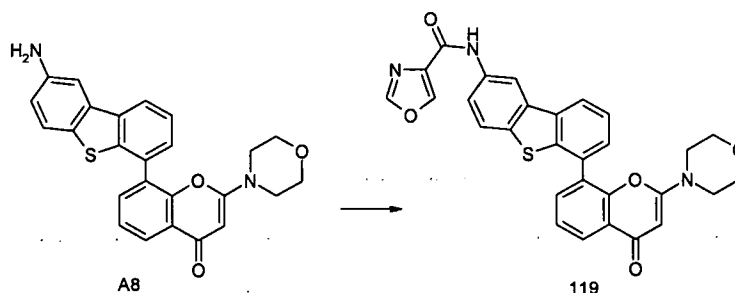
2-(5-methylpyridin-3-yl)-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (117)

- 5 8-(8-Aminodibenzothiophen-4-yl)-2-morpholin-4-ylchromen-4-one (A8, 100mg, 0.23 mmol) was added in one portion to a solution of 2-(5-methylpyridin-3-yl)acetic acid (V1, 42.3 mg, 0.28 mmol), HATU (106 mg, 0.28 mmol) and DIPEA (0.122 mL, 0.70 mmol) in dry DMA (1 mL) under nitrogen and stirred at room temperature overnight. The mixture was incomplete by LCMS so further HATU (106 mg, 0.28 mmol), 2-(5-methylpyridin-3-yl)acetic acid (42.3
- 10 mg, 0.28 mmol) and DIPEA (0.122 mL, 0.70 mmol) were added and the stirring continued for a further 24 hours. The volatiles were removed in vacuo and to the residue water (10mL) was added with stirring to produce a suspension. The crude solid was filtered off and washed with water (2mL), dried in vacuo and purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 18 mm diameter, 100 mm length), using decreasingly polar
- 15 mixtures of water (containing 0.1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the still impure solid. This was further purified by flash silica chromatography, eluent 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-(5-methylpyridin-3-yl)-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (60 mg, 46%) as a white solid; ¹H NMR
- 20 (400 MHz, CDCl₃) δ 2.38 (3H, s), 3.05 (4H, t), 3.47 (4H, t), 3.78 (2H, s), 5.48 (1H, s), 7.36 - 7.38 (1H, m), 7.46 - 7.49 (2H, m), 7.55 (1H, t), 7.61 (1H, s), 7.69 (1H, d), 7.73 - 7.76 (1H, m), 7.98 (1H, s), 8.16 - 8.18 (1H, m), 8.27 - 8.29 (1H, m), 8.44 (2H, d), 8.66 (1H, d); m/z: 562.34 (MH⁺).

Example 84

N-[6-(2-morpholin-4-yl)-4-oxopyrido[1,2-a]pyrimidin-9-yl]dibenzothiophen-2-yl]pyridine-3-carboxamide (118)

- 5 9-(8-Aminodibenzothiophen-4-yl)-2-morpholin-4-ylpyrido[1,2-a]pyrimidin-4-one (B3, 181 mg, 0.42 mmol) was added to nicotinic acid (62.3 mg, 0.51 mmol), *N,N*-diisopropylethylamine (0.176 mL, 1.01 mmol) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (192 mg, 0.51 mmol) in DMA (1 mL). The reaction mixture was evaporated to dryness and redissolved in EtOAc (250 mL), and washed with water (100 mL).
- 10 The organic layer was dried over MgSO_4 , filtered and evaporated onto silica gel (5 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford *N*-[6-(2-morpholin-4-yl)-4-oxopyrido[1,2-a]pyrimidin-9-yl]dibenzothiophen-2-yl]pyridine-3-carboxamide (167 mg, 74%) as a white solid; ^1H NMR (400 MHz, DMSO) δ 3.33 (4H, t), 3.47 (4H, t), 5.68 (1H, s), 7.24 (1H, t), 7.61 - 7.68 (3H, m), 7.85 (1H, dd), 7.98 (1H, d), 8.08 (1H, d), 8.30 (1H, dd), 8.37 - 8.40 (1H, m), 8.78 - 8.84 (2H, m), 8.94 (1H, dd), 9.20 (1H, d), 10.69 (1H, s); m/z : 534.11 (MH^+).
- 15

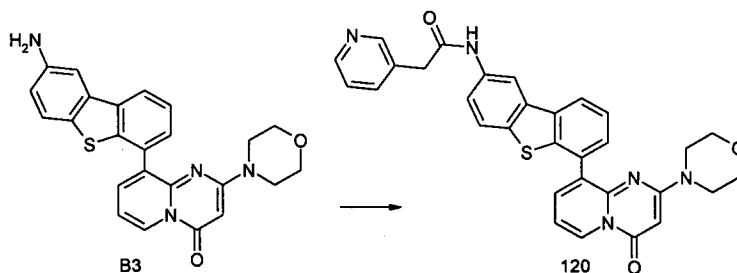
Example 85

N-[6-(2-morpholin-4-yl)-4-oxochromen-8-yl]dibenzothiophen-2-yl]-1,3-oxazole-4-carboxamide (119).

- 20 8-(8-Aminodibenzothiophen-4-yl)-2-morpholin-4-ylchromen-4-one (A8, 183 mg, 0.43 mmol) was added to 1,3-oxazole-4-carboxylic acid (58 mg, 0.51 mmol), *N,N*-diisopropylethylamine (0.179 mL, 1.03 mmol) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium
- 25

hexafluorophosphate (195 mg, 0.51 mmol) in DMA (1 mL). The reaction mixture was evaporated to dryness and redissolved in EtOAc (50 mL), and washed with water (50 mL). The precipitate was collected by filtration. The organic layer was separated then dried over MgSO₄, filtered and evaporated onto silica gel (5 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]-1,3-oxazole-4-carboxamide (158 mg, 71%) as a white solid. The precipitate was dissolved in MeOH/DCM (100 mL) then evaporated onto silica gel (5 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]-1,3-oxazole-4-carboxamide (53.4 mg, 26%) as a white solid; ¹H NMR (400 MHz, DMSO) δ 3.33 (4H, t), 3.46 (4H, t), 5.68 (1H, s), 7.23 (1H, t), 7.63 - 7.67 (2H, m), 7.94 (2H, s), 8.07 (1H, dd), 8.26 - 8.30 (1H, m), 8.67 (1H, s), 8.82 (1H, s), 8.86 (1H, s), 8.94 (1H, dd), 10.38 (1H, s); m/z: 524.13 (MH⁺).

Example 86

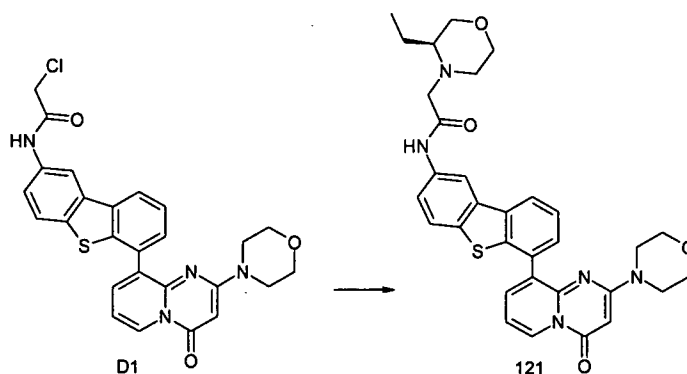


N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]-2-pyridin-3-ylacetamide (120)

9-(8-Aminodibenzothiophen-4-yl)-2-morpholin-4-ylpyrido[1,2-a]pyrimidin-4-one (B3, 180 mg, 0.42 mmol) was added to 2-(pyridin-3-yl)acetic acid hydrochloride (87.6 mg, 0.50 mmol), N,N-diisopropylethylamine (0.249 mL, 1.43 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (192 mg, 0.50 mmol) in DMA (1 mL). The reaction mixture was diluted with EtOAc (25 mL), and washed sequentially with water (25 mL) and saturated brine (5 mL). The organic layer was dried over MgSO₄, filtered and evaporated onto silica gel (2 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness and the product was purified by crystallisation from MeOH to afford N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]-2-pyridin-3-ylacetamide (67.9 mg, 29.5 %) as an off white crystalline solid. The mother liquors were evaporated onto silica gel (2 g). The crude product was purified by flash silica chromatography, eluting with 5 MeOH in

DCM. Pure fractions were evaporated to dryness then The crude dry film was triturated with isohexane/diethyl ether to give a solid which was collected by filtration and dried under vacuum to give N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]-2-pyridin-3-ylacetamide (79.0 mg, 34.3 %) as a brown solid. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]-2-pyridin-3-ylacetamide (6.60 mg, 3%); ¹H NMR (400 MHz, CDCl₃) δ 3.34 (4H, t), 3.55 (4H, t), 3.81 (2H, s), 5.62 (1H, s), 7.01 (1H, t), 7.31 - 7.42 (3H, m), 7.51 - 7.56 (2H, m), 7.69 (1H, d), 7.79 (1H, dt), 7.85 (1H, dd), 8.17 (1H, dd), 8.56 (1H, s), 8.61 (1H, dd), 8.65 (1H, s), 9.03 (1H, dd); m/z: 548.07 (MH⁺).

Example 87

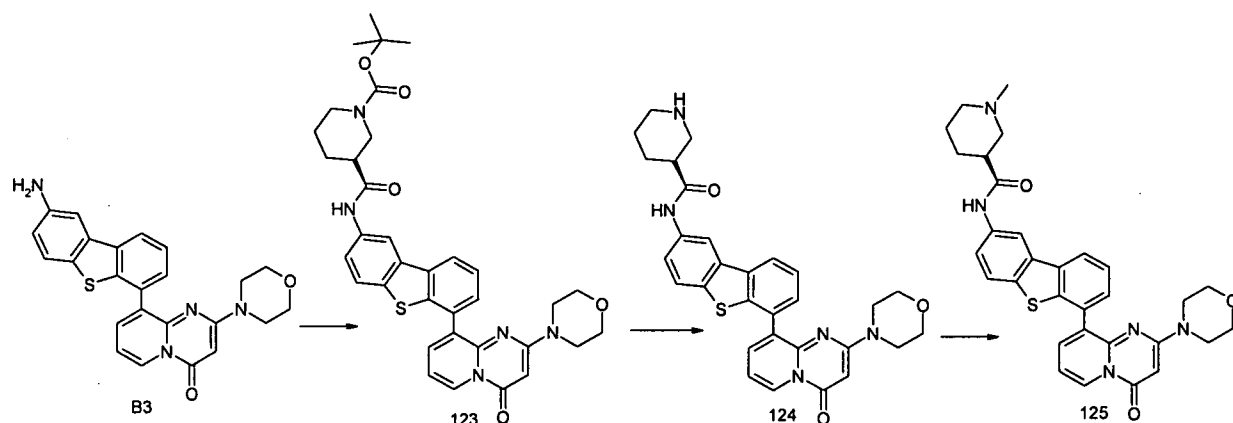


2-[(3S)-3-ethylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]acetamide (121)

A solution of 2-chloro-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]acetamide (D1, 0.178 g, 0.353 mmol) in DCM (5 mL) was added in one portion to a stirred solution of (3S)-3-ethylmorpholine hemi oxalate salt (DD3, 0.113 g, 0.71 mmol), sodium iodide (0.001 g, 6.67 μ mol) and N,N-Diisopropylethylamine (0.068 mL, 0.39 mmol) in DCM (1 mL). The resulting solution was stirred at room temperature for 3 days. The reaction was incomplete so the temperature was increased to reflux and the reaction mixture was stirred for a further 12 hours. The reaction mixture was diluted with DCM (15 mL), and washed with water (15 mL). The organic layer was dried over MgSO₄, filtered and evaporated onto silica gel (2 g). The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM, then re-purified by flash silica chromatography, eluting isocratically with 2% MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-[(3S)-3-ethylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-

oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]acetamide (0.075 g, 36%) as an off white solid; ^1H NMR (400 MHz, DMSO) δ 0.87 (3H, t), 1.38 - 1.50 (1H, m), 1.54 - 1.65 (1H, m), 2.44 - 2.64 (4H, m), 2.79 - 2.86 (1H, m), 3.18 (1H, d), 3.24 - 3.28 (1H, m), 3.34 - 3.53 (7H, m), 3.61 - 3.68 (1H, m), 3.70 - 3.81 (2H, m), 5.67 (1H, s), 7.23 (1H, t), 7.61 - 7.66 (2H, m), 7.76 (1H, dd), 7.91 (1H, d), 8.06 (1H, dd), 8.27 - 8.32 (1H, m), 8.65 (1H, d), 8.93 (1H, dd), 9.91 (1H, s); m/z : 584.49 (MH^+).

