

XANTHINE DERIVATIVES AS SELECTIVE HM74A AGONISTS

The present invention relates to compounds which are xanthine derivatives, processes for the manufacture of said derivatives, pharmaceutical formulations containing these compounds and the use of the compounds in therapy, for example, in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial.

Dyslipidaemia is a general term used to describe individuals with aberrant lipoprotein profiles. Clinically, the main classes of compounds used for the treatment of patients with dyslipidaemia, and therefore at risk of cardiovascular disease are the statins, fibrates, bile-acid binding resins and nicotinic acid. Nicotinic acid (Niacin, a B vitamin) has been used clinically for over 40 years in patients with various forms of dyslipidaemia. The primary mode of action of nicotinic acid is via inhibition of hormone-sensitive triglyceride lipase (HSL), which results in a lowering of plasma non-esterified fatty acids (NEFA) which in turn alters hepatic fat metabolism to reduce the output of LDL and VLDL (low and very low density lipoprotein). Reduced VLDL levels are thought to lower cholesterol ester transfer protein (CETP) activity to result in increased HDL (high density lipoprotein) levels which may be the cause of the observed cardiovascular benefits. Thus, nicotinic acid produces a very desirable alteration in lipoprotein profiles; reducing levels of VLDL and LDL whilst increasing HDL. Nicotinic acid has also been demonstrated to have disease modifying benefits, reducing the progression and increasing the regression of atherosclerotic lesions and reducing the number of cardiovascular events in several trials.

The observed inhibition of HSL by nicotinic acid treatment is mediated by a decrease in cellular cyclic adenosine monophosphate (cAMP) caused by the G-protein-mediated inhibition of adenylyl cyclase. Recently, the G-protein coupled receptors HM74 and HM74A have been identified as receptors for nicotinic acid (PCT patent application WO02/84298; Wise et. al. J Biol Chem., 2003, 278 (11), 9869-9874). The DNA sequence of human HM74A may be found in Genbank; accession number AY148884. Two further papers support this discovery, (Tunaru et. al. Nature Medicine, 2003, 9(3), 352-255 and Soga et. al. Biochem Biophys Res Commun., 2003, 303 (1) 364-369), however the nomenclature differs slightly. In the Tunaru paper what they term human HM74 we term HM74A and in the Soga paper HM74b is identical to HM74A. Cells transfected to express HM74A and/or HM74 gain the ability to elicit G_i G-protein mediated responses following exposure to nicotinic acid. In mice lacking the homologue of HM74A (m-PUMA-G) nicotinic acid fails to reduce plasma NEFA levels.

Certain xanthine derivatives have been synthesised and disclosed in the prior art. For example, EP0389282 discloses xanthine derivatives as potential mediators of cerebrovascular disorders. A range of xanthine derivatives were identified as

adenosine receptor antagonists by Jacobson et. al. in J. Med. Chem., 1993, 36, 2639-2644.

We now present a group of xanthine derivatives which are selective agonists of the nicotinic acid receptor HM74A and are thus of potential benefit in the treatment, prophylaxis and suppression of diseases where under-activation of this receptor either contributes to the disease or where activation of the receptor will be beneficial.

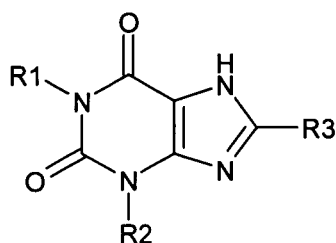
Summary of the Invention

The present invention provides xanthine derivatives and the use of these derivatives in therapy, for example, in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial. For example, in treatment of diseases of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia. As such, the compounds may also find favour as therapeutics for coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke, as well as the cardiovascular indications associated with type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. The compounds may also be of use in the treatment of inflammatory diseases or conditions, as set out further below.

Intermediates, formulations, methods and processes described herein form further embodiments of the invention.

Detailed Description of the Invention

According to one aspect of this invention we provide at least one chemical entity selected from compounds of formula (I)



(I)

and pharmaceutically acceptable derivatives thereof, wherein

R¹ represents $-(\text{alkylene})_m\text{-X-(alkylene)}_n\text{-Y}$;

Wherein m and n represent the number of carbon atoms in the alkylene chain;

5 Wherein X represents a group selected from heteroaryl and heterocyclyl;

Wherein Y represents a group selected from aryl, heteroaryl and O-aryl;

which may be optionally substituted by one or more groups independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, $-(\text{CH}_2)_q\text{NR}^5\text{R}^7$,

10 $-(\text{CH}_2)_q\text{-(O)}_p\text{-(CH}_2)_q\text{-N(R}^5\text{)C(O)OR}^8$, $-(\text{CH}_2)_q\text{-N(R}^5\text{)C(O)R}^8$,
 $-(\text{CH}_2)_q\text{-(O)}_p\text{-(CH}_2)_q\text{-C(O)NR}^5\text{R}^6$, $-(\text{CH}_2)_q\text{-N(R}^5\text{)C(O)NR}^5\text{R}^6$,
 $-(\text{CH}_2)_q\text{-C(O)N}((\text{CH}_2)_m\text{OH})\text{R}^5$, $-(\text{CH}_2)_q\text{-N(R}^5\text{)-S(O)}_2\text{R}^8$, $-\text{CH}_2\text{-S(O)}_2\text{NR}^5\text{R}^6$,
 $-\text{C}_{1-6}\text{ haloalkyl}$, $-\text{OCF}_3$, $-\text{OCH(F)}_2$, $-\text{OCH}_2\text{F}$, $-\text{C(O)OR}^5$, $-\text{OR}^5$, $-\text{R}^8\text{CN}$, CN , $-\text{SO}_2\text{R}^9$,
 $-(\text{CH}_2)_n\text{heteroaryl}$, $-(\text{CH}_2)_n\text{heterocyclyl}$, $-(\text{CH}_2)_n\text{cycloalkyl}$, $-(\text{CH}_2)_n\text{cycloalkenyl}$, and
15 $-(\text{CH}_2)_n\text{aryl}$;

R² represents C₁₋₆ alkyl which may be optionally substituted by one or more groups independently selected from cycloalkyl, C₁₋₆ haloalkyl, halogen, $-\text{CN}$ and $-\text{OR}^4$;

20 R³ represents halogen;

R⁴ represents a group selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, $-(\text{CH}_2)_n\text{ cycloalkyl}$, $-(\text{CH}_2)_n\text{ cycloalkenyl}$, $-(\text{CH}_2)_n\text{ heterocyclyl}$, $-(\text{CH}_2)_n\text{ aryl}$, and $-(\text{CH}_2)_n\text{ heteroaryl}$;

25 R⁵ and R⁶ are independently selected from hydrogen and C₁₋₄ alkyl;

R⁷ represents a group selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, $-(\text{CH}_2)_t\text{ cycloalkyl}$, $-(\text{CH}_2)_t\text{ cycloalkenyl}$, $-(\text{CH}_2)_t\text{ heterocyclyl}$, $-(\text{CH}_2)_t\text{ aryl}$, and $-(\text{CH}_2)_t\text{ heteroaryl}$;

30 R⁸ represents C₁₋₄ alkyl;

R⁹ represents a group selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, $-(\text{CH}_2)_n\text{ cycloalkyl}$, $-(\text{CH}_2)_n\text{ cycloalkenyl}$, $-(\text{CH}_2)_n\text{ heterocyclyl}$, $-(\text{CH}_2)_n\text{ aryl}$, $-(\text{CH}_2)_n\text{ heteroaryl}$, and
35 CN ;

m represents an integer selected from 3 and 4;

n represents an integer selected from 0 and 1;

40 p represents an integer selected from 0 and 1;

q represents an integer selected from 0, 1 and 2; and

t represents an integer selected from 1 and 2.

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The compound(s) are believed to be of use in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial. For example in treatment of diseases of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia. As such, the compounds may also find favour as therapeutics for coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke, as well as the cardiovascular indications associated with type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. As such the compounds of the present invention may find use as agonists or partial agonists of HM74A. The compounds may also be of use in the treatment of inflammatory diseases or conditions, as set out further below.

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In one embodiment of the present invention, X represents a heteroaryl. In another embodiment X represents a heteroaryl comprising a nitrogen heteroatom, for example, triazolyl, furazanyl, oxadiazolyl, tetrazolyl, imidazolyl or pyrazolyl. In a further embodiment X represents a group selected from oxadiazolyl and tetrazolyl.

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In another embodiment, Y represents an optionally substituted group selected from aryl, for example phenyl or naphthyl, heteroaryl, for example pyridinyl, thiazolyl, thienyl, benzofuranyl or indolyl, and O-aryl, for example O-phenyl. In a further embodiment, Y represents an optionally substituted group selected from aryl and heteroaryl. In one embodiment Y is selected from aryl.

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In one embodiment of the present invention, Y may be optionally substituted by one or more of: C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, -NH₂, -(CH₂)_q-(O)_p-(CH₂)_q-N(R⁵)C(O)OR⁸, -(CH₂)_q-N(R⁵)C(O)R⁸, -(CH₂)_q-(O)_p-(CH₂)_q-C(O)NR⁵R⁶, -(CH₂)_q-N(R⁵)C(O)N(R⁵)R⁶, -(CH₂)_q-C(O)N((CH₂)_mOH)R⁵, -(CH₂)_q-N(R⁵)-S(O)₂R⁸, -CH₂-S(O)₂N(R⁵)R⁶, -C₁₋₆ haloalkyl, -OCF₃, -OCH(F)₂, -OCH₂F, -C(O)OR⁵, -OR⁵, -R⁸CN, CN -SO₂R⁹, -(CH₂)_nheteroaryl, -(CH₂)_nheterocycyl, -(CH₂)_ncycloalkyl, -(CH₂)_ncycloalkenyl, -(CH₂)_naryl;

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In a further embodiment, Y is substituted by one or more groups selected from OR⁵ for example OH or OCH₃, halogen, for example F or Cl, aryl, for example phenyl, C₁₋₆ haloalkyl for example CF₃ or CH₂CF₃, OCF₃, R⁸CN, CN,

$(\text{CH}_2)_q\text{-N}(\text{R}^5)\text{-S}(\text{O})_2\text{R}^8$, for example NHSO_2CH_3 and SO_2R^9 , for example SO_2CH_3 .