Example 88



(3S)-1-methyl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (125)

(a) (3S)- tert-butyl 3-[[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]carbamoyl]piperidine-1-carboxylate (123)

9-(8-Aminodibenzothiophen-4-yl)-2-morpholin-4-ylpyrido[1,2-a]pyrimidin-4-one (B3, 181 mg, 0.42 mmol) was added to (S)-1-(tert-butoxycarbonyl)piperidine-3-carboxylic acid (115.9 mg, 0.51 mmol), N,N-diisopropylethylamine (0.176 mL, 1.01 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (192 mg, 0.51 mmol) in DMA (1 mL).

The reaction mixture was evaporated to dryness and redissolved in EtOAc (50 mL), and washed with water (50 mL). The precipitate was collected by filtration. The organic layer was separated then dried over MgSO_4 then filtered. The precipitate was dissolved in MeOH/DCM (100 mL) and combined with the ethyl acetate layer. The resulting solution was evaporated onto silica gel (5 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford (3S)- tert-butyl 3-[[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]carbamoyl]piperidine-1-carboxylate (211 mg, 78 %) as a white solid; ^1H NMR (400 MHz, CDCl_3) δ 1.42 - 1.47 (1H, m), 1.49 (9H, s), 1.52 - 1.59 (1H, m), 1.91 - 2.00 (1H, m), 2.12 - 2.26 (1H, m), 2.55 - 2.64 (1H, m), 3.26 - 3.43 (5H, m), 3.49 - 3.75 (7H,

m), 3.80 - 3.91 (1H, m), 5.62 (1H, s), 7.01 (1H, t), 7.46 - 7.56 (3H, m), 7.68 (1H, d), 7.85 (1H, dd), 8.18 (1H, dd), 8.70 (1H, s), 9.03 (1H, dd); m/z: 640.13 (MH⁺).

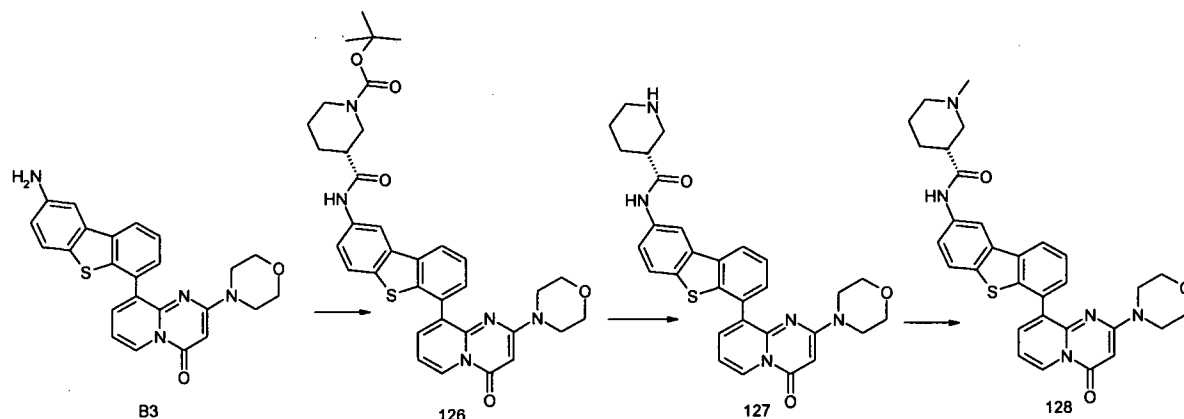
(b) (S)-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (124)

(3S)- Tert-butyl 3-[[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]carbamoyl]piperidine-1-carboxylate (123, 203 mg, 0.32 mmol) was stirred in TFA (1 mL) and DCM (20 mL). The resulting solution was stirred at room temperature for 1 hour. The reaction mixture was evaporated to dryness and redissolved in MeOH (5 mL).

The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were evaporated to dryness to afford (S)-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (261 mg, 152 %) as a white solid; ¹H NMR (400 MHz, D₄ acetic acid) δ 1.89 - 2.08 (4H, m), 2.14 - 2.21 (1H, m), 2.96 - 3.04 (1H, m), 3.27 - 3.36 (2H, m), 3.38 (4H, t), 3.43 - 3.50 (1H, m), 3.57 (4H, t), 3.62 - 3.68 (1H, m), 7.05 (1H, t), 7.50 - 7.57 (3H, m), 7.70 (1H, d), 7.88 (1H, dd), 8.17 - 8.21 (1H, m), 8.63 (1H, d), 9.05 (1H, dd); m/z: 540.12 (MH⁺).

(c) (3S)-1-methyl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (125)

(S)-N-[6-(2-Morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (124, 170 mg, 0.32 mmol) was added to paraformaldehyde (284 mg, 3.15 mmol), sodium cyanotrihydroborate (79 mg, 1.26 mmol) and magnesium sulfate (76 mg, 0.63 mmol) in methanol (100 mL) under nitrogen. The resulting suspension was stirred at 40°C for 90 minutes. The reaction mixture was filtered, then concentrated in vacuo onto silica gel (3 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 10% methanolic ammonia in DCM. Pure fractions were evaporated to dryness to afford (3S)-1-methyl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (120 mg, 68.8 %) as a white solid; ¹H NMR (400 MHz, DMSO, 373K) δ 1.44 - 1.55 (1H, m), 1.58 - 1.75 (2H, m), 1.83 - 1.92 (1H, m), 2.40 (3H, s), 2.56 - 2.63 (2H, m), 2.70 - 2.92 (1H, m, obscured by water peak), 3.03 - 3.09 (2H, m), 3.18 (4H, t), 3.33 (4H, t), 5.45 (1H, s), 7.05 (1H, t), 7.45 - 7.49 (2H, m), 7.54 (1H, dd), 7.69 (1H, d), 7.85 (1H, dd), 8.04 - 8.09 (1H, m), 8.46 (1H, d), 8.78 (1H, dd), 9.97 (1H, s); m/z: 554.15 (MH⁺).

Example 89

(3R)-1-methyl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (128)

- 5 (a) (R)- tert-butyl 3-[[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]carbamoyl]piperidine-1-carboxylate (126)

9-(8-aminodibenzothiophen-4-yl)-2-morpholin-4-ylpyrido[1,2-a]pyrimidin-4-one (B3, 218 mg, 0.51 mmol) was added to (R)-1-(tert-butoxycarbonyl)piperidine-3-carboxylic acid (116.7 mg, 0.51 mmol), N,N-Diisopropylethylamine (0.213 mL, 1.22 mmol) and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (232 mg, 0.61 mmol) in DMA (1 mL) then stirred at room temperature for 18 hours. The reaction mixture was evaporated to dryness and redissolved in EtOAc (50 mL), and washed with water (50 mL). The precipitate was collected by filtration. The organic layer was separated then dried over MgSO₄ then filtered. The precipitate was dissolved in MeOH/DCM (100 mL) and combined with the ethyl acetate layer. The resulting solution was evaporated onto silica gel (5 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford (R)- tert-butyl 3-[[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]carbamoyl]piperidine-1-carboxylate (238 mg, 73%) as a white solid; ¹H NMR (400 MHz, DMSO) δ 1.38 - 1.52 (10H, m), 1.68 - 1.81 (2H, m), 1.98 - 2.06 (1H, m), 2.53 - 2.60 (1H, m), 2.83 - 2.90 (1H, m), 3.05 (1H, d), 3.31 (4H, t), 3.46 (4H, t), 3.87 (1H, d), 4.06 (1H, d), 5.57 (1H, s), 7.18 (1H, t), 7.58 - 7.68 (3H, m), 7.82 (1H, d), 7.98 (1H, dd), 8.18 - 8.22 (1H, m), 8.60 (1H, d), 8.91 (1H, dd), 9.83 (1H, s); m/z: 640.41 (MH⁺).

- 25 (b) (R)-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (127)

(R)- tert-butyl 3-[[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]carbamoyl]piperidine-1-carboxylate (126, 215 mg, 0.34 mmol) was stirred in TFA (1 mL)

and DCM (20 mL). The resulting solution was stirred at room temperature for 1 hour. The reaction mixture was evaporated to dryness and redissolved in MeOH (5 mL).

The crude product was purified by ion exchange chromatography, using an SCX column.

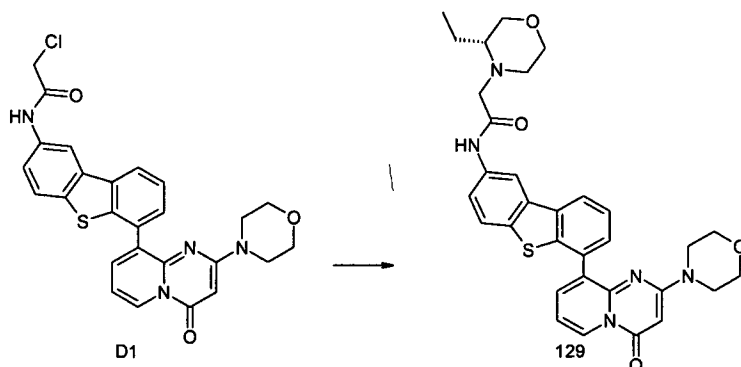
The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions

5 were evaporated to dryness to afford (R)-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (228 mg, 126 %) as a white solid; ¹H NMR (400 MHz, DMSO, 373K) δ 1.40 - 1.51 (1H, m), 1.63 - 1.78 (2H, m), 1.90 - 1.98 (1H, m), 2.53 - 2.67 (2H, m), 2.76 - 2.88 (2H, m), 3.09 (2H, d), 3.31 (4H, t), 3.46 (4H, t), 5.58 (1H, s), 7.18 (1H, t), 7.57 - 7.68 (3H, m), 7.80 (1H, d), 7.98 (1H, dd), 8.18 - 8.22 (1H, m), 8.60
10 (1H, d), 8.91 (1H, dd), 9.86 (1H, s); m/z: 540.12 (MH⁺).

(c) (3R)-1-methyl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (128)

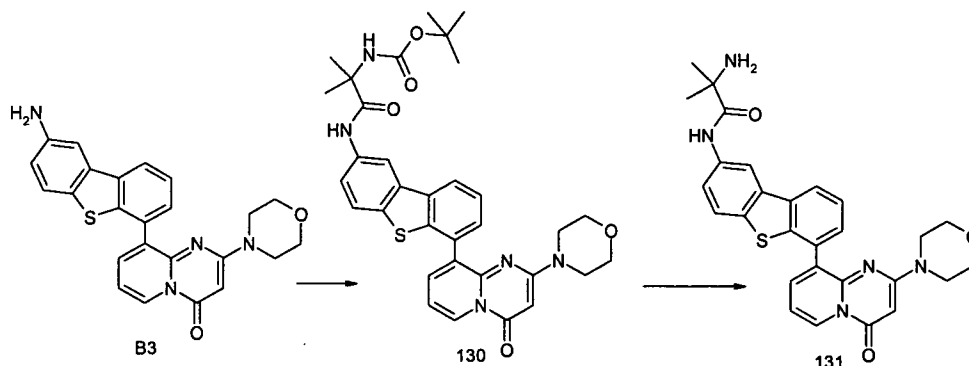
(R)-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]piperidine-
15 3-carboxamide (127, 183 mg, 0.34 mmol) was added to paraformaldehyde (306 mg, 3.40 mmol), sodium cyanotrihydroborate (85 mg, 1.36 mmol) and magnesium sulfate (82 mg, 0.68 mmol) in methanol (100 mL) under nitrogen. The resulting suspension was stirred at room temperature for 90 minutes. The reaction mixture was filtered, then concentrated in vacuo onto silica gel (3 g). The resulting powder was purified by flash silica

20 chromatography, elution gradient 0 to 10% methanolic ammonia in DCM. Pure fractions were evaporated to dryness to afford (3R)-1-methyl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]piperidine-3-carboxamide (180 mg, 96 %) as a white solid; ¹H NMR (400 MHz, DMSO, 373K) δ 1.68 - 1.79 (1H, m), 1.83 - 1.99 (2H, m), 2.07 - 2.15 (1H, m), 2.65 - 2.74 (4H, m), 2.85 - 3.19 (3H, m, obscured by water peak), 3.33 (1H, d),
25 3.40 (4H, t), 3.55 (4H, t), 5.67 (1H, s), 7.27 (1H, t), 7.68 - 7.73 (2H, m), 7.76 (1H, dd), 7.92 (1H, d), 8.08 (1H, dd), 8.27 - 8.31 (1H, m), 8.68 (1H, d), 9.01 (1H, dd), 10.20 (1H, s); m/z: 554.41 (MH⁺).