In yet a further embodiment Y is substituted by one or more groups selected from OR^5 , halogen, C_{1-6} haloalkyl, and $-(\text{CH}_2)_q\text{-N}(\text{R}^5)\text{C}(\text{O})\text{R}^8$.

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In another embodiment, Y is substituted by one or more groups selected from halogen, and C_{1-6} haloalkyl.

In yet another embodiment, Y is not further substituted.

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In one embodiment of the present invention, X and Y each independently represent a heteroaryl comprising a nitrogen heteroatom. In a further embodiment X represents oxadiazolyl and Y represents pyridinyl. In another embodiment X represents tetrazolyl and Y represents phenyl. In yet another embodiment of the present invention X

15 represents oxadiazolyl and Y represents phenyl

In one embodiment of the invention, m is 4 and n is 0. In a further embodiment, m is 3 and n is 1.

20 In one embodiment of the present invention, R^2 is selected from C_{3-6} alkyl, for example butyl or pentyl, for example n-butyl or n-pentyl.

In a further embodiment of the present invention, R^3 is selected from chlorine and bromine. In another embodiment, R^3 represents chlorine.

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In one embodiment of the present invention R^7 represents a group selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(\text{CH}_2)_i$ cycloalkyl, $-(\text{CH}_2)_n$ cycloalkenyl, $-(\text{CH}_2)_i$ heterocyclyl, $-(\text{CH}_2)_i$ aryl, and $-(\text{CH}_2)_i$ heteroaryl;

30 In one embodiment of the present invention X represents oxadiazolyl, Y represents phenyl, R^2 is butyl, R^3 represents chlorine and m is 4 and n is 0.

With regard to stereoisomers, the compounds of formula (I) may have one or more asymmetric carbon atom and may occur as recemates, racemic mixtures and as
35 individual enantiomers or diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof.

40 Where a compound of formula (I) contains an alkenyl or alkenylene group, cis (E) and trans (Z) isomerism may also occur. The present invention includes the individual stereoisomers of the compound of the invention and, where appropriate, the individual tautomeric forms thereof, together with mixtures thereof.

Separation of diastereoisomers or cis and trans isomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or HPLC of a stereoisomeric mixture of the agent may also be prepared from a corresponding optically pure intermediate or by resolution, such as HPLC of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

Furthermore, some of the crystalline forms of the compounds of formula (I) may exist as polymorphs, which are included in the present invention. One form may have an advantage over another form, for example one form may have improved stability over another form.

It is to be understood that the present invention includes any combination of particular embodiments and covers all combinations of particular substituents described hereinabove.

Throughout the present specification and the accompanying claims the words "comprise" and "include" and variations such as "comprises", "comprising", "includes" and "including" are to be interpreted inclusively. That is, these words are intended to convey the possible inclusion of other elements or integers not specifically recited, where the context allows.

As used herein, the term "alkyl" (when used as a group or as part of a group) refers to a straight or branched hydrocarbon chain unless specified otherwise, containing the specified number of carbon atoms. For example, C₃-C₆alkyl means a straight or branched hydrocarbon chain containing at least 3 and at most 6 carbon atoms. Examples of alkyl as used herein include, but are not limited to methyl (Me), ethyl (Et), n-propyl and i-propyl.

The term "alkylene" as used herein means both straight and branched saturated or unsaturated chain, or cyclic saturated hydrocarbon linker groups. Examples of alkylene groups include methylene (-CH₂-), ethylene (-CH₂CH₂-), ethene (-CH=CH-), or cyclopropylene and the like. For example, as used herein, -(alkylene)_m-, where m is 3 represents -(CH₂)₃-, -C(CH₃)₂-, -CH₂CH=CH-, or -cyclopropylene- and the like. For example as used herein, -(alk)_m- where m is 4 represents -(CH₂)₄-, -CH₂C(CH₃)₂-, -CH₂CH=CHCH₂-, or -CH₂cyclopropylene- and the like. For example, as used herein -(alkylene)_n where n = 1 means -CH₂-. As used herein -(alkylene)_n where n = 0 means there is no alkylene linker at this position.

The term "alkenyl" as used herein refers to a straight or branched hydrocarbon chain containing the specified number of carbon atoms which contains one or more double bonds.

- 5 The term "alkynyl" as used herein refers to a straight or branched hydrocarbon chain containing the specified number of carbon atoms which contains one or more triple bonds.

- 10 The term "cycloalkyl" as used herein refers to a saturated monocyclic hydrocarbon ring of 3 to 8 carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

- 15 The term "cycloalkenyl" as used herein refers to an unsaturated non-aromatic monocyclic hydrocarbon ring of 3 to 8 carbon atoms containing one or more carbon-carbon double bonds. Examples of such groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl and the like.

- 20 The term "aryl" as used herein refers to a C₆₋₁₂ monocyclic, bicyclic or tricyclic hydrocarbon ring wherein at least one ring is aromatic. Examples of such groups include phenyl, naphthyl or tetrahydronaphthalenyl and the like.

- 25 The term "heteroaryl" as used herein refers to a 5-6 membered monocyclic aromatic ring or a fused 8-10 membered bicyclic aromatic ring, containing 1 to 4 heteroatoms, each independently selected from oxygen, nitrogen and sulphur. There may be one or more optional oxo substituents on the ring carbon atoms. Examples of such monocyclic aromatic rings include thienyl, furyl, furazanyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyranlyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl, triazinyl, tetrazinyl and the like. Examples of such fused aromatic rings include quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pteridinyl, cinnolinyl, phthalazinyl, naphthyridinyl, indolyl, isoindolyl, azaindolyl, indoliziny, indazolyl, purinyl, pyrrolopyridinyl, furopyridinyl, benzofuranyl, isobenzofuranyl, benzothienyl, benzoimidazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

- 35 The term "heterocycl" as used herein refers to a 4-7 membered monocyclic ring or a fused 8-12 membered bicyclic ring which may be saturated or partially unsaturated containing 1 to 4 heteroatoms each independently selected from oxygen, nitrogen or sulphur. There may be one or more optional oxo substituents on the ring carbon atoms. Examples of such monocyclic rings include pyrrolidinyl, azetidiny, pyrazolidinyl, oxazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, dioxolanyl, dioxanyl, oxathiolanyl, oxathianyl, dithianyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl,

tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, diazepanyl, azepanyl and the like. Examples of such bicyclic rings include indolinyl, isoindolinyl, benzopyranyl, quinuclidinyl, 2,3,4,5-tetrahydro-1*H*-3-benzazepine, tetrahydroisoquinolinyl and the like.

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The terms "halogen" or "halo" as used herein refer to for example, a fluorine, chlorine, bromine or iodine atom.

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The term "C₁₋₆ haloalkyl" as used herein refers to a C₁₋₆ alkyl group as defined herein wherein at least one hydrogen atom is replaced with halogen. Examples of such groups include fluoroethyl, trifluoromethyl, trifluoroethyl and the like.

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As used herein, where a group is referred to as being "substituted" by another group or having "one or more substituents" unless a particular position for such a substitution is specified it is to be understood that a substitution may be present at any position in the group.

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The term "pharmaceutically acceptable derivative" as used herein refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, salts, solvates or esters, which upon administration to a mammal, such as a human, is capable of providing (directly or indirectly) such a compound or an active metabolite thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles And Practice, which is incorporated

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As used herein, the term "pharmaceutically acceptable" used in relation to an ingredient (active ingredient, diluent, excipient or carrier) which may be included in a pharmaceutical formulation for administration to a patient, refers to that ingredient

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As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a pharmaceutically acceptable derivative thereof) and a solvent. Such solvents for the purposes of the present invention may not interfere with the biological activity of the solute. The solvent used may be a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. An example of a solvent that may be used is water, in which case the solvate may be

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It will be appreciated that, for pharmaceutical use, the "salt or solvate" referred to above will be a pharmaceutically acceptable salt or solvate. However, other salts or solvates may find use, for example, in the preparation of a compound of formula (I) or in the preparation of a pharmaceutically acceptable salt or solvate thereof.

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Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Suitable pharmaceutically acceptable salts include alkali metal salts formed from the addition of alkali metal bases such as alkali metal hydroxides. Examples of suitable alkali metal salts include sodium salts and potassium salts. Other suitable pharmaceutically acceptable salts include alkaline earth metal salts such as calcium salts and magnesium salts, ammonium salts; or salts with organic bases such as ethanolamine, triethanolamine, ethylene diamine, triethylamine, choline and meglumine; or salts with amino acids such as arginine, lysine and histidine.

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Esters may be active in their own right and/or be hydrolysable under *in vivo* conditions in the human body. Suitable pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt. An ester may be formed at a carboxylic acid (-C(O)OH) group, by methods well known in the art involving reaction with the corresponding alcohol. For example, esters may be C₁₋₆alkyl esters, e.g. methyl esters, ethyl esters, and the like.

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As used herein, the term "compounds of the invention" means the compounds according to Formula I and the pharmaceutically acceptable derivatives thereof. The term "a compound of the invention" means any one of the compounds of the invention as defined above.

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As used herein the term "at least one chemical entity" means at least one chemical substance chosen from the group of compounds consisting of compounds of formula I and pharmaceutically acceptable derivatives thereof.

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In one aspect of the invention there is provided substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 1. In another aspect of the invention there is provided substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 2.

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Thermal analysis on samples of substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione forms 1 and 2 was carried out. Thus, there is provided substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione (form 1 or

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form 2) having a melting point onset measured by DSC ($\pm 0.5^{\circ}\text{C}$) of: 160°C or greater and 147°C or greater, respectively.

Samples of substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 1, and 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 2, prepared as described hereinafter, gave the X-ray powder diffraction patterns of Figures 1-2. The X-ray diffraction pattern is unique to the crystalline form. The substantially crystalline forms exhibit diffraction patterns with a unique set of diffraction peaks which can be expressed in 2 theta angles ($^{\circ}$).