Example 90

2-[(3R)-3-ethylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]acetamide (129)

- 5 A solution of 2-chloro-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]acetamide (D1, 0.178 g, 0.353 mmol) in DCM (5 mL) was added in one portion to a stirred solution of (3R)-3-ethylmorpholine hemi oxalate salt (CC3, 0.113 g, 0.71 mmol), sodium iodide (0.001 g, 6.67 μ mol) and N,N-diisopropylethylamine (0.068 mL, 0.39 mmol) in DCM (1 mL). The resulting solution was stirred at room temperature for 3
- 10 days. The reaction was incomplete so the temperature was increased to reflux and the reaction mixture was stirred for a further 6 hours. The reaction mixture was diluted with DCM (15 mL), and washed with water (15 mL). The organic layer was dried over MgSO_4 , filtered and evaporated onto silica gel (2 g). The crude product was purified by flash silica
- 15 chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford (2-[(3R)-3-ethylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]acetamide (0.113 g, 55%) as a beige solid; ^1H NMR (400 MHz, CDCl_3) δ 0.94 (3H, t), 1.43 - 1.54 (1H, m), 1.61 - 1.70 (1H, m), 2.47 - 2.54 (1H, m), 2.61 - 2.69 (1H, m), 2.87 - 2.92 (1H, m), 3.10 (1H, d), 3.35 (4H, t), 3.44 - 3.53 (2H, m), 3.56 (4H, t), 3.72 - 3.78 (1H, m), 3.84 - 3.93 (2H, m), 5.63 (1H, s), 7.01 (1H, t), 7.44 (1H, dd),
- 20 7.53 - 7.57 (2H, m), 7.72 (1H, d), 7.86 (1H, dd), 8.22 - 8.26 (1H, m), 8.65 (1H, d), 9.04 (1H, dd), 9.42 (1H, s); m/z: 584.49 (MH^+).

Example 91

2-amino-2-methyl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]propanamide (131)

- 5 (a) *tert-butyl N-[2-methyl-1-[[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]amino]-1-oxopropan-2-yl]carbamate (130)*

9-(8-aminodibenzothiophen-4-yl)-2-morpholin-4-ylpyrido[1,2-a]pyrimidin-4-one (B3, 180 mg, 0.42 mmol) was added to 2-(tert-butoxycarbonylamino)-2-methylpropanoic acid (102 mg, 0.50 mmol), N,N-diisopropylethylamine (0.176 mL, 1.01 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (192 mg, 0.50 mmol) in DMA (1 mL), then stirred at room temperature overnight. The reaction mixture was evaporated to dryness and redissolved in EtOAc (200 mL), and washed with water (50 mL). The organic layer was dried over MgSO₄, filtered and evaporated onto silica gel (2 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM.

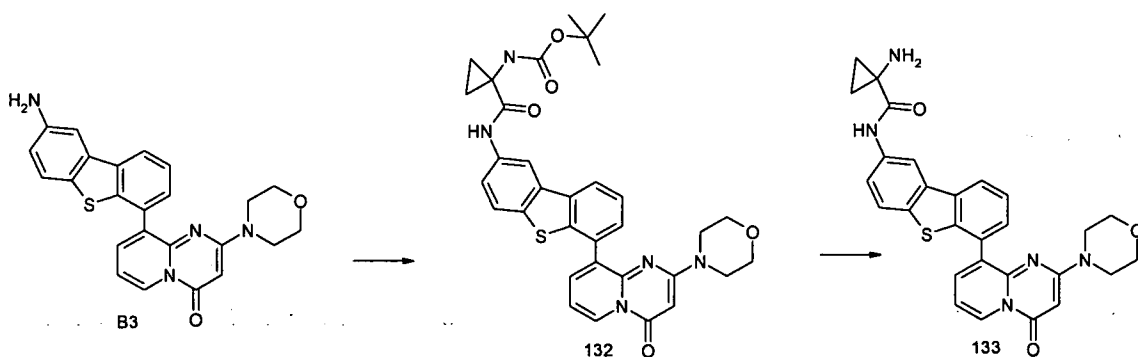
- 10 Pure fractions were evaporated to dryness to afford *tert-butyl N-[2-methyl-1-[[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]amino]-1-oxopropan-2-yl]carbamate (213 mg, 83 %)* as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.48 (9H, s), 1.64 (6H, s), 3.35 (4H, t), 3.56 (4H, t), 4.94 (1H, s), 5.64 (1H, s), 7.01 (1H, t), 7.38 (1H, dd), 7.51 - 7.55 (2H, m), 7.69 (1H, d), 7.86 (1H, dd), 8.17 - 8.22 (1H, m), 8.67 (1H, d), 9.03 (1H, dd), 9.36 (1H, br s); m/z: 614.10 (MH⁺).

(b) *2-amino-2-methyl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]propanamide (131)*

- 25 *Tert-butyl N-[2-methyl-1-[[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]amino]-1-oxopropan-2-yl]carbamate (130, 206 mg, 0.34 mmol)* was stirred in DCM (20 mL) and TFA (2 mL) over a period of 3 hours at room temperature. The reaction mixture was evaporated to dryness and redissolved in MeOH (5 mL). The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH then concentrated in vacuo onto

silica gel (2 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-amino-2-methyl-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]propanamide (120 mg, 70%) as a white solid; ¹H NMR (400 MHz, DMSO) δ 1.37 (6H, s), 3.29 (3H, s), 3.32 (4H, t), 3.46 (4H, t), 5.66 (1H, s), 7.22 (1H, t), 7.60 - 7.65 (2H, m), 7.81 (1H, dd), 7.89 (1H, d), 8.06 (1H, dd), 8.26 - 8.31 (1H, m), 8.70 (1H, d), 8.93 (1H, dd); m/z: 514.12 (MH⁺).

Example 92



1-amino-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (133)

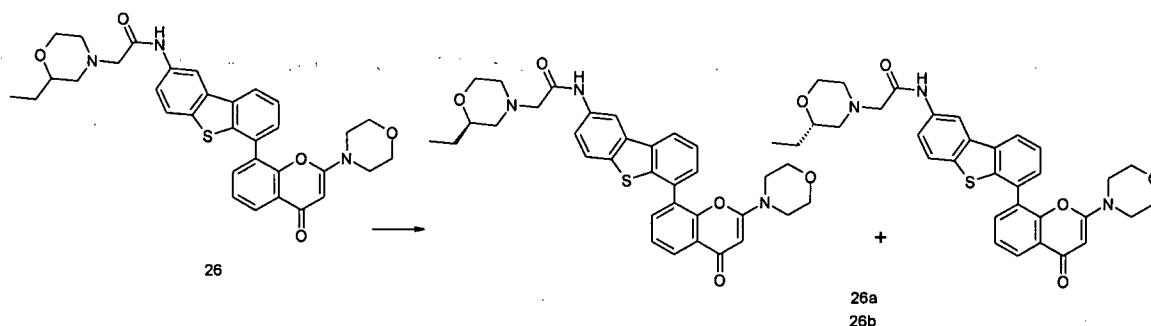
(a) tert-butyl N-[1-[[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]carbamoyl]cyclopropyl]carbamate (132)

9-(8-Aminodibenzothiophen-4-yl)-2-morpholin-4-ylpyrido[1,2-a]pyrimidin-4-one (B3, 180 mg, 0.42 mmol) was added to 1-(tert-butoxycarbonylamino)cyclopropanecarboxylic acid (101 mg, 0.50 mmol), N,N-diisopropylethylamine (0.176 mL, 1.01 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (192 mg, 0.50 mmol) in DMA (1 mL), then stirred at room temperature overnight. The reaction mixture was evaporated to dryness and redissolved in EtOAc (100 mL), and washed with water (50 mL). The organic layer was dried over MgSO₄, filtered and evaporated onto silica gel (2 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford tert-butyl N-[1-[[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]carbamoyl]cyclopropyl]carbamate (200 mg, 78 %) as a white solid; ¹H NMR (400 MHz, DMSO) δ 1.05 (2H, q), 1.39 - 1.50 (11H, m), 3.32 (4H, t), 3.46 (4H, t), 5.66 (1H, s), 7.22 (1H, t), 7.40 (1H, s), 7.60 - 7.65 (2H, m), 7.72 (1H, d), 7.88 (1H, d), 8.06 (1H, dd), 8.22 - 8.26 (1H, m), 8.63 (1H, d), 8.93 (1H, dd), 9.65 (1H, s); m/z: 612.11 (MH⁺).

(b) 1-amino-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (133)

Tert-butyl N-[1-[[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]carbamoyl]cyclopropyl]carbamate (132, 200 mg, 0.33 mmol) was stirred in DCM (20 mL) and TFA (2 mL) over a period of 4 hours at room temperature. The reaction mixture was evaporated to dryness and redissolved in DCM (100 mL), and washed sequentially with saturated NaHCO₃ (100 mL), water (100 mL), and saturated brine (25 mL). The organic layer was dried over MgSO₄, filtered and evaporated onto silica gel (2 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford 1-amino-N-[6-(2-morpholin-4-yl-4-oxopyrido[1,2-a]pyrimidin-9-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (144 mg, 86 %) as a white solid; ¹H NMR (400 MHz, DMSO) δ 0.94 (2H, q), 1.20 - 1.27 (2H, m), 2.80 (2H, s), 3.31 (4H, t), 3.44 (4H, t), 5.65 (1H, s), 7.21 (1H, t), 7.58 - 7.64 (2H, m), 7.80 (1H, dd), 7.87 (1H, d), 8.04 (1H, dd), 8.26 (1H, dd), 8.68 (1H, d), 8.91 (1H, dd), 10.26 (1H, s); m/z: 512.07 (MH⁺).

Example 93



2-[(2R)-2-ethylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide and 2-[(2S)-2-ethylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (26a) & (26b) - absolute stereochemistry not defined

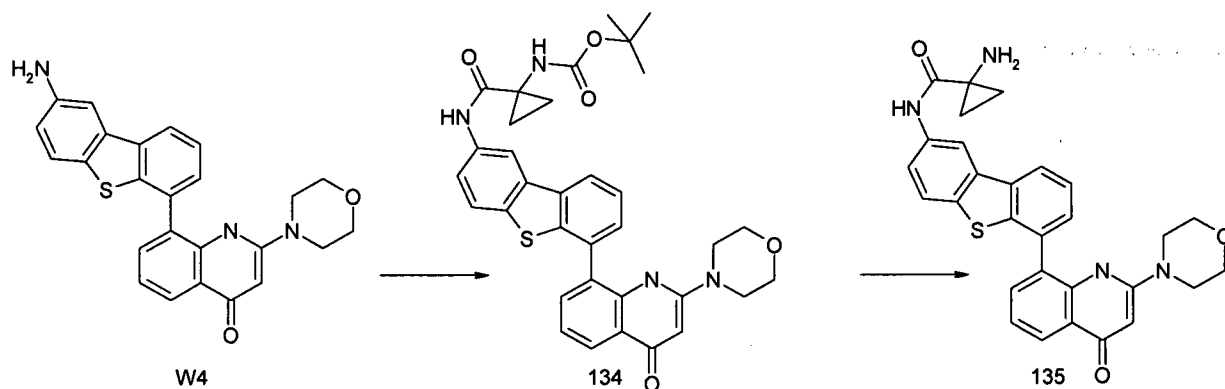
A sample of racemic 2-(2-ethylmorpholin-4-yl)-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]acetamide (26, 58 mg) was taken and the two enantiomers

separated by preparative chiral-HPLC on a Merck 50mm 20µm Chiralpak AS - No BD004 column, eluting with MeCN/MeOH 90/10 as eluent. The fractions containing the desired compound were evaporated to dryness to afford the two separated isomers. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water

(containing 1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness.

The first eluted isomer was 26a (15.7 mg); *m/z*: 584.30 (MH⁺). The second eluted isomer was 26b (18.6 mg); ¹H NMR (700 MHz, CDCl₃) δ 0.99 (3H, t), 1.47 - 1.62 (2H, m, obscured by water peak), 2.20 (1H, s), 2.50 (1H, s), 2.83 (2H, d), 3.08 (4H, t), 3.22 (2H, s), 3.50 (4H, t), 3.53 (1H, s), 3.76 (1H, s), 3.99 (1H, d), 5.50 (1H, s), 7.44 (1H, s), 7.48 - 7.50 (2H, m), 7.58 (1H, t), 7.74 - 7.77 (2H, m), 8.25 (1H, d), 8.29 (1H, d), 8.72 (1H, s), 9.29 (1H, s); *m/z*: 584.33 (MH⁺).

Example 94



1-amino-N-[6-(2-morpholin-4-yl)-4-oxo-1H-quinolin-8-yl]dibenzothiophen-2-yl]cyclopropane-1-carboxamide (135)

(a) *tert*-butyl N-[1-[[6-(2-morpholin-4-yl)-4-oxo-1H-quinolin-8-yl]dibenzothiophen-2-yl]carbamoyl]cyclopropyl]carbamate (134)

A solution of 8-(8-aminodibenzothiophen-4-yl)-2-morpholin-4-yl-1H-quinolin-4-one (W4, 34 mg, 0.08 mmol) in DMA (5 mL) was added to a stirred solution of 1-(*tert*-butoxycarbonylamino)cyclopropanecarboxylic acid (17.60 mg, 0.09 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (39.3 mg, 0.10 mmol) and N,N-Diisopropylethylamine (0.036 mL, 0.21 mmol) in DMA (5 mL). The resulting solution was stirred at room temperature for 18 hours. The reaction mixture was diluted with EtOAc (25 mL), and washed with water (100 mL). The organic layer was dried over MgSO₄, filtered and evaporated onto silica gel (1 g). The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford *tert*-butyl N-[1-[[6-(2-morpholin-4-yl)-4-oxo-1H-quinolin-8-yl]dibenzothiophen-2-yl]carbamoyl]cyclopropyl]carbamate (17 mg, 35%) as a brown solid; *m/z*: 611.16 (MH⁺).

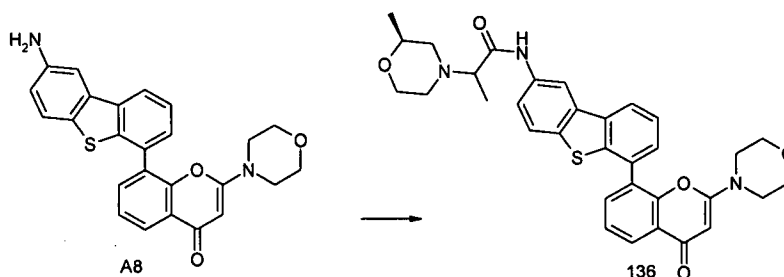
(b) 1-amino-N-[6-(2-morpholin-4-yl-4-oxo-1H-quinolin-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (135)

Tert-butyl N-[1-[[6-(2-morpholin-4-yl-4-oxo-1H-quinolin-8-yl)dibenzothiophen-2-

yl]carbamoyl]cyclopropyl]carbamate (134, 17 mg, 0.03 mmol) was treated with TFA (0.5 mL) in DCM (2.5 mL). The resulting solution was stirred at room temperature for 4 hours. The reaction mixture was evaporated to dryness and redissolved in MeOH (1 mL). The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH and pure fractions were

evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 8% MeOH in DCM. Pure fractions were evaporated to dryness then triturated with methyl *tert*-butylether to give a solid which was collected by filtration and dried under vacuum to give 1-amino-N-[6-(2-morpholin-4-yl-4-oxo-1H-quinolin-8-yl)dibenzothiophen-2-yl]cyclopropane-1-carboxamide (5.70 mg, 40%) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 0.98 - 1.04 (2H, m), 1.63 - 1.66 (2H, m), 3.00 (4H, s), 3.66 (4H, t), 5.76 (1H, s), 7.39 - 7.77 (8H, m), 8.29 (1H, d), 8.40 (1H, d), 8.86 (1H, s), 10.14 (1H, s); m/z: 511.16 (MH⁺).

Example 95

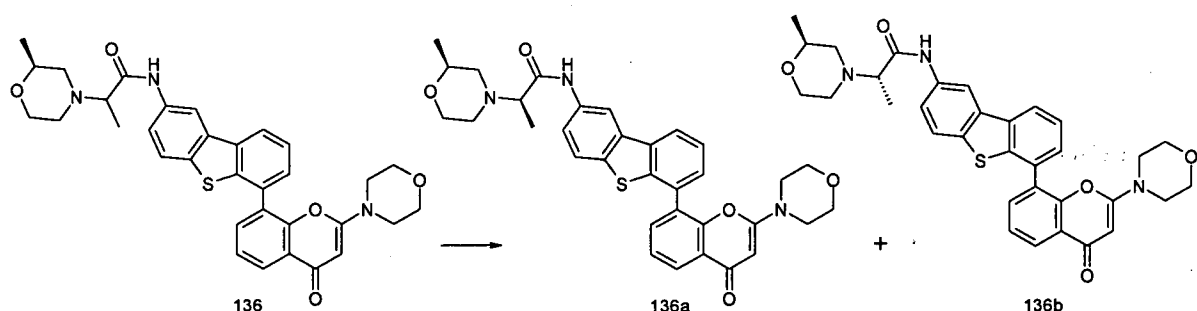


2-[(2S)-2-methylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide (136)

2-Chloropropanoyl chloride (0.034 mL, 0.35 mmol) was added to 8-(8-aminodibenzothiophen-4-yl)-2-morpholin-4-ylchromen-4-one (A8, 150 mg, 0.35 mmol) and N,N-diisopropylethylamine (0.201 mL, 1.16 mmol) in DMA (2 mL). The resulting suspension was stirred at room temperature for 2 hours. (S)-2-methylmorpholine hydrobromide (127 mg, 0.70 mmol) and Sodium iodide (2 mg, 0.01 mmol) were added and the reaction mixture was heated in the microwave to 100°C for 30 minutes. The reaction mixture was evaporated to dryness and redissolved in EtOAc (100 mL), and washed sequentially with water (100 mL) and saturated brine (10 mL). The organic layer was dried over MgSO₄, filtered and evaporated onto silica gel (1 g). The crude product was purified by flash silica

chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-[(2S)-2-methylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzo[thiophen-2-yl]propanamide (135 mg, 66%) as a beige solid; ¹H NMR (400 MHz, CDCl₃) δ 1.21 (3H, q), 1.39 (3H, d), 2.14 & 2.31 (1H, dt) 2.61 - 2.77 & 2.46 (3H, m), 3.07 (4H, t), 3.22 - 3.31 (1H, m), 3.49 (4H, t), 3.69 - 3.83 (2H, m), 3.99 (1H, t), 5.49 (1H, s), 7.40 (1H, dd), 7.46 - 7.50 (2H, m), 7.57 (1H, t), 7.72 - 7.77 (2H, m), 8.24 (1H, d), 8.28 (1H, dd), 8.76 (1H, d), 9.43 (1H, s); m/z: 584.15 (MH⁺).

Example 96



(2R)-2-[(2S)-2-methylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzo[thiophen-2-yl]propanamide (136a) and (2S)-2-[(2S)-2-methylmorpholin-4-yl]-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzo[thiophen-2-yl]propanamide (136b)

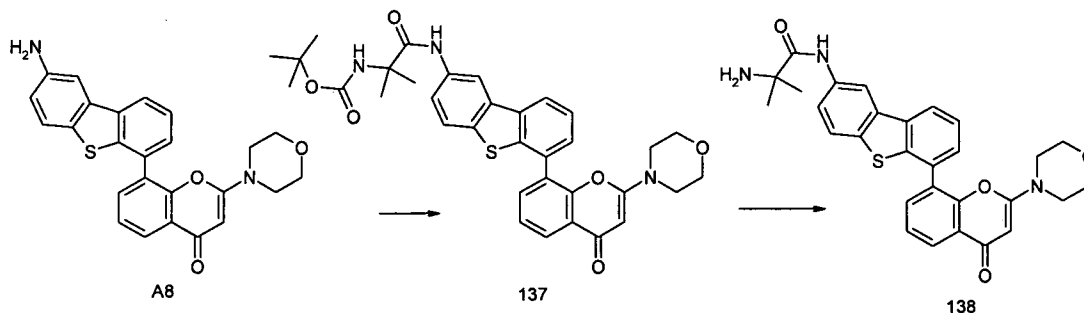
The diastereomer mixture (136, 125 mg) was purified by preparative chiral-HPLC on a Merck 50mm 20µm Chiralcel OJ column, eluting isocratically with 20% MeOH/EtOH in isohexane as eluent. The fractions containing the desired compound were evaporated to dryness to afford the two desired products. Each sample was repurified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-((S)-2-methylmorpholino)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)propanamide (29.1 mg, 23%) as a white solid and 2-((S)-2-methylmorpholino)-N-(6-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo[b,d]thiophen-2-yl)propanamide (25.8 mg, 21%) as a white solid.

136a; ¹H NMR (400 MHz, CDCl₃) δ 1.22 (3H, d), 1.39 (3H, d), 2.13 (1H, t), 2.58 - 2.75 (3H, m), 3.08 (4H, t), 3.28 (1H, q), 3.50 (4H, t), 3.69 - 3.83 (2H, m), 3.98 (1H, d), 5.50 (1H, s), 7.39 (1H, dd), 7.47 - 7.52 (2H, m), 7.58 (1H, t), 7.73 - 7.78 (2H, m), 8.24 - 8.33 (2H, m), 8.77 (1H, d), 9.45 (1H, s); m/z: 584.22 (MH⁺).

136b; ¹H NMR (400 MHz, CDCl₃) δ 1.21 (3H, d), 1.39 (3H, d), 2.31 (1H, t), 2.43 - 2.49 (1H, m), 2.68 (1H, d), 2.76 (1H, d), 3.08 (4H, t), 3.25 (1H, q), 3.50 (4H, t), 3.71 - 3.83 (2H, m),

4.01 (1H, d), 5.50 (1H, s), 7.40 (1H, dd), 7.47 - 7.53 (2H, m), 7.58 (1H, t), 7.72 - 7.81 (2H, m), 8.23 - 8.32 (2H, m), 8.77 (1H, d), 9.45 (1H, s); m/z: 584.22 (MH⁺).