2 Theta diffraction angles account for positions of various peaks in the X-ray diffraction pattern. Slight variations in observed 2 theta angles are expected based on the specific diffractometer employed and the analyst's sample preparation technique.

The substantially crystalline forms of 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione can be identified by the presence of a characteristic 2 theta angle peak, or by multiple 2 theta angles which are reasonably characteristic of the particular crystalline forms. To identify substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione (form 1), these peaks occur at the following positions, expressed in 2 theta angles (± 0.1 degrees): 5.4, 6.7, 9.7, 11.1, 12.9, 14.0, 15.6, 16.3, 16.7, 23.1 degrees. To identify substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione (form 2), these peaks occur at the following positions, expressed in 2 theta angles (± 0.1 degrees): 5.2, 6.6, 10.4, 11.2, 13.4, 15.6, 18.1, 19.5, 20.9 degrees. In one embodiment at least one of the foregoing 2 theta angles are employed to identify substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 1 and substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 2. In other embodiments at least 2, 3, 4 or 5 (where applicable) of the foregoing 2 theta angles are employed to identify substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 1, substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 2.

Some margin of error is present in each of the 2 theta angle assignments. The margin of error in the foregoing 2 theta angles is approximately ± 0.1 degrees for each of the foregoing peak assignments.

Since some margin of error is possible in the assignment of 2 theta angles, the preferred method of comparing X-ray powder diffraction patterns in order to identify a

particular crystalline form is to overlay the X-ray powder diffraction pattern of the unknown form over the X-ray powder diffraction pattern of a known form. For example, one skilled in the art can overlay an X-ray powder diffraction pattern of an unidentified form of 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione, obtained using the methods described herein, see Figure 3 for example, and readily determine whether the X-ray diffraction pattern of the unidentified form is substantially the same as the X-ray powder diffraction pattern of substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione Form 1 or 2. If the X-ray powder diffraction pattern is substantially the same as that shown in any of Figures 1-2, the previously form can be readily and accurately identified.

As used herein, the term "substantially crystalline form" means that it is substantially free of amorphous form 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione. By "substantially free" is meant containing less than 50% of the amorphous form, in one aspect less than 20% of the amorphous form, in another aspect less than 10% of the amorphous form, in another aspect less than 5% of the amorphous form, in another aspect less than 2% of the amorphous form, in another aspect less than 1% of the amorphous form.

The present invention provides a method for the preparation of substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form as described herein.

Compounds of formula (I) are of potential therapeutic benefit in the treatment and amelioration of the symptoms of many diseases of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. As such, the compounds may also find favour as therapeutics for coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke.

It has been reported that the HM74 and HM74A receptors are involved in inflammation (WO02084298). Inflammation represents a group of vascular, cellular and neurological responses to trauma. Inflammation can be characterised as the movement of inflammatory cells such as monocytes, neutrophils and granulocytes into the tissues. This is usually associated with reduced endothelial barrier function and oedema into the tissues. Inflammation with regards to disease typically is referred to as chronic inflammation. Such chronic inflammation may manifest itself through disease symptoms. The aim of anti-inflammatory therapy is therefore to reduce this chronic

inflammation and allow for the physiological process of healing and tissue repair to progress.

5 Examples of inflammatory diseases or conditions for which the compounds of the present invention may demonstrate utility include those of the joint, for example arthritis (e.g. rheumatoid arthritis, osteoarthritis, prosthetic joint failure), or the gastrointestinal tract (e.g. ulcerative colitis, Crohn's disease, and other inflammatory bowel and gastrointestinal diseases, gastritis and mucosal inflammation resulting from infection, the enteropathy provoked by non-steroidal anti-inflammatory drugs), of the lung (e.g. adult respiratory distress syndrome, asthma, cystic fibrosis, or chronic obstructive pulmonary disease), of the heart (e.g. myocarditis), of nervous tissue (e.g. multiple sclerosis), of the pancreas, (e.g. inflammation associated with diabetes melitus and complications thereof, of the kidney (e.g. glomerulonephritis), of the skin (e.g. dermatitis, psoriasis, eczema, urticaria, burn injury), of the eye (e.g. glaucoma) as well as of transplanted organs (e.g. rejection) and multi-organ diseases (e.g. systemic lupus erythematosus, sepsis) and inflammatory sequelae of viral or bacterial infections and inflammatory conditions associated with atherosclerosis and following hypoxic or ischaemic insults (with or without reperfusion), for example in the brain or in ischaemic heart disease.

20 In one embodiment, the compounds of this invention are useful in the treatment and prevention of inflammation, diabetes and cardiovascular diseases or conditions including atherosclerosis, arteriosclerosis, hypertriglyceridemia, and mixed dyslipidaemia.

25 Nicotinic acid has a significant side effect profile, possibly because it is dosed at high level (gram quantities daily). The most common side effect is an intense cutaneous flushing. In certain embodiments of the present invention the compounds may exhibit reduced side effects compared to nicotinic acid. HM74A has been identified as a high affinity receptor for nicotinic acid whilst HM74 is a lower affinity receptor. The compounds of the present invention show greater affinity for HM74A than for HM74 therefore may find use as selective HM74A agonists or partial agonists.

30 The potential for compounds of formula (I) to activate HM74A may be demonstrated, for example, using the following in vitro whole cell assays:

In-vitro testing

40 For transient transfections, HEK293T cells (HEK293 cells stably expressing the SV40 large T-antigen) were maintained in DMEM containing 10% foetal calf serum and 2mM glutamine. Cells were seeded in 90mm culture dishes and grown to 60-80% confluence

(18-24h) prior to transfection. Human HM74A (GenBank™ accession number AY148884) was subcloned in to a mammalian expression vector (pcDNA3; Invitrogen) and transfected using Lipofectamine™ reagent. For transfection, 9µg of DNA was mixed with 30µl Lipofectamine in 0.6ml of Opti-MEM (Life Technologies Inc.) and was incubated at room temperature for 30min prior to the addition of 1.6ml of Opti-MEM. Cells were exposed to the Lipofectamine/DNA mixture for 5h and 6ml of 20% (v/v) foetal calf serum in DMEM was then added. Cells were harvested 48h after transfection. Pertussis toxin treatment was carried out by supplementation into media at 50ngml⁻¹ for 16h. All transient transfection studies involved co-transfection of receptor together with the G_{i/o} G protein, G_{o1}α.

For generation of stable cell lines the above method was used to transfect CHO-K1 cells seeded in six well dishes grown to 30% confluence. These cells were maintained in DMEM-Ham's F-12 media (available from Invitrogen) containing 10% foetal calf serum and 2mM glutamine. 48h post-transfection the media was supplemented with 400µg/ml Geneticin (G418, Gibco) for selection of antibiotic resistant cells. Clonal CHO-K1 cell lines stably expressing HM74A were confirmed by [³⁵S]-GTPγS binding measurements, following the addition of nicotinic acid.

P2 membrane preparation - Plasma membrane-containing P2 particulate fractions were prepared from cell pastes frozen at -80°C after harvest. All procedures were carried out at 4°C. Cell pellets were resuspended in 1 ml of 10mM Tris-HCl and 0.1mM EDTA, pH 7.5 (buffer A) and by homogenisation for 20s with a Ultra Turrax followed by passage (5 times) through a 25-gauge needle. Cell lysates were centrifuged at 1,000g for 10 min in a microcentrifuge to pellet the nuclei and unbroken cells and P2 particulate fractions were recovered by microcentrifugation at 16,000g for 30min. P2 particulate fractions were resuspended in buffer A and stored at -80°C until required.

[³⁵S]-GTPγS binding - assays were performed at room temperature in 384-well format based on methods described previously, (Wieland, T. and Jakobs, K.H. (1994) *Methods Enzymol.* **237**, 3-13). Briefly, the dilution of standard or test compounds were prepared and added to a 384-well plate in a volume of 10µl. Membranes (HM74A or HM74) were diluted in assay buffer (20mM HEPES, 100mM NaCl, 10mM MgCl₂, pH7.4) supplemented with saponin (60µg/ml), Leadseeker WGA beads (Amersham; 250µg/well) and 10µM GDP, so that the 20µl volume added to each well contains 5µg of membranes. [³⁵S]-GTPγS (1170 Ci/mmol, Amersham) was diluted (1:1500) in assay buffer and 20µl added to each well. Following the addition of the radioligand, the plates were sealed, pulse spun and incubated for 4hours at room temperature. At the end of the incubation period the plates were read on a Leadseeker machine (VIEWLUX PLUS; Perkin-Elmer) to determine the levels of specific binding.

These assays were refined by reducing the final assay volume to 10 μ l. For this 10 μ l assay a revised protocol was used. This involved the use of only 100 nl of standard or test compound per well of a 384-well plate and 1.5 μ g membrane and 100 μ g Leadseeker WGA beads. For the low volume protocol, membrane, beads and [³⁵S]-GTP γ S were mixed together and then 10 μ l of this mix were dispensed to each well. Incubation and plate read were identical for the 10 μ l and 50 μ l assays.

All exemplified compounds were tested in one or both of the [³⁵S]-GTP γ S binding assays described above (i.e. the 10 μ l and 50 μ l assays).

Data was analysed by curve fitting as carried out using a Four Parameter Logistical equation using the XC50 software package (max 2 points deleted from any one curve). Specific binding is expressed as pEC₅₀ and as % efficacy compared to the maximal response of nicotinic acid binding.

In-vivo testing

Compounds of the invention can be tested in male Spague-Dawley rats (200-250g) which have been fasted for at least 12 hours prior to the study. The compounds are dosed intravenously at either 1 or 3mg/kg (5ml/kg) or by oral gavage at doses ranging from 1-30mg/kg (10ml/kg). Blood samples (0.3ml tail vein bleed) can be taken pre-dose and at three times post-dose (times ranging from 15 minutes to 6 hours post-dose). Each blood sample is transferred to a heparin tube (Becton Dickinson Microtainer, PST LH) and centrifuged (10,000g for 5 minutes) to produce a plasma sample. The plasma samples are assayed for levels of non-esterified fatty acids (NEFA) using a commercially available kit (Randox). Inhibition of plasma NEFA levels, relative to pre-dose levels, are used as a surrogate for HM74A agonist activity.

In order to determine whether compounds of the invention exhibit the flushing response associated with nicotinic acid they can be dosed to conscious guinea-pigs. Male Dunkin Hartley guinea pigs (300-600g; n=10-20 per group) are fasted for at least 12 hours, but not in excess of 24 hours prior to experimentation. Pre-study blood samples (0.5ml) are taken from each animal by cardiac puncture under recovery anaesthesia (Isoflurane 3.5% with additional O₂ (1L/min)). Ear temperature measurements are taken by placing the left ear of each animal over an infra-red temperature probe. Measurements are taken at one minute intervals from 5 minutes pre-dose to 30 minutes post-dose. Temperature measurements are then taken at 15 minute intervals up to 2 hours post-dose. Animals receive test compounds by oral gavage (5ml/kg). Blood samples (0.5ml) are taken by cardiac puncture under terminal anaesthesia. Blood samples are taken from individual animals to provide data at 0.5, 1, 2, 3, and 4 hours post-dose. All blood samples are placed on a blood roller for 5 minutes then

stored on ice until the end of the study. Following centrifugation (12000g for 5min) the plasma is transferred into fresh tubes and stored at -20°C until assayed for NEFA concentrations.

- 5 Some compounds according to Formula (I) have been synthesised (see synthetic examples below) and tested in the [³⁵S]-GTP_γS binding assays discussed above.

Some compounds according to formula (I) including:

- 8-chloro-3-(3,3-dimethylbutyl)-1-[2-(ethyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione;
10 have utility as intermediates in the production of other compounds according to formula (I).

- The exemplified compounds (Examples 1 - 512) have a pEC₅₀ of 4.3 (+/- 0.3 log unit) or greater and an efficacy of 30% or greater (in relation to nicotinic acid) in the [³⁵S]-
15 GTP_γS binding assays described above, in which they were tested.

General purification and analytical methods:

20 LC/MS: Method

- Analytical HPLC was conducted on a SupelcosilTM ABZ+PLUS column (Supelco) (3μm, 3.3cm x 4.6mm ID) eluting with 0.1% HCO₂H and 0.01 M ammonium acetate in water (solvent A), and 95% MeCN and 5% water (containing 0.5% HCO₂H) (solvent B), using the following elution gradient 0-0.7min 0%B, 0.7-4.2min 0→100%B, 4.2-4.6minutes
25 100%B, 4.6-4.8min 100→0%B at a flow rate of 3 ml/min. The diode array UV detection was carried out in the range 215 to 330nm. The mass spectra (MS) were recorded on a Waters ZQ mass spectrometer using electrospray positive ionisation [(ES+ve to give MH⁺ and M(NH₄)⁺ molecular ions] or electrospray negative ionisation [(ES-ve to give (M-H)⁻ molecular ion] modes. Only the parent ion of major isotopes quoted.

30

¹H NMR spectra were recorded using a Bruker DPX 400MHz spectrometer using tetramethylsilane as the standard.

- BiotageTM chromatography refers to purification carried out using either the Flash 40i or
35 Flash 150i purification systems, sold by Biotage AB, using cartridges pre-packed with KPSil (silica).

- CompanionTM system refers to the Teledyne Isco Combiflash CompanionTM purification system. This is a gradient controlled purification system with integral, variable
40 wavelength UV detection with the capability to trigger automated fraction collection by UV threshold.

Mass directed autoprep (MDAP) refers to methods where the material was purified by high performance liquid chromatography using either a Supelcosil™ ABZ+ 5µm column (10cm x 20mm i.d.) or a Supelcosil™ ABZ+ 10µm column (15cm x 30mm i.d.) with a suitable gradient of solvent A: 0.1% HCO₂H in water and solvent B: 95% MeCN, 5% water (containing 0.5% HCO₂H). The Waters 2767 inject / collector was triggered by a MicroMass ZQ Mass Spectrometer on detecting the mass of interest (using Micromass MassLynx software).

Preparative HPLC (Autoprep HPLC or Autoprep) refers to methods where the material was purified by high performance liquid chromatography on a Supelcosil™ ABZ+ 5µm column (10cm x 21.2mm i.d.) with a suitable gradient of 0.1% HCO₂H in water and MeCN (with 0.5% HCO₂H). The Gilson 233 fraction collector was triggered by UV detection.

SPE (solid phase extraction) refers to the use of polyethylene cartridges which are pre-packed with sorbent used for purification. The sorbent contained in these cartridges will be specified. Examples used are detailed below:

C18 SPE refers to the use of cartridges pre-packed with 40µm C18 functionalised silica sorbent (sold by Varian Inc.). The compound was loaded, typically in 50:50 DMSO / MeOH, onto a cartridge previously conditioned with MeCN and equilibrated with 5% MeCN in water. The product was eluted with a suitable gradient of 0.1% HCO₂H in water and MeCN (0.5% HCO₂H).

Aminopropyl SPE or column refers to the use of cartridges pre-packed with 40µm-120µm aminopropyl functionalized silica (sold by Varian Inc.). The crude product is typically loaded in DCM / MeOH mixtures onto a cartridge previously conditioned with MeOH. The neutral components were eluted with MeOH and/or DCM (3 or 4 column volumes) and the acidic components usually eluted with an eluent containing a proportion of AcOH (2-20%).

Oasis™ Cartridges / Oasis™ SPE's refer to SPE cartridges packed with a polymeric sorbent manufactured by the Waters Corporation. These are typically conditioned with 3 column volumes of MeOH and equilibrated with water before the sample is loaded. Salts and inorganics are eluted with water and the product typically eluted with MeOH or MeCN.

GreenHouse™ refers to a 24 reaction parallel synthesiser platform available from RDT Ltd, UK

As indicated above, compounds of Formula (I) may find use in human or veterinary medicine, for example as activators of HM74A, in the management of dyslipidaemia and hyperlipoproteinaemia.

Thus, there is provided as another embodiment of the present invention at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof, for use in human or veterinary medicine, for example in the treatment of disorders of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia such as diabetic
5 dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa and obesity. As such, the compounds are also provided for use in the treatment of coronary artery disease, thrombosis, angina,
10 chronic renal failure, peripheral vascular disease and stroke.

There is provided as a further embodiment of the present invention at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof, for use in the manufacture of a medicament for the treatment of disorders of lipid metabolism
15 including dyslipidaemia and hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. As such, the compounds are also provided for use in the treatment of coronary artery
20 disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke.

It will be appreciated that references herein to treatment extend to prophylaxis, prevention of recurrence and suppression of symptoms as well as the treatment of
25 established conditions.

In one embodiment of the invention, there is provided at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of disorders of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia. For
30 example, the use is provided of at least one compound of Formula (I) or a pharmaceutically acceptable derivative thereof in the treatment of diabetic dyslipidaemia, mixed dyslipidaemia, heart failure, hypercholesterolaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity, coronary artery disease, thrombosis, angina, chronic renal failure, stroke and
35 cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia.

It is to be understood that this embodiment of the present invention includes any combination of particular embodiments and covers all combinations of particular
40 substituents described herein above for compounds of Formula (I).

Additionally, the present invention provides the use of at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment of inflammatory diseases or conditions of the joint, for example, arthritis (e.g. rheumatoid arthritis, osteoarthritis, prosthetic joint failure), or of the gastrointestinal tract (e.g. ulcerative colitis, Crohn's disease, and other inflammatory bowel and gastrointestinal diseases, gastritis and mucosal inflammation resulting from infection, the enteropathy provoked by non-steroidal anti-inflammatory drugs), of the lung (e.g. adult respiratory distress syndrome, asthma, cystic fibrosis, or chronic obstructive pulmonary disease), of the heart (e.g. myocarditis), of nervous tissue (e.g. multiple sclerosis), of the pancreas, (e.g. inflammation associated with diabetes melitus and complications thereof, of the kidney (e.g. glomerulonephritis), of the skin (e.g. dermatitis, psoriasis, eczema, urticaria, burn injury), of the eye (e.g. glaucoma) as well as of transplanted organs (e.g. rejection) and multi-organ diseases (e.g. systemic lupus erythematosus, sepsis) and inflammatory sequelae of viral or bacterial infections and inflammatory conditions associated with atherosclerosis and following hypoxic or ischaemic insults (with or without reperfusion), for example in the brain or in ischaemic heart disease.

In a further or alternative embodiments there is provided a method for the treatment of a human or animal subject with a condition where under-activation of the HM74A receptor contributes to the condition or where activation of the receptor will be beneficial, which method comprises administering to said human or animal subject an effective amount of at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof.

Again, it is to be understood that this embodiment of the present invention includes any combination of particular embodiments and covers all combinations of particular substituents described herein above for compounds of Formula (I).

In one embodiment, the present invention provides a method for the treatment of disorders of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa and obesity, which method comprises administering to said human or animal subject an effective amount of at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof. As such, these compounds may also find favour in methods for the treatment of coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke, which methods comprise administering to said human or animal subject an effective amount of at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof.

The amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof which is required to achieve the desired biological effect will, of course, depend on a number of factors, for example, the mode of administration and the precise clinical condition of the recipient. In general, the daily dose will be in the range of 0.1mg - 1g/kg, typically 0.1 - 100mg/kg. An intravenous dose may, for example, be in the range of 0.01mg to 0.1g/kg, typically 0.01mg to 10mg/kg, which may conveniently be administered as an infusion of from 0.1 μ g to 1mg, per minute. Infusion fluids suitable for this purpose may contain, for example, from 0.01 μ g to 0.1mg, per millilitre. Unit doses may contain, for example, from 0.01 μ g to 1g of a compound of the invention. Thus ampoules for injection may contain, for example, from 0.01 μ g to 0.1g and orally administrable unit dose formulations, such as tablets or capsules, may contain, for example, from 0.1mg to 1g, for example from 5mg to 50mg.