Example 97



2-amino-2-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide (138)

(a) Tert-butyl N-[2-methyl-1-[[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]amino]-1-oxopropan-2-yl]carbamate (137)

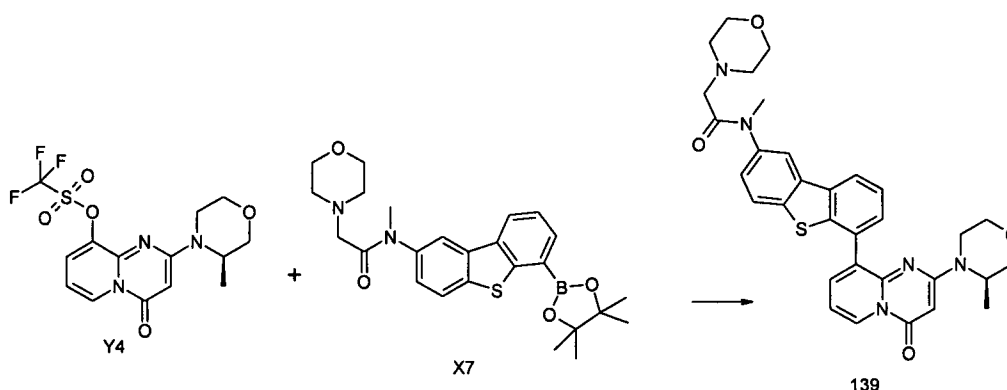
O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (115 mg, 0.30 mmol) was added in one portion to 8-(8-aminodibenzothiophen-4-yl)-2-morpholin-4-ylchromen-4-one (A8, 100mg, 0.23 mmol), 2-(tert-butoxycarbonylamino)-2-methylpropanoic acid (52.2 mg, 0.26 mmol) and N,N-diisopropylethylamine (106 μ L, 0.61 mmol) in DMA (1997 μ L) at ambient temperature. The resulting suspension was stirred at ambient temperature for 18 hours. The reaction mixture was added to water (20 mL) and stirred for 3 hours and the mixture filtered. The white solid obtained was washed with ether to afford tert-butyl N-[2-methyl-1-[[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]amino]-1-oxopropan-2-yl]carbamate (143 mg, 100 %) as a cream solid; m/z: 614.41 (MH⁺).

(b) *2-amino-2-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide (138)*

A solution of HCl 5-6M in IPA (466 μ L, 2.33 mmol) was added to a stirred suspension tert-butyl N-[2-methyl-1-[[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]amino]-1-oxopropan-2-yl]carbamate (137, 0.143 g, 0.23 mmol) in 2-propanol (8mL) at 22°C. The reaction mixture went into solution then a solid came back out on addition of HCl. The resulting suspension was stirred at 60°C for 4 hours after which time a solid was still present but LC-MS indicated completion. The reaction was allowed to cool overnight. This was filtered through a nylon filter cup, washed with IPA (1 mL) and then stirred in filtercup with diethyl ether (2 x 3 mL) before filtering to afford Hydrochloride salt (126mg). This was solubilised in MeOH (10mL) and treated with MP-Carbonate (1.0 mmol/g, 2g (8 eq)). The mixture was

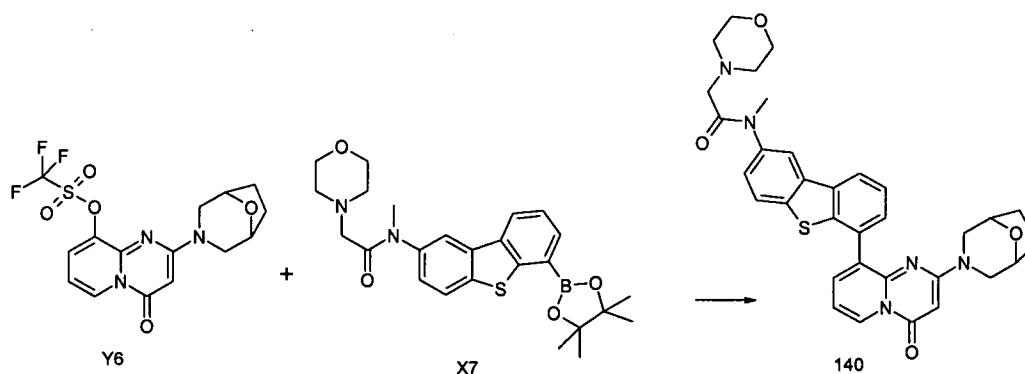
stirred for 2 hours then filtered and evaporated to give gum which was purified by flash silica chromatography, elution gradient 0 to 10% 7N NH₃/ MeOH in DCM. Pure fractions were evaporated to dryness to afford 2-amino-2-methyl-N-[6-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-2-yl]propanamide (0.075 g, 63 %) as a beige solid; ¹H NMR (400 MHz, DMSO) δ 1.36 (6H, s), 3.11 (4H, m), 3.38 (2H, s), 3.43 (4H, m), 5.57 (1H, s), 7.56 (1H, t), 7.66 (2H, m), 7.84 (1H, m), 7.90 (2H, m), 8.08 (1H, dd), 8.33 (1H, dd), 8.74 (1H, d); m/z: 514.31 (MH⁺).

Example 98



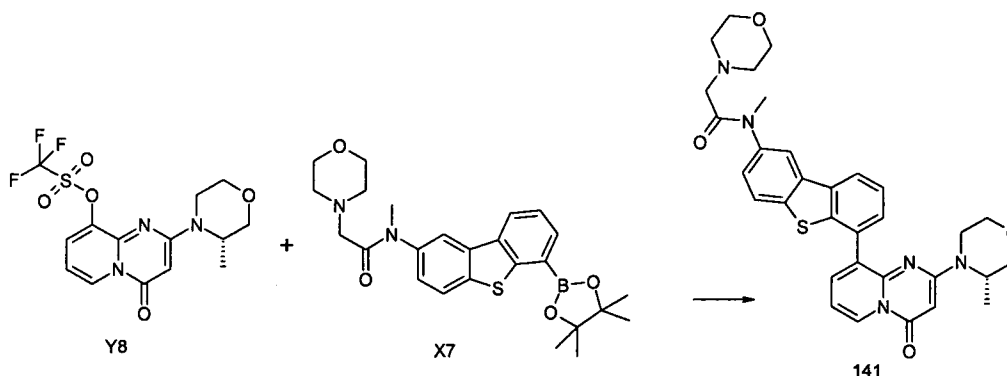
N-methyl-N-[6-[2-[(3R)-3-methylmorpholin-4-yl]-4-oxopyrido[1,2-a]pyrimidin-9-yl]dibenzothiophen-2-yl]-2-morpholin-4-ylacetamide (139)

Tetrakis(triphenylphosphine)palladium(0) (11 mg, 9.53 μmol) was added to [2-[(3R)-3-methylmorpholin-4-yl]-4-oxopyrido[1,2-a]pyrimidin-9-yl] trifluoromethanesulfonate (Y4, 75 mg, 0.19 mmol), *N*-methyl-2-morpholin-4-yl-N-[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dibenzothiophen-2-yl]acetamide (X7, 119 mg, 0.19 mmol) and sodium carbonate solution (0.286 mL, 0.57 mmol) in dioxane (10 mL) under nitrogen. The resulting suspension was stirred at reflux for 18 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (50 mL), and washed with water (50 mL). The organic layer was dried over MgSO₄, filtered and evaporated onto silica gel (1 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford *N*-methyl-N-[6-[2-[(3R)-3-methylmorpholin-4-yl]-4-oxopyrido[1,2-a]pyrimidin-9-yl]dibenzothiophen-2-yl]-2-morpholin-4-ylacetamide (96 mg, 86 %) as a white solid; ¹H NMR (400 MHz, DMSO, 373K) δ 0.99 (3H, d), 2.35 (4H, t), 3.03 (2H, s), 3.18 - 3.30 (2H, m), 3.32 (3H, s), 3.36 - 3.45 (2H, m), 3.47 (4H, t), 3.57 - 3.71 (2H, m), 4.01 (1H, d), 5.54 (1H, s), 7.19 (1H, t), 7.44 (1H, dd), 7.58 - 7.69 (2H, m), 7.95 (1H, d), 7.99 (1H, dd), 8.33 (1H, d), 8.40 (1H, dd), 8.91 (1H, dd); m/z: 584.22 (MH⁺).

Example 99

N-methyl-2-morpholin-4-yl-N-[6-[2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-4-oxopyrido[1,2-a]pyrimidin-9-yl]dibenzothiophen-2-yl]acetamide (140)

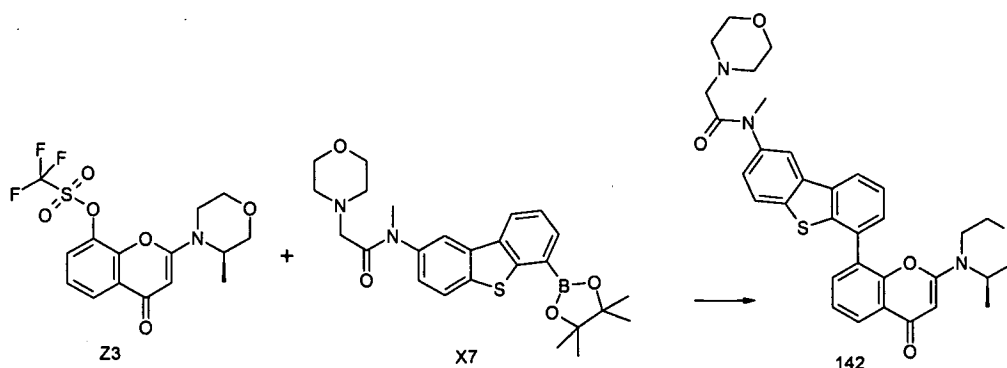
- 5 Tetrakis(triphenylphosphine)palladium(0) (27 mg, 0.02 mmol) was added to [2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-4-oxopyrido[1,2-a]pyrimidin-9-yl] trifluoromethanesulfonate (Y6, 190 mg, 0.47 mmol), *N*-methyl-2-morpholin-4-yl-N-[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dibenzothiophen-2-yl]acetamide (X7, 291 mg, 0.47 mmol) and sodium carbonate solution (0.703 mL, 1.41 mmol) in dioxane (10 mL) under nitrogen. The resulting
- 10 suspension was stirred at reflux for 18 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (100 mL), and washed with water (100 mL). The organic layer was dried over MgSO₄, filtered and evaporated onto silica gel (1 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to *N*-methyl-2-morpholin-4-yl-N-[6-[2-(8-oxa-3-
- 15 azabicyclo[3.2.1]octan-3-yl)-4-oxopyrido[1,2-a]pyrimidin-9-yl]dibenzothiophen-2-yl]acetamide (206 mg, 74%) as a white solid; ¹H NMR (400 MHz, DMSO, 373K) δ 1.46 - 1.59 (2H, m), 1.59 - 1.73 (2H, m), 2.33 - 2.39 (4H, m), 2.84 (2H, dd), 3.03 (2H, s), 3.31 (3H, d), 3.42 - 3.50 (4H, m), 3.59 (2H, d), 4.14 (2H, d), 5.50 (1H, s), 7.18 (1H, t), 7.44 (1H, dd), 7.56 - 7.68 (2H, m), 7.95 (1H, d), 7.98 (1H, dd), 8.33 (1H, d), 8.37 - 8.45 (1H, m), 8.91 (1H, dd); m/z: 596.25
- 20 (MH⁺).

Example 100

N-methyl-*N*-[6-[2-[(3*S*)-3-methylmorpholin-4-yl]-4-oxopyrido[1,2-*a*]pyrimidin-9-yl]dibenzothiophen-2-yl]-2-morpholin-4-ylacetamide (141)

- 5 Tetrakis(triphenylphosphine)palladium(0) (23.50 mg, 0.02 mmol) was added to [2-[(3*S*)-3-methylmorpholin-4-yl]-4-oxopyrido[1,2-*a*]pyrimidin-9-yl] trifluoromethanesulfonate (Y8, 160 mg, 0.41 mmol), *N*-methyl-2-morpholin-4-yl-*N*-[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dibenzothiophen-2-yl]acetamide (X7, 253 mg, 0.41 mmol) and sodium carbonate (0.610 mL, 1.22 mmol) in dioxane (10 mL) under nitrogen. The resulting
- 10 suspension was stirred at reflux for 18 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (100 mL), and washed with water (50 mL). The organic layer was dried over MgSO_4 , filtered and evaporated onto silica gel (2 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford *N*-methyl-*N*-[6-[2-[(3*S*)-3-
- 15 methylmorpholin-4-yl]-4-oxopyrido[1,2-*a*]pyrimidin-9-yl]dibenzothiophen-2-yl]-2-morpholin-4-ylacetamide (156 mg, 66%) as a white solid; ^1H NMR (400 MHz, DMSO) δ 1.26 (3H, d), 2.55 (4H, s), 3.19 (3H, d), 3.42 - 3.82 (10H, m), 3.93 (2H, t), 4.28 (1H, d), 5.89 (1H, s), 7.50 (1H, t), 7.76 (1H, d), 7.93 (2H, dt), 8.30 (1H, d), 8.34 (1H, dt), 8.63 - 8.81 (2H, m), 9.19 (1H, dd); m/z : 584.22 (MH^+).

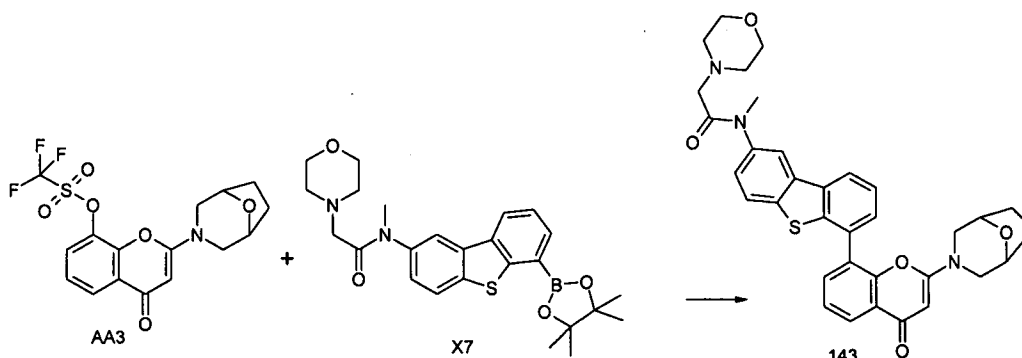
20

Example 101

N-methyl-*N*-[6-[2-[(3*R*)-3-methylmorpholin-4-yl]-4-oxochromen-8-yl]dibenzothiophen-2-yl]-2-morpholin-4-ylacetamide (142)

Tetrakis(triphenylphosphine)palladium(0) (5.14 mg, 4.45 μ mol) was added to ([2-[(3*R*)-3-methylmorpholin-4-yl]-4-oxochromen-8-yl] trifluoromethanesulfonate (Z3, 35 mg, 0.09 mmol),
 5 *N*-methyl-2-morpholin-4-yl-*N*-[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dibenzothiophen-2-yl]acetamide (X7, 55.3 mg, 0.09 mmol) and sodium carbonate solution (0.133 mL, 0.27 mmol) in DME (2 mL) and water (0.500 mL) under nitrogen. The resulting suspension was stirred at reflux for 2 hours. The reaction mixture was filtered and then purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm
 10 diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford *N*-methyl-*N*-[6-[2-[(3*R*)-3-methylmorpholin-4-yl]-4-oxochromen-8-yl]dibenzothiophen-2-yl]-2-morpholin-4-ylacetamide (21.6 mg, 42 %) as a white solid; ¹H
 NMR (400 MHz, DMSO, 373K) δ 0.97 (3H, d), 2.35 (4H, t), 2.98 - 3.08 (3H, m), 3.16 (1H, d),
 15 3.22 - 3.30 (1H, m), 3.32 (3H, s), 3.37 (2H, s), 3.44 - 3.56 (5H, m), 3.61 (1H, dd), 5.45 (1H, s), 7.46 (1H, dd), 7.54 (1H, t), 7.66 (2H, dt), 7.83 (1H, dd), 7.98 (1H, d), 8.09 (1H, dd), 8.37 (1H, d), 8.44 (1H, dd); *m/z*: 584.08 (MH⁺).

Example 102

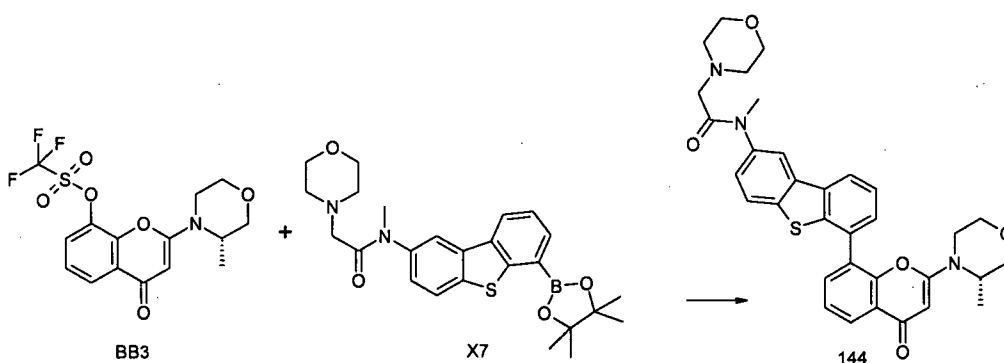


N-methyl-2-morpholin-4-yl-*N*-[6-[2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-4-oxochromen-8-yl]dibenzothiophen-2-yl]acetamide (143)

Tetrakis(triphenylphosphine)palladium(0) (17.75 mg, 0.02 mmol) was added to [2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-4-oxochromen-8-yl] trifluoromethanesulfonate (AA3, 166 mg, 0.31 mmol), *N*-methyl-2-morpholin-4-yl-*N*-[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dibenzothiophen-2-yl]acetamide (X7, 191 mg, 0.31 mmol) and sodium carbonate solution (0.461 mL, 0.92 mmol) in dioxane (10 mL) under nitrogen. The resulting suspension was stirred at reflux for 4 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (100 mL), and washed with water (50 mL). The organic layer was dried

over MgSO_4 , filtered and evaporated onto silica gel (2 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Product containing fractions were evaporated to dryness. The crude product (160 mg) was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness then triturated with methyl tert-butyl ether to afford N-methyl-2-morpholin-4-yl-N-[6-[2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-4-oxochromen-8-yl]dibenzothiophen-2-yl]acetamide (27.4 mg, 15%) as a white solid; ^1H NMR (400 MHz, DMSO) δ 1.54 (4H, t), 2.31 (5H, s), 2.92 (4H, t), 3.08 (2H, d), 3.47 (5H, s), 4.12 (2H, s), 5.45 (1H, s), 7.51 (1H, d), 7.57 (1H, t), 7.63 - 7.79 (2H, m), 7.88 (1H, d), 8.07 (2H, t), 8.36 - 8.60 (2H, m); m/z : 596.17 (MH^+).

Example 103

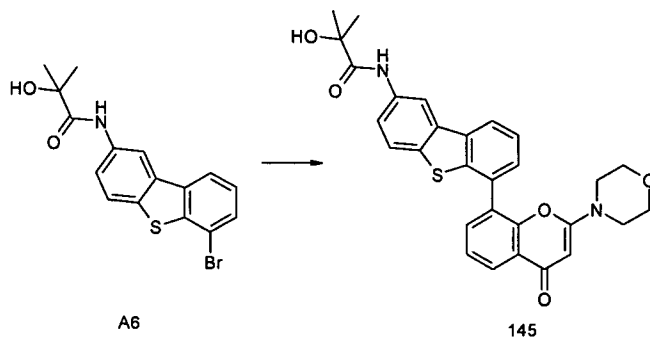


15 *N*-Methyl-N-[6-[2-[(3S)-3-methylmorpholin-4-yl]-4-oxochromen-8-yl]dibenzothiophen-2-yl]-2-morpholin-4-ylacetamide (144)

Tetrakis(triphenylphosphine)palladium(0) (14.40 mg, 0.01 mmol) was added to 2-[(3S)-3-methylmorpholin-4-yl]-4-oxochromen-8-yl trifluoromethanesulfonate (BB3, 98 mg, 0.25 mmol), N-methyl-2-morpholin-4-yl-N-[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dibenzothiophen-2-yl]acetamide (X7, 155 mg, 0.25 mmol) and sodium carbonate solution (0.374 mL, 0.75 mmol) in dioxane (10 mL) under nitrogen. The resulting suspension was stirred at reflux for 18 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (100 mL), and washed with water (50 mL). The organic layer was dried over MgSO_4 , filtered and evaporated onto silica gel (2 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford N-methyl-N-[6-[2-[(3S)-3-methylmorpholin-4-yl]-4-oxochromen-8-yl]dibenzothiophen-2-yl]-2-morpholin-4-ylacetamide (132 mg, 91 %) as a white solid; ^1H NMR (400 MHz, DMSO) δ 0.99 (3H, d), 2.31 (4H, s), 2.97 (2H, d), 3.04 (1H, dd), 3.09 (2H, d), 3.17 (2H, t), 3.37 (3H, d), 3.46 (3H, s), 3.50 - 3.58 (2H, m), 3.63 (1H, d),

5.52 (1H, s), 7.51 (1H, d), 7.57 (1H, t), 7.72 (2H, t), 7.89 (1H, d), 8.07 (2H, dd), 8.48 (2H, dd); m/z: 584.15 (MH⁺).

Example 104



2-Hydroxy-2-methyl-N-[6-(2-morpholin-4-yl-4-oxo-4H-chromen-8-yl)-dibenzothiophen-2-yl]-propionamide (145)

A mixture of 2-morpholin-4-yl-8-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-chromen-4-one (0.020 g, 0.060 mmol), N-(6-bromo-dibenzothiophen-2-yl)-2-hydroxy-2-methyl propionamide (A6, 0.022 g, 0.06 mmol), Pd(PPh₃)₄ (0.003 g, 5% mmol), 3 M aqueous solution of Na₂CO₃ (0.1 mL) and DME (2 mL), was heated under microwave irradiation at 175°C, for 30 minutes. The resulting mixture was poured into a saturated solution of NH₄Cl and the product was extracted into EtOAc. The combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed to give crude product that was purified using flash chromatography employing as gradient eluent system MeOH/petrol/ DCM (3:10:87 v/v/v) to give 2-hydroxy-2-methyl-N-[6-(2-morpholin-4-yl-4-oxo-4H-chromen-8-yl)-dibenzothiophen-2-yl]-propionamide as a white solid (0.015 g, 47%). R_f 0.29 (MeOH/petrol/ DCM 4:10:86); m.p.: 287-288°C (dec.); λ_{max} (EtOH)/nm 242, 294; IR ν_{max}/cm⁻¹: 3356, 3049, 2922, 1673, 1615, 1557, 1412, 1270, 1109, 1037, 981, 787; ¹H NMR (300 MHz, CDCl₃); δ 1.65 (6H, s, 2 × CH₃), 1.89 (1H, s br, -OH exchange in D₂O), 3.02-3.05 (4H, m, 4 × morpholine-H), 3.43-3.46 (4H, m, 4 × morpholine-H), 5.48 (1H, s, COC(3)H=C), 7.40-7.57 (4H, m, Ar-H), 7.69 (1H, d, J = 8.5 Hz, Ar-H), 7.76 (1H, d, J = 7.4 Hz, Ar-H), 8.19 (1H, d, J = 7.7 Hz, Ar 3'-H), 8.28 (1H, d, J = 7.8 Hz, Ar 1'-H), 8.78 (1H, s, Ar-H), 9.11 (1H, s, NH exchange in D₂O); ¹³C NMR (75 MHz, CDCl₃); δ 28.3, 45.0, 66.3, 74.8, 87.2, 113.2, 120.1, 122.0, 122.1, 123.1, 123.9, 124.9, 126.3, 128.4, 128.9, 131.8, 133.5, 135.0, 135.7, 136.3, 136.6, 141.1, 151.0, 162.6, 175.1, 177.3; LCMS (ESI⁺) m/z = 515.3 [M+H]⁺; HRMS (ESI⁺) [M+H]⁺ m/z Calc. for C₂₉H₂₆N₂O₅S: 515.1631 Found 515.1631. Found: C 67.29 H 5.20 Calc. for C₂₉H₂₆N₂O₅S: C 67.32 H 5.21%.