A compound of formula (I) or a pharmaceutically acceptable derivative thereof may be employed as the compound *per se* in the treatment of a disease where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial, an example of this is where a compound of the present invention is presented with an acceptable carrier in the form of a pharmaceutical formulation. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the formulation and must not be deleterious to the recipient. The carrier may be a solid or a liquid, or both, and may be formulated with the compound of the invention as a unit-dose formulation, for example, a tablet, which may contain from 0.05% to 95% by weight of the compound of the invention.

The formulations include those suitable for oral, rectal, topical, buccal (e.g. sub-lingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal or intravenous) administration.

There is also provided according to the invention a process for preparation of such a pharmaceutical composition which comprises mixing the ingredients.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges or tablets, each containing a predetermined amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. In general, the formulations are prepared by uniformly and intimately admixing the compound of formula (I) or a pharmaceutically acceptable derivative thereof, with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet may be prepared by compressing or moulding a powder or granules of the compound of formula (I) or a pharmaceutically acceptable derivative thereof optionally with one or

more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Moulded tablets may be made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the invention in a flavoured base, usually sucrose and acacia or tragacanth, and pastilles comprising the compound of the invention in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of formula (I) or a pharmaceutically acceptable derivative thereof, the formulation may be isotonic with the blood of the intended recipient. These preparations could be administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the compound of formula (I) or a pharmaceutically acceptable derivative thereof with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of the compound of formula (I) or a pharmaceutically acceptable derivative thereof.

Thus, formulations of the present invention suitable for parenteral administration comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof may be formulated for parenteral administration by bolus injection or continuous
5 infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or toxicity adjusting agents.

10 Examples of formulations suitable for oral administration include formulations comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof, in 10% DMSO and 90% sodium hydrogen carbonate in sterile saline.

Examples of formulations suitable for intravenous administration include formulations
15 comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof, in 5% or 10% DMSO and 95% or 90% sodium hydrogen carbonate in sterile water. Alternatively, the therapeutically active agent may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container
20 and freeze-drying.

Formulations suitable for rectal administration may be presented as unit-dose suppositories. These may be prepared by admixing a compound of formula (I) or a
25 pharmaceutically acceptable derivative thereof with one or more conventional solid carriers, for example, cocoa butter or glycerides and then shaping the resulting mixture.

Formulations suitable for topical application to the skin may take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used
30 include vaseline, lanolin, polyethylene glycols, alcohols, and combinations of two or more thereof. The compound of formula (I) or a pharmaceutically acceptable derivative thereof is generally present at a concentration of from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

By topical administration as used herein, we include administration by insufflation and
35 inhalation. Examples of various types of preparation for topical administration include ointments, creams, lotions, powders, pessaries, sprays, aerosols, capsules or cartridges for use in an inhaler or insufflator or drops (e.g. eye or nose drops).

Ointments and creams may, for example, be formulated with an aqueous or oily base
40 with the addition of suitable thickening and/or gelling agents and/or solvents. Such bases may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil or a solvent such as a polyethylene glycol.

Thickening agents which may be used include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, microcrystalline wax and beeswax.

5 Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

10 Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents or suspending agents.

15 Spray compositions may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2-tetrafluoroethane, carbon dioxide or other suitable gas.

20 Capsules and cartridges for use in an inhaler or insufflator, of for example gelatin, may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

25 The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example in combination with other classes of dyslipidaemic drugs (e.g. statins, fibrates, bile-acid binding resins or nicotinic acid).

30 The compounds of the instant invention may be used in combination with one or more other therapeutically active agents for example in combination with other classes of dyslipidaemic drugs e.g. 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) or fibrates or bile acid binding resins or nicotinic acid. The invention thus provides, in a further embodiment, the use of such a combination in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial and the use of at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof in the manufacture of
35 a medicament for the combination therapy of disorders of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus,
40 type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa and obesity.

When the compounds of the present invention are used in combination with other therapeutically active agents, the compounds may be administered either together or separately, sequentially or simultaneously by any convenient route.

- 5 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above optimally together with a pharmaceutically acceptable carrier or excipient comprise a further embodiment of the invention. The individual components of such combinations may be administered either together or separately,
10 sequentially or simultaneously in separate or combined pharmaceutical formulations.

- When combined in the same formulation it will be appreciated that the two components must be stable and compatible with each other and the other components of the formulation and may be formulated for administration. When formulated separately
15 they may be provided in any convenient formulation, conveniently in such a manner as are known for such compounds in the art.

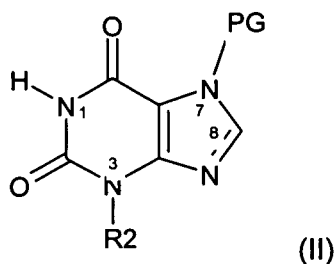
- When in combination with a second therapeutic agent active against the same disease, the dose of each component may differ from that when the compound is used alone.
20 Appropriate doses will be readily appreciated by those skilled in the art.

- The invention thus provides, in a further embodiment, a combination comprising at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof together with another therapeutically active agent.
25

- The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier thereof represent a further embodiment of the invention.
30

- The compounds of the present invention and pharmaceutically acceptable derivatives thereof may be prepared by the methodology described hereinafter, constituting a further embodiment of this invention.

- 35 In one embodiment the present invention provides a method for the preparation of compound(s) of formula (I) from an appropriate starting material, for example compound(s) of formula (II):



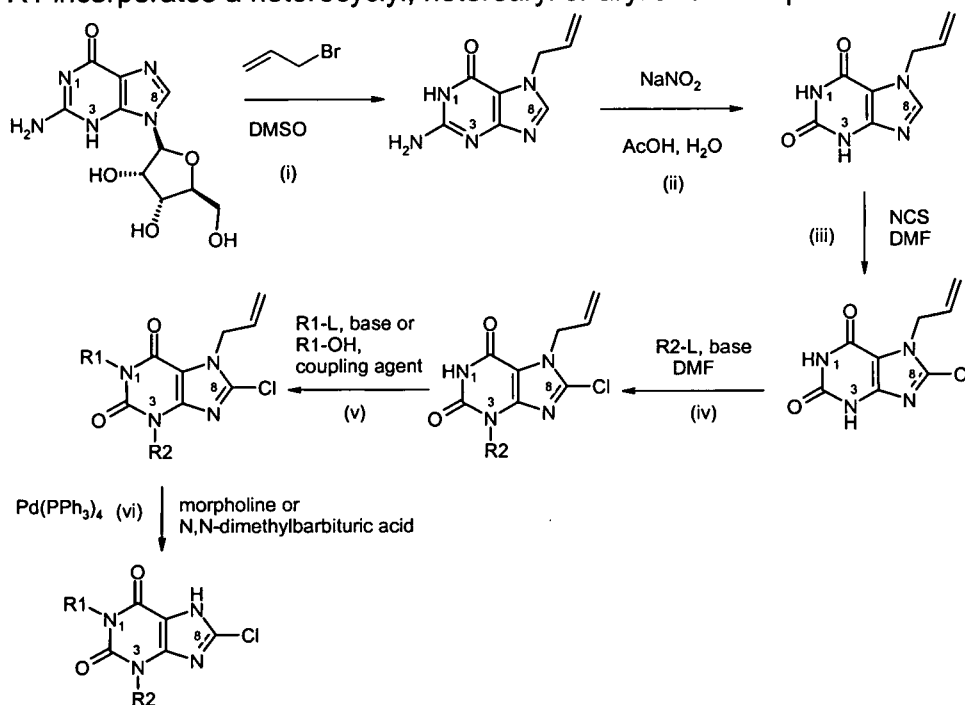
wherein PG = protecting group, the method comprising:

- (i) alkylation at N1 of an N7 protected xanthine;
- (ii) alkylation at N3 of an N7 protected xanthine;
- (iii) halogenation at C8; and
- (iv) de-protection of N7;

in any order providing de-protection is carried out after alkylation.

Process 1:

A process according to the invention for preparing compound(s) of formula (I) in which R1 incorporates a heterocyclyl, heteroaryl or aryl and R1 represents Cl.



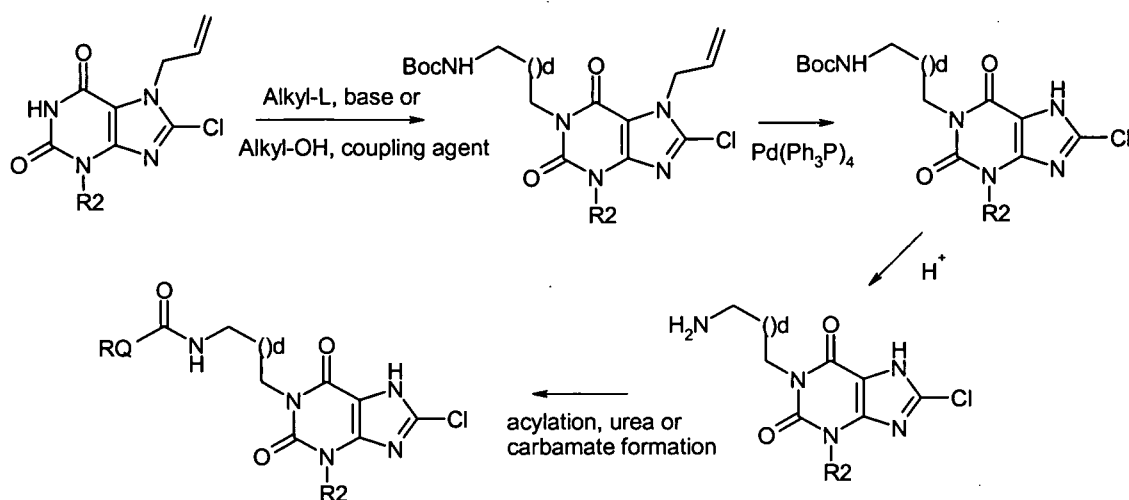
- i) Alkylation of guanine with allyl bromide
- ii) Diazotisation with sodium nitrite followed by hydrolysis to form the xanthine
- iii) Chlorination
- iv) Alkylation at N3 (Examples of suitable bases include Na_2CO_3 , Cs_2CO_3 , K_2CO_3)
- v) Alkylation at N1 (Examples of suitable bases include Na_2CO_3 , Cs_2CO_3 , K_2CO_3)
- vi) Palladium catalysed removal of the allyl group

wherein L represents a leaving group, for example halogen.

5 Process 2:

A process according to the invention for preparing intermediates in which R1 incorporates an amide, carbamate or urea, which may be useful for production of compound(s) of formula (I).

10



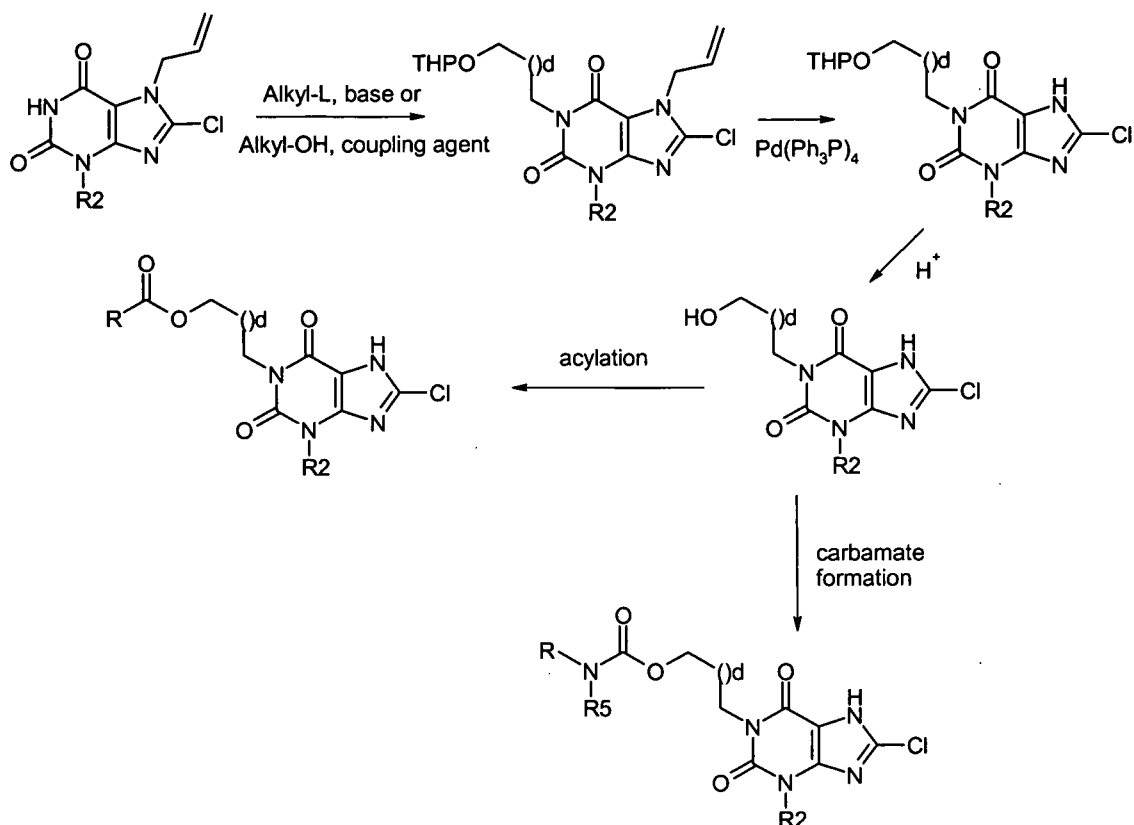
wherein L represents a leaving group, for example halogen, d represents (m-1) (i.e. d together with the preceding methylene = m), R represents -(alkylene)_n-Y and Q may or may not be present, and if present represents either O or NR₅.

15

Process 3:

A process for preparing intermediates in which R1 incorporates a 'reverse' carbamate or ester, which may be useful for production of compound(s) of formula (I).

20



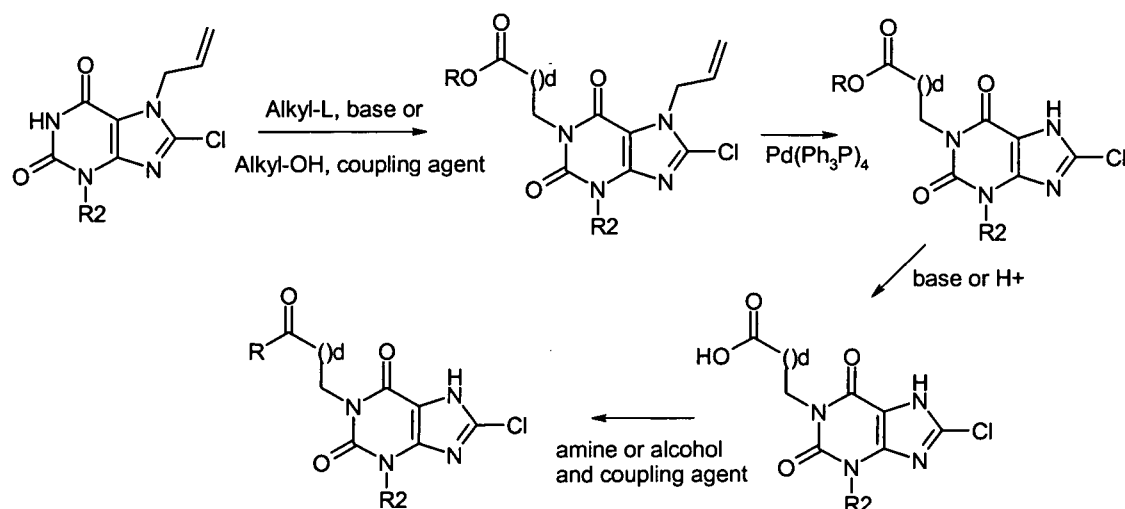
wherein L represents a leaving group, for example halogen, d represents (m-1), and R represents -(alk)_n-Y.

5

Process 4:

A process according to the invention for preparing intermediates in which R₁ incorporates an ester or amide, which may be useful for production of compound(s) of formula (I).

10

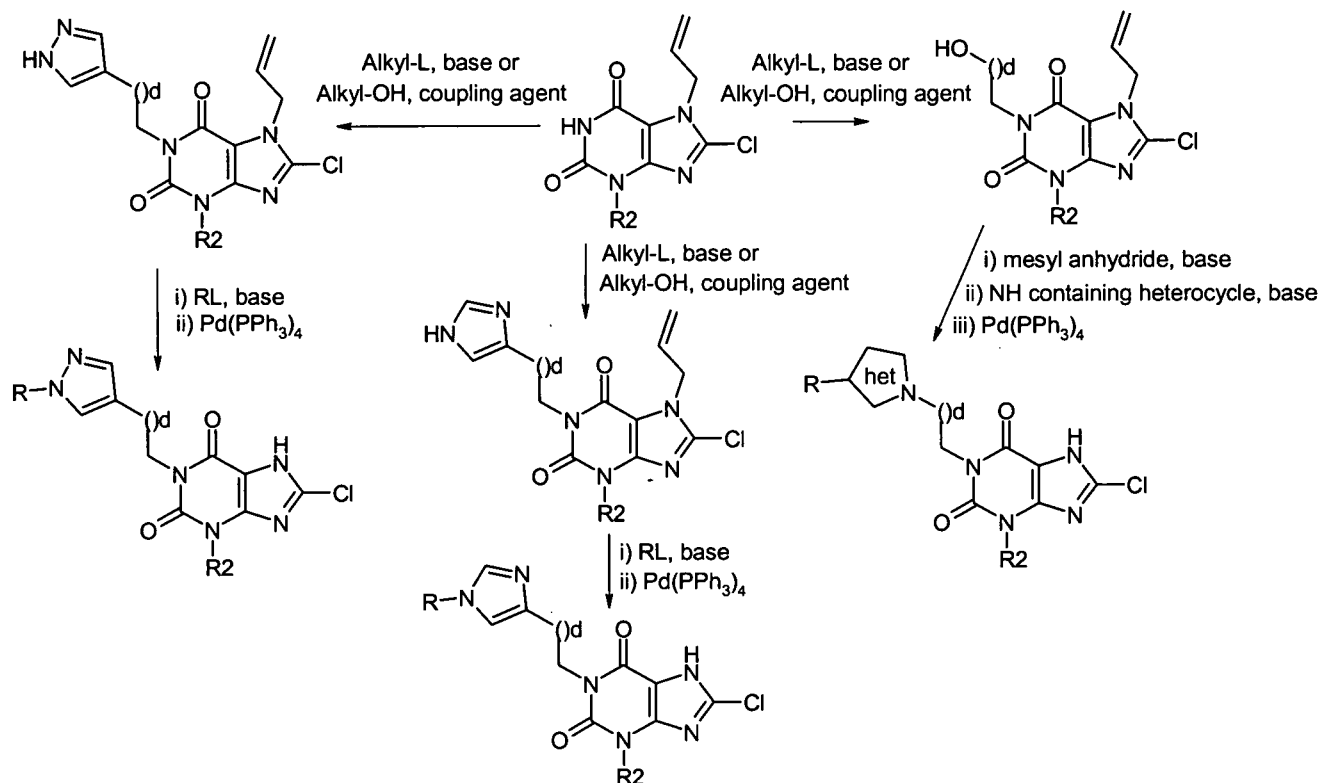


wherein L represents a leaving group, for example halogen, d represents (m-1), and R represents $-NR^5R^7$ or $-OR^5$.

5

Process 5:

A process according to the invention for preparing compound(s) of formula (I) in which X incorporates a pyrazole, imidazole or tetrazole.



10

wherein L represents a leaving group, for example halogen, d represents (m-1), and R represents $-(alk)_n-Y$.