Biological Examples

DNA-PK inhibition

In order to assess the inhibitory action of the compounds against DNA-PK *in vitro*, the following ELISA-based assay was used to determine IC₅₀ values.

Mammalian DNA-PK (0.4 mg/ml total protein) was isolated from HeLa cell nuclear extract (Gell, D. and Jackson S.P., *Nucleic Acids Res.* 27:3494-3502 (1999)) following chromatography utilising Q-sepharose, S-sepharose and Heparin agarose.

Serial dilutions of putative DNAPK inhibitors are prepared in 50% DMSO (v/v) to the desired concentration range and 2.5 µl of these dilutions pipetted in duplicate into 96 well polypropylene plates.

To assess the effect upon DNAPK; 37.5 µl of buffer (25 mM Hepes, 12.5 mM MgCl₂, 50 mM KCl, 1mM DTT, 10% Glycerol, 0.05% NP-40, pH7.6) containing DNA-PK (50 µg of total protein from above preparation), 0.25 µg of the substrate GST-p53N66 (the amino terminal 66 amino acid residues of human wild type p53 fused to glutathione S-transferase) and a 10 µg of a 30mer double stranded DNA oligonucleotide, is added and incubated for 10 minutes at 30°C with shaking. (NB: for negative control wells the inactive GST-p53N66 (ser15ala) substrate is used). To initiate the reaction, 10 µl of 250 µM ATP (50 µM final) is added to each well and the plates incubated at 30°C with shaking for a further 30 minutes. The reaction is then terminated by adding 150 µl of 30 % v/v acetic acid. 10 µl of this solution is then transferred to a 96 well opaque white plate containing 40 µl of phosphate buffered saline (PBS) per well and incubated at room temperature for 90 minutes with shaking, to allow binding of the GST-p53 substrate.

To detect the phosphorylation event on the serine 15 residue of p53 elicited by DNA-PK a p53 phosphoserine-15 antibody (Cell Signaling Technology) was used in a basic ELISA procedure. An anti-rabbit HRP conjugated secondary antibody (Pierce) was then employed in the ELISA before the addition of chemiluminescence reagent (NEN Renaissance) to detect the signal as measured by chemiluminescent counting via a TopCount NXT (Packard).

The % inhibition of each compound at a specific dose is then calculated using the following equation:

$$\% \text{ Inhibition} = 100 - \left[\frac{(\text{cpm of well} - \text{mean negative cpm}) \times 100}{(\text{mean positive cpm} - \text{mean negative cpm})} \right]$$

The % inhibitions are then used to calculate the IC₅₀ using the 4 Parameter Logistic Model or Sigmoidal Dose-Response Model.

$$\text{fit} = (A + ((B - A) / (1 + ((C/x)^D))))$$

$$\text{inv} = (C / (((B - A) / (y - A)) - 1)^{(1/D)})$$

$$\text{res} = (y - \text{fit})$$

where A = Minimum y value (% Inhibition)

B = Maximum y value (% Inhibition)

C = logIC₅₀ value

D = Slope Factor

15 Dose Modification Ratio

Dose Modification Ratio (DMR) is a ratio of the enhancement of cell kill elicited by the DNA-PK inhibitor after 2 Grays of irradiation compared to unirradiated control cells. DNA-PK inhibitors were used at a concentration of 50, 100, 250, and/or 500nM. Radiation was delivered by a Faxitron 43855D machine at a dose rate of 1 Gy per minute. The DMR at 2 Grays irradiation was calculated from the formula:

$$\% \text{ Survival} = \left[\frac{\text{Average number of colonies } (-/+ \text{ compound } -/+ \text{ IR})}{\text{Average number of colonies } (\text{control})} \right] \times 100$$

$$\text{DMR} = \frac{\% \text{ Survival } (\text{control} + \text{IR})}{\% \text{ Survival } (+\text{compound} + \text{IR})}$$

The degree of cell killing was monitored by a standard clonogenic survival assay. Briefly, tissue culture treated 6-well plates were seeded with HeLa cells at 1000 cells/ml/well in full growth medium and returned to the incubator for 4 hrs or overnight in order to allow the cells to attach. Four hours later or the following day, compound or vehicle control was added to the medium (10μl dosing volume). The cells were then incubated for 1 hour in the presence of inhibitor prior to irradiation at 2 Gray using a Faxitron 43855D cabinet X-ray machine. The cells were then incubated for a further 16 hours before the media was replaced with fresh full growth medium in the absence of DNA-PK inhibitor. After 4-5 days, colonies formed (approximately 50 cells/colony) were fixed and stained with Giemsa (Sigma, Poole, UK) and

counted using an automated colony counter (Oxford Optronics Ltd, Oxford, UK). The data was calculated as described above.

Results

Compound	DMR (at 0.1 μ M)	DNA-PK IC ₅₀ (μ M)
1	2.38	0.0259
2	2.14	0.0323
3	1.6	0.0227
4	1.2	0.00379
5	1.05	0.0096
6	1.56	0.0272
7	1.1	0.0222
8	7.55	0.0124
9	4	0.00359
10	1.85	0.0124
11	2.25	0.00365
12	2.65	0.0193
13	1.48	0.0200
14	1.68	0.0286
15	1.3	0.2002
16	1.75	0.00706
17	1.25	0.0594
18	1.25	0.0868
19	1.57	0.0345
20	1.48	0.0795
21	4.35	0.00589
22	4.05	0.00796
23	3.5	0.00309
24	2.8	0.00243
25	2.9	0.00248
26	2.3	0.00253
26a	-	0.03038
26b	-	0.03643
27	1.97	0.1237

28	1	0.0105
29	2.3	0.00631
30	1.75	0.03198
31	1.63	0.0423
32	-	0.00587
33	2.2	0.00437
33a	2.25	0.00371
33b	2.3	0.01338
34	-	0.960
35		0.00440
36	-	0.360
37	-	0.280
38	-	0.172
39	-	0.799
40	1.15	0.00171
41	-	0.0110
42	-	0.0503
43	-	0.228
44	1.35	0.00447
45	4	0.00312
46	3.5	0.00350
47	2.85	0.00376
48	4	0.00218
49	3.6	0.00248
50	5.25	0.0165
51	4.15	0.00645
51a	4.85	0.01301
51b	3.575	0.01153
52	1.4	0.0063
53	1.15	0.0198
54	1.2	0.01103
55	1.45	0.0034
56	1.15	0.01124
58	1.1	0.001793

60	1	0.0009
61	0.85	0.00352
62	5.0	0.01792
63	1.75	0.029
65	1.45	0.019
67	1.2	0.00161
69	1.9	0.01653
70	1.25	0.02375
71	1.725	0.01259
72	2.075	0.03447
73	1.38	0.036
74	2.74	0.01068
75	1.56	0.01248
76	1.48	0.04472
77	1.725	0.02092
78	2.833	0.01916
79	2.3	0.0166
80	3.125	0.01253
82	0.9333	0.02753
83	1.55	0.03865
84	1.75	0.03045
85	1.75	0.01952
87	1	0.06283
89	0.975	0.06836
90	1.65	0.02701
91	1.5	0.1636
92	3.65	0.004665
93	3.05	0.1089
94	1.45	0.002095
95	1.15	0.006563
96	1.375	0.02948
97	1.275	0.04171
98	1.25	0.2119
99	2.775	0.01043

100	1.517	0.07163
101	1.683	0.08482
103	1.183	0.0497
104	1.2	0.1561
105	-	0.0824
106	-	0.03224
107	-	0.04433
108	-	0.03508
109	-	0.1136
111	-	0.02966
113	-	0.03455
114	1.033	2.65*
115	1.72	0.05495
116	3.15	0.02167
117	-	0.05059
118	3.3	0.005641
119	1.4	0.009607
120	2.4	0.006746
121	2	0.008487
125	2.75	0.01487
128	1.3	0.0242
129	1.3	0.01388
131	1.7	0.04243
133	1.075	0.0789
135	1.1	0.06788
136a	1.75	0.115
136b	2.925	0.007132
138	2.25	0.01524
139	-	0.4552
140	-	0.04296
141	-	0.1791
142	-	0.2567
143	-	0.0619
144	-	0.05612

145	1.9	0.03954
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* The result for compound 114 may be affected by its low solubility.

PI3K alpha enzyme assay

- 5 To determine inhibition of compounds against PI3K alpha in vitro, the following assay was used to determine IC₅₀ values

60 nl of test compound dilutions in 100% DMSO are added to Greiner low volume assay plates (Cat No 4316) by acoustic dispensing followed by a 3 µl addition of 4 µg/ml in-house preparation of recombinant PI3K alpha in enzyme in reaction buffer. Final assay
 10 concentration is 50 mM Tris pH 7.4, 0.05% CHAPS, 2.1 mM DTT, 10 mM MgCl₂. After a 20 min incubation 3 µl of a mix containing 80 µM PIP2 substrate (Cell Signals # 901) and 8 µM ATP in reaction buffer (see above) are added to start the enzyme reaction for 90 minutes at room temperature.

15 4µl / well of Kinase Glo Plus Reagent (Promega V3772) detection solution is added at end of the incubation period. The solution is made up as described in the suppliers manual. The plates are incubated for a further 30 min at room temperature and read the Luminescence using Pherostar Instrument.

20

Results

Compound	PI3a glo Mean IC50 (µM)
1	0.218
2	0.369
3	0.212
4	0.836
5	0.0006
6	0.737
7	1.18
8	0.164
9	0.330
10	0.24

11	0.237
12	1.14
13	0.913
14	1.09
15	1.136
16	0.560
17	1.13
18	0.533
19	0.577
20	0.0452
21	0.330
22	0.213
23	0.610
24	0.406
25	0.589
26	0.585
26a	0.5785
26b	0.858
27	0.0947
28	0.0236
29	0.0341
30	0.00611
31	0.0417
32	0.0172
33	0.521
33a	0.6813
33b	0.7038
34	0.519
35	0.264
36	0.0980
37	0.150
38	0.216
39	0.258
40	0.498

41	0.199
42	0.553
43	0.525
44	0.236
45	0.141
46	0.269
47	0.661
48	0.239
49	0.238
50	0.621
51	0.451
51a	1.103
51b	0.5736
52	0.3120
53	0.920
54	0.478
55	0.357
56	0.633
58	0.285
60	0.382
61	0.169
62	0.298
63	0.408
65	0.236
67	0.185
69	0.05099
70	0.03622
71	0.03533
72	0.006983
73	0.02557
74	0.03427
75	0.03144
76	0.04169
77	0.1395

78	0.1041
79	0.3269
80	0.3327
82	0.1346
83	0.008126
84	1.408
85	0.7011
87	0.04134
89	0.04305
90	0.8292
91	0.2566
92	1.301
93	0.1334
94	0.7375
95	0.3811
96	0.3398
97	0.01727
98	0.2286
99	0.0367
100	0.6381
101	0.5914
103	0.3161
104	1.018
105	2.118
106	0.4352
107	0.6248
108	0.6874
109	2.315
111	0.4093
113	1.086
114	>10
115	0.393
116	0.2886
117	0.4389

200

118	0.1556
119	0.1153
120	0.2017
121	0.4716
125	0.7158
128	1.48
129	0.6221
131	0.6927
133	0.556
135	1.995
136a	1.003
136b	1.072
138	0.192
139	0.7049
140	24.36
141	0.1465
142	0.4725
143	51.02
144	0.04982

As mentioned above, the selectivity of the compounds may be measured by a ratio of the PI3a IC₅₀ (glo assay) to the DNA-PK assay IC₅₀. For example, this ratio for compound 11 is 65.