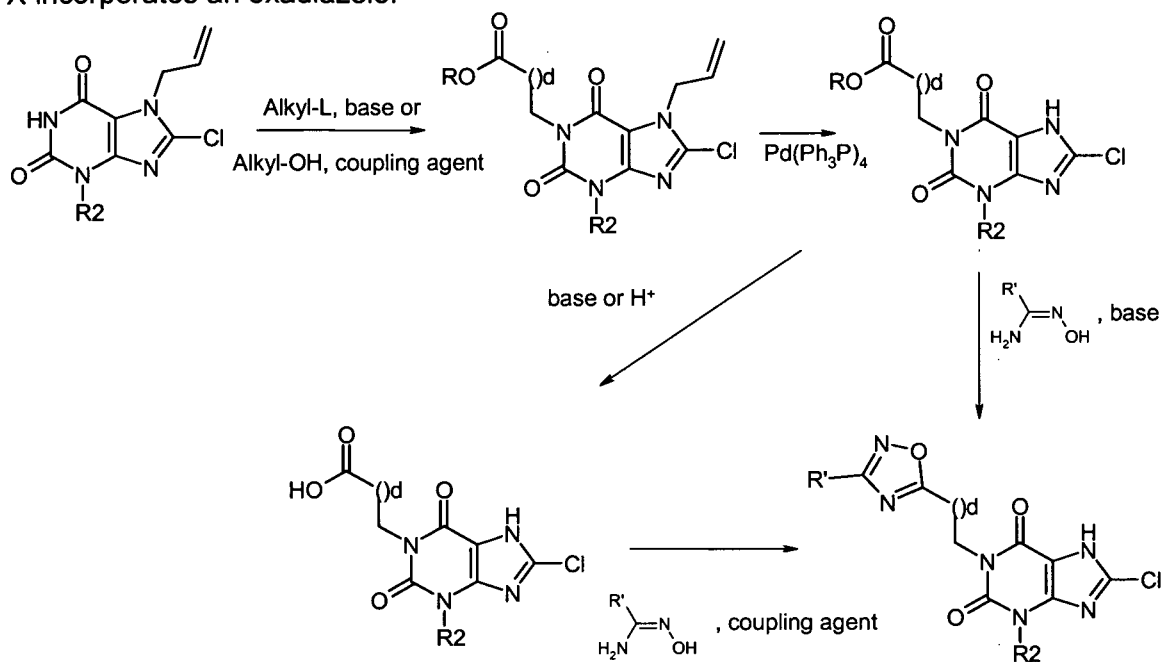
15

20

5

Process 6:

A process according to the invention for preparing compound(s) of formula (I) in which X incorporates an oxadiazole.

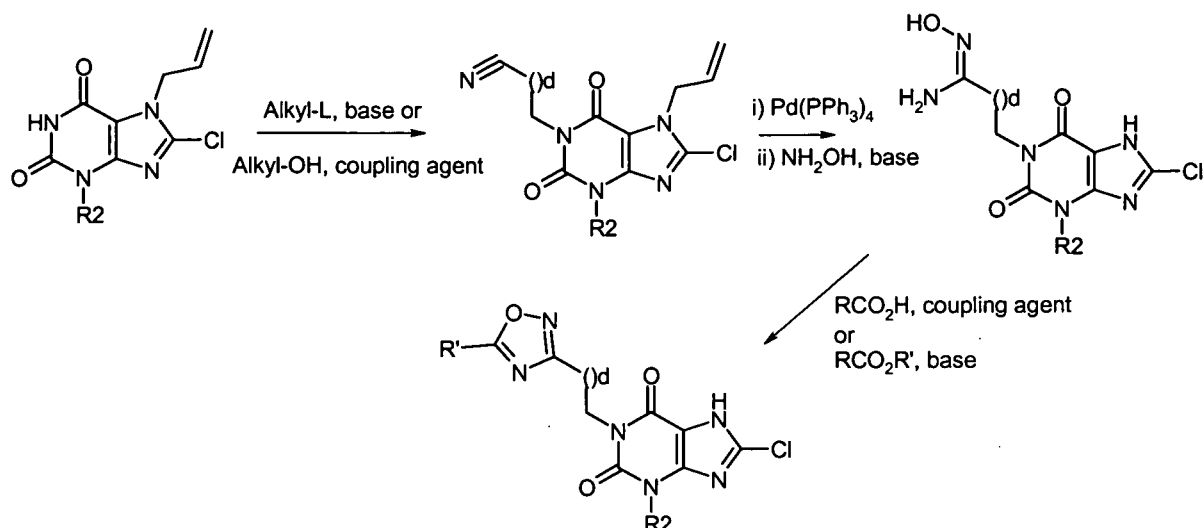


10

wherein L represents a leaving group, for example halogen, d represents (m-1), R represents an alkyl group and R' represents -(alk)_n-Y.

15 Process 7:

A process according to the invention for preparing compound(s) of formula (I) in which X incorporates an oxadiazole

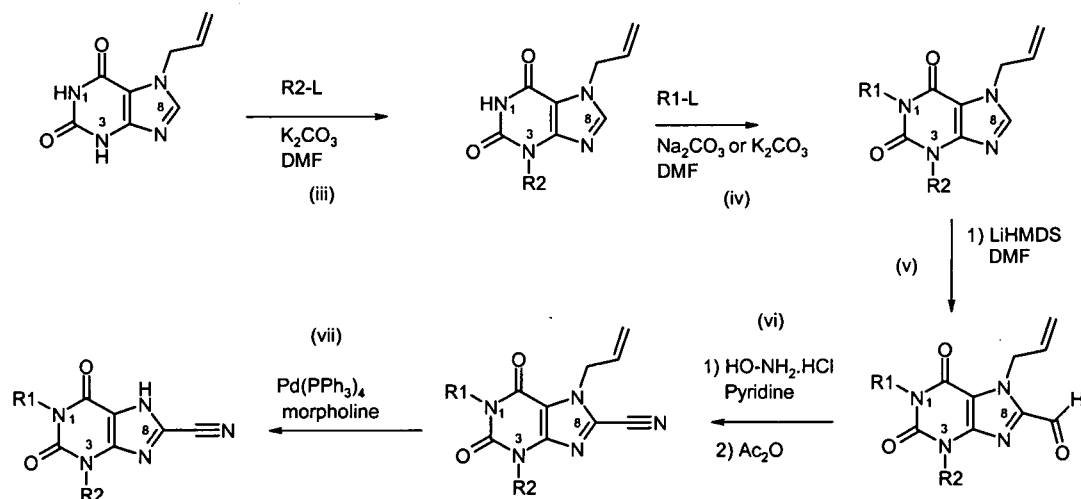


wherein L represents a leaving group, for example halogen, d represents (m-1), R represents an alkyl group and R' represents $-(\text{alk})_n-\text{Y}$.

Process 8:

A process according to the invention for preparing intermediates in which R^3 is CN, which may be useful for preparation of compound(s) of formula (I).

This comprises steps (i) and (ii) of Process 1 followed by:



iii) Alkylation at N3

iv) Alkylation at N1

v) Formation of aldehyde at C8 by lithiation with LiHMDS and DMF quench

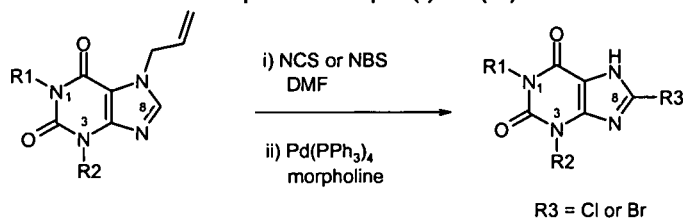
vi) Conversion of the aldehyde to the nitrile

vii) Palladium catalysed removal of the allyl group

wherein L represents a leaving group.

Process 9:

- 5 A process according to the invention for preparing compound(s) of formula (I) in which R^3 is Cl or Br comprises steps (i) to (iv) of Process 8 followed by:

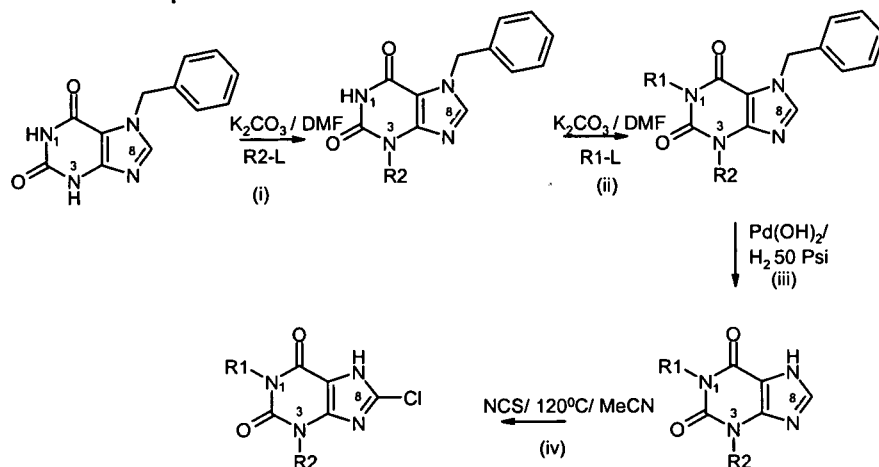


- i) Halogenation at C8 using NCS or NBS
 ii) Palladium catalysed removal of the allyl group

10

Process 10:

- 15 A process according to the invention for preparing compound(s) of formula (I) in which R^3 is Cl comprises:



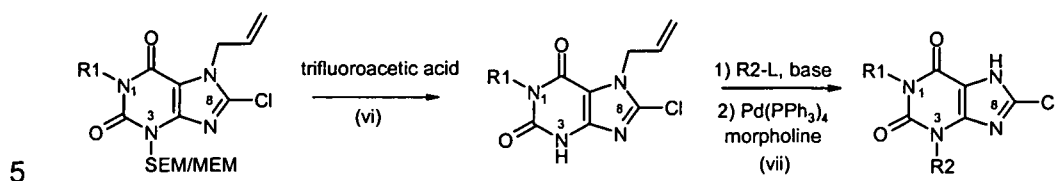
- 20 i) Alkylation at N3
 ii) Alkylation at N1
 iii) Debenzylation
 iii) Chlorination at C8

wherein L represents a leaving group

25

Process 11:

A process according to the invention for preparing compound(s) of formula (I) in which R^1 differs from R^2 and R^3 is Cl comprises steps (i) to (v) of Process 1 (where R^2 from process 1 is specifically SEM or MEM) followed by:



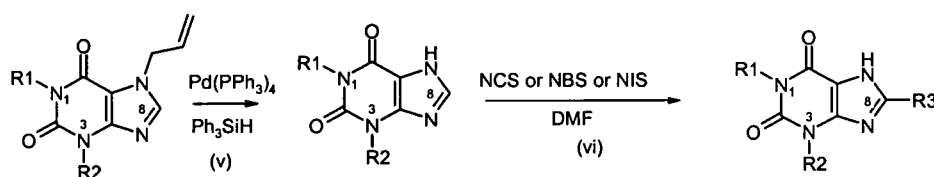
vi) Cleavage of MEM or SEM protecting group

vii) Alkylation of N3 followed by palladium catalysed removal of the allyl group

10 wherein L represents a leaving group

Process 12:

15 A process according to the invention for preparing compound(s) of formula (I) in which R^3 is Cl, Br or I comprises steps (i) to (iv) of Process 8 followed by:

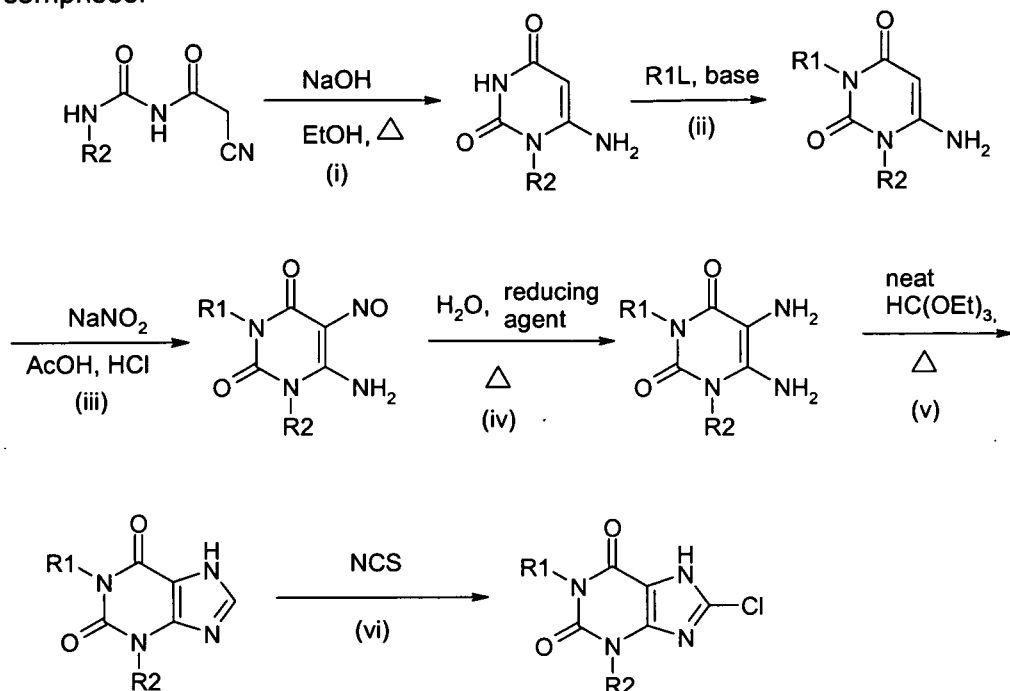


v) Palladium catalysed removal of allyl group

20 vi) Halogenation at C8 using NCS, NBS or NIS

Process 13:

A process according to the invention for preparing compound(s) of formula (I) comprises:



5

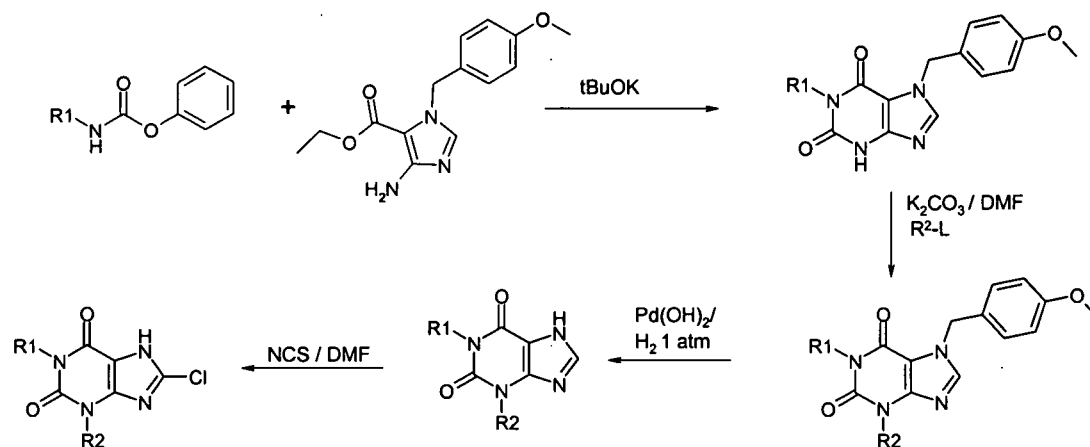
- i) Pyrimidinedione formation
- ii) Alkylation at N1
- iii) Nitrosation
- iv) Reduction using $\text{Na}_2\text{S}_2\text{O}_4$ or a similar reducing agent
- v) Xanthine formation
- vi) Halogenation at C8 using NCS

10

wherein L represents a leaving group

Process 14:

A process according to the invention for preparing compound(s) of formula (I):



5

wherein L represents a leaving group.

As an additional step to the general processes described above, and in particular for use in the preparation of the examples below, there are several ways of purifying resulting compounds, one or more of which may be of use in the present invention, for example the use of MDAP, by recrystallisation from one or more suitable solvents such as ethyl acetate, absolute ethanol, acetonitrile or methanol, or by use of purification column such as Silica RedisepTM cartridges and subsequent eluting with a suitable solvent such as dichloromethane containing ethyl acetate.

Where desired or necessary, as a final stage in any of the above synthetic processes, a resultant compound of formula (I) can be converted into a pharmaceutically acceptable derivative, for example a resultant compound of formula (I) can be converted into a salt form or vice versa or converting one salt form into another pharmaceutically acceptable salt form. These processes will be known to a person skilled in the art.

ABBREVIATIONS

AcOH	Acetic acid
atm	Atmosphere
br	Broad (NMR)
CDI	Carbonyldiimidazole
d	Doublet (NMR)
DBAD	Di- <i>t</i> -butylazodicarboxylate
DCM	Dichloromethane
DIPEA	Diisopropylethylamine
DMSO	Dimethylsulfoxide
DMF	N,N-Dimethylformamide
EtOAc	Ethyl acetate
EtOH	Ethanol
h	Hour(s)
IPA	Isopropyl alcohol
m	Multiplet (NMR)
MDAP	Mass directed autoprep
MeCN	Acetonitrile
MeOH	Methanol
min	Minute(s)
NCS	N-Chlorosuccinimide
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
q	Quartet (NMR)
rt	Room temperature
RT	Retention time
s	Singlet (NMR)
SPE	Solid phase extraction cartridge
t	Triplet (NMR)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
DMEM	Dulbecco's Modified Eagle's Medium
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulphonic acid
LiHMDS	Lithium hexamethyldisilylamide
△	Heat
SEM	2-(trimethylsilyl)ethoxymethyl
MEM	2-methoxyethoxymethyl
Boc	<i>t</i> -butoxycarbonyl
THP	tetrahydropyran

Brief description of Figures

Figure 1: XRPD data of substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 1.

5

Figure 2: XRPD data of substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione form 2.

10

Figure 3: Overlay of XRPD data for substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione Form 1 and Form 2.

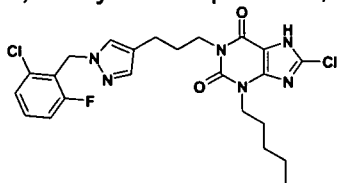
The following non-limiting examples illustrate the present invention:

Synthetic Examples

- 5 It should be noted that the assignment of (Z)-stereochemistry set out in the compounds exemplified below has not been confirmed by experimental data. The person skilled in the art will also recognise that there can be interconversion between E & Z isomers. (Dondoni, Alessandro; Lunazzi, Lodovico; Giorgianni, Patrizia; Macciantelli, Dante. Carbon-nitrogen rotational barrier as a stereochemical probe of benzamidoximes. 10 Journal of Organic Chemistry (1975), 40(20), 2979-80)

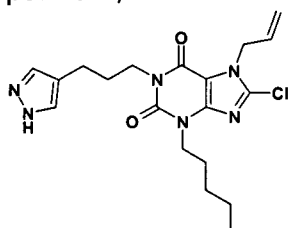
Example 1 : 8-Chloro-1-(3-{1-[(2-chloro-6-fluorophenyl)methyl]-1H-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione

- 15 a) 8-Chloro-1-(3-{1-[(2-chloro-6-fluorophenyl)methyl]-1H-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione



- 8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1H-pyrazol-4-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione (61mg, 0.15mmol) in dry DMF (2ml) was stirred with sodium carbonate (64mg, 0.6mmol) and 2-chloro-6-fluorobenzyl bromide (134mg, 0.6mmol) and heated at 45°C for 18h under nitrogen. After cooling to rt the mixture was degassed by evacuating and readmitting nitrogen, and stirred with tetrakis(triphenylphosphine)palladium(0) (35mg, 0.303mmol) and morpholine (0.13ml) for 5.5h. The mixture was partitioned between EtOAc and 2M HCl, the organic phase 25 separated and evaporated and the residue purified by aminopropyl SPE (5g, washing with THF-MeOH (1:1) then neat MeOH and finally eluting with DCM-MeOH (1:1) containing 5% AcOH) to give the title compound (57mg) as a solid. LC/MS: m/z 507 [MH]⁺, RT 3.64min.

- 30 b) 8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1H-pyrazol-4-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione