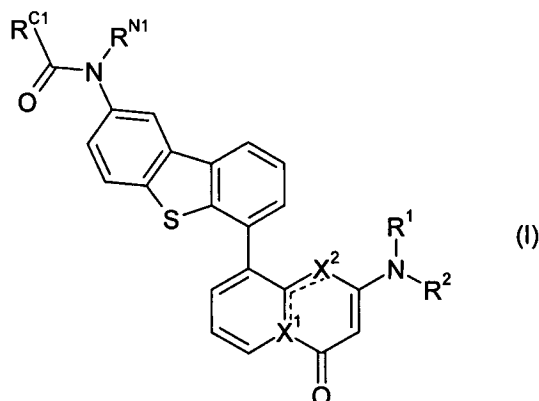
Solubility

The solubility of the test compounds was measured following a method described in Leach, A., et al., J Med Chem (2006), 49(23), 6672-6682:

Solubility values are determined from agitation of compounds in 0.1 M phosphate buffer at pH 7.4 for 24 hours at 25°C. The supernatant is separated from undissolved material by double centrifugation and subsequently analysed and quantified against a standard of known concentration in DMSO using generic HPLC-UV methodology coupled with mass spectral peak identification.

CLAIMS

1. A compound of formula I:



5 wherein:

X^1 and X^2 may be either (a) C and O, (b) N and N, or (c) C and NH, where the dotted bonds represents a double bond in the appropriate location;

R^1 and R^2 are independently selected from hydrogen, an optionally substituted C_{1-7} alkyl group, an optionally substituted C_{3-20} heterocyclyl group, or an optionally substituted C_{5-20}

10 aryl group, or may together form, along with the nitrogen atom to which they are attached, an optionally substituted heterocyclic ring having from 4 to 8 ring atoms;

R^{N1} is selected from hydrogen and an optionally substituted C_{1-4} alkyl group;

R^{C1} is selected from an optionally substituted C_{1-7} alkyl group, an optionally substituted C_{3-20} heterocyclyl group, or an optionally substituted C_{5-20} aryl group;

15 or R^{N1} and R^{C1} may together form an optionally substituted C_{2-4} alkylene group.

2. A compound according to claim 1, wherein R^1 and R^2 form, along with the nitrogen atom to which they are attached, a heterocyclic ring having 6 ring atoms.

20 3. A compound according to claim 2, wherein R^1 and R^2 form, along with the nitrogen atom to which they are attached, a group selected from morpholino, thiomorpholino, and thiazoliny.

4. A compound according to claim 3, wherein R^1 and R^2 form, along with the nitrogen atom to which they are attached, morpholino.

25 5. A compound according to any one of claims 1 to 4, wherein R^{N1} is hydrogen.

6. A compound according to any one of claims 1 to 4, wherein R^{N1} is optionally substituted C_{1-4} alkyl group, wherein the optional substituents are selected from halo, hydroxy, nitro, cyano, $-NH_2$ and thiol.

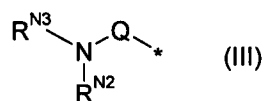
7. A compound according to any one of claims 1 to 4, wherein R^{N1} is selected from hydrogen, unsubstituted methyl and unsubstituted cyclopropylmethyl.

8. A compound according to any one of claims 1 to 7, wherein R^{C1} is an optionally substituted C_{1-7} alkyl group wherein the optional substituents are selected from: C_{5-20} aryl, C_{3-20} heterocyclyl, halo, hydroxy, ether, oxo, imino, formyl, acyl, carboxy, ester, acyloxy, amido, acylamido, acylureido, carbamate, thioamido, tetrazolyl, amino, imino, amidine, carbazoyl, nitro, nitroso, azido, cyano, isocyano, cyanato, thiocyanato, isothiocyano, thiol, thioether, disulfide, sulfone, sulfine, sulfonyloxy, sulfinyloxy, sulfamino, sulfonamino, sulfonamino, phosphoramidite and phosphoramidate.

9. A compound according to claim 8, wherein the optional substituents are selected from: C_{5-20} aryl, C_{3-20} heterocyclyl, halo, hydroxy, ether, carboxy, ester, acyloxy, amido, acylamido, amino, nitro, cyano, thiol and thioether.

10. A compound according to claim 8, wherein the optional substituents are selected from: amino, C_6 aryl, hydroxy, cyano, ester, carboxy, sulfone and acylamido.

11. A compound according to any one of claims 1 to 7, wherein R^{C1} is of formula III:



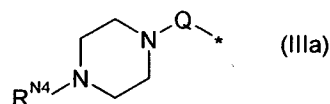
where Q represents a C_{1-7} or C_{1-4} alkylene group, and R^{N2} and R^{N3} are independently selected from hydrogen, an optionally substituted C_{1-7} alkyl group, an optionally substituted C_{3-20} heterocyclyl group, or an optionally substituted C_{5-20} aryl group, or may together form, along with the nitrogen atom to which they are attached, an optionally substituted heterocyclic ring having from 4 to 8 ring atoms.

12. A compound according to claim 11, wherein R^{N2} and R^{N3} are independently selected from hydrogen and an optionally substituted C_{1-4} alkyl group.

13. A compound according to claim 11, wherein R^{N2} and R^{N3} together form, along with the nitrogen atom to which they are attached, an optionally substituted heterocyclic ring having 6 ring atoms.

5 14. A compound according to claim 13, wherein the optional substituent is a C_{1-7} alkyl group.

15. A compound according to claim 11, wherein R^{C1} is of formula IIIa:



10 where Q represents a C_{1-7} or C_{1-4} alkylene group and R^{N4} is an optionally substituted C_{1-7} or C_{1-4} alkyl group.

16. A compound according to claim 15, wherein optional substituents for R^{N4} are selected from: hydroxy, halo and cyano.

15

17. A compound according to any one of claims 11 to 16, wherein Q is methylene or ethylene.

20

18. A compound according to any one of claims 1 to 7, wherein R^{C1} is a pyridyl substituted methyl or ethyl group.

19. A compound according to any one of claims 1 to 7, wherein R^{C1} is an optionally substituted C_{5-6} aryl group.

25

20. A compound according to claim 19, wherein the C_{5-6} aryl group is a C_5 aryl group selected from furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, and oxatriazolyl.

30

21. A compound according to claim 19, wherein the C_{5-6} aryl group is a C_6 aryl group selected from phenyl, isoxazinyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl.

22. A compound according to claim 19, wherein the C_{5-6} aryl group is selected from phenyl, pyrrolyl, oxazolyl and pyridyl.

23. A compound according to any one of claims 1 to 7, wherein R^{C1} is an optionally substituted C₉₋₁₀ aryl group.
24. A compound according to claim 23, wherein the C₉₋₁₀ aryl group is a C₉ aryl group
5 derived from benzofuran, isobenzofuran, indole, isoindole, purine, benzothiophene and benzimidazole.
25. A compound according to claim 23, wherein the C₉₋₁₀ aryl group is a C₁₀ aryl group
10 derived from quinoline, isoquinoline, benzodiazine, pyridopyridine, quinoxaline and naphthalene.
26. A compound according to claim 23, wherein the C₉₋₁₀ aryl group is indolyl.
27. A compound according to any one of claims 19 to 26, wherein the optional
15 substituents on the C₅₋₆ aryl or C₉₋₁₀ aryl group are selected from hydroxy, C₁₋₄ alkoxy, carboxy, C₁₋₄ alkyl ester, cyano, nitro and halo.
28. A compound according to claim 27, wherein the optional substituents are selected
20 from hydroxy, cyano and carboxy.
29. A compound according to any one of claims 1 to 7, wherein R^{C1} is either oxazolyl or pyridyl.
30. A compound according to any one of claims 1 to 7, wherein R^{C1} is an optionally
25 substituted C₄₋₆ heterocyclic group.
31. A compound according to claim 30, wherein R^{C1} is a C₄ heterocyclic group derived from azetidine, oxetane, thietane, dioxetane and dithiethane.
- 30 32. A compound according to claim 30, wherein R^{C1} is a C₅ heterocyclic group derived from pyrrolidine, oxolane, thiolane, imidazoline, oxazolidine, thiazolidine, dioxolane and dithiolane.
- 35 33. A compound according to claim 30, wherein R^{C1} is a C₆ heterocyclic group derived from piperidine, tetrahydropyran, thiane, piperazine, oxazine, dithiane, dioxane and trioxane.

34. A compound according to claim 30, wherein R^{C1} is selected from azetidiny and piperidiny.

35. A compound according to any one of claims 30 to 34, wherein the optional substituents on the C₄₋₆ heterocyclic group are selected from: C₁₋₂₀ alkyl, C₅₋₂₀ aryl, halo, hydroxy, ether, oxo, imino, formyl, acyl, carboxy, ester, acyloxy, amido, acylamido, acylureido, carbamate, thioamido, tetrazolyl, amino, imino, amidine, carbazoyl, nitro, nitroso, azido, cyano, isocyano, cyanato, thiocyanato, isothiocyano, thiol, thioether, disulfide, sulfone, sulfine, sulfonyloxy, sulfinyloxy, sulfamino, sulfonamino, sulfonamino, phosphoramidite and phosphoramidate.

36. A compound according to claim 35, wherein the optional substituents are selected from: C₁₋₂₀ alkyl, C₅₋₂₀ aryl, halo, hydroxy, ether, carboxy, ester, acyloxy, amido, acylamido, amino, nitro, cyano, thiol and thioether.

37. A compound according to claim 36, wherein the optional substituents are C₁₋₄ alkyl.

38. A compound according to any one of claims 1 to 7, wherein R^{C1} is an N-methyl piperidiny group.

39. A composition comprising a compound according to any one of claims 1 to 38, and a pharmaceutically acceptable carrier or diluent.

40. A compound according to any one of claims 1 to 38 for use in a method of therapy.

41. The use of a compound according to any one of claims 1 to 38 in the preparation of a medicament for treating a disease ameliorated by the inhibition of DNA-PK.

42. The use according to claim 41, wherein the compound according to any one of claims 1 to 39 selectivity inhibits the activity of DNA-PK compared to PI 3-kinase.

43. The use according to either claim 41 or claim 42, wherein the compounds is either:

(a) used in the preparation of a medicament for use as an adjunct in cancer therapy or for potentiating tumour cells for treatment with ionising radiation or chemotherapeutic agents;

or

(b) used in the preparation of a medicament for the treatment of, retroviral mediated diseases.

44. A compound according to any one of claims 1 to 38 for use in the method of
5 treatment of a disease ameliorated by the inhibition of DNA-PK.

45. A compound according to claim 44, wherein the compound selectively inhibits the activity of DNA-PK compared to PI 3-kinase.

10 46. A compound according to either claim 44 or claim 45, wherein the compound is either:

(a) used as an adjunct in cancer therapy or for potentiating tumour cells for treatment with ionising radiation or chemotherapeutic agents; or

(b) used for the treatment of retroviral mediated diseases.

15

47. A method of inhibiting DNA-PK *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound according to any one of claims 1 to 38.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/001075

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D409/04 C07D409/14 C07D413/14 C07D471/04 C07D498/08
C07D519/00 A61K31/381 A61K31/519 A61P35/00

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/024949 A1 (CANCER REC TECH LTD [GB]; GRIFFIN ROGER JOHN [GB]; GOLDING BERNARD THO) 27 March 2003 (2003-03-27) cited in the application page 1, paragraph 1 page 145; compound 413 claim 1 ----- -/--	1-48

☒ 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

8 July 2010

Date of mailing of the international search report

15/07/2010

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Fanni, Stefano

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2010/001075

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LEAHY J J J ET AL: "Identification of a highly potent and selective DNA-dependent protein kinase (DNA-PK) inhibitor (NU7441) by screening of chromenone libraries" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB LNKD-DOI:10.1016/J.BMCL.2004.09.060, vol. 14, no. 24, 20 December 2004 (2004-12-20), pages 6083-6087, XP004645161 ISSN: 0960-894X table 1	1-48
A	WO 2006/109081 A1 (KUDOS PHARM LTD [GB]; CANCER REC TECH LTD [GB]; SMITH GRAEME CAMERON M) 19 October 2006 (2006-10-19) cited in the application page 1, paragraph 1 examples 3-12 claim 1	1-48

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2010/001075

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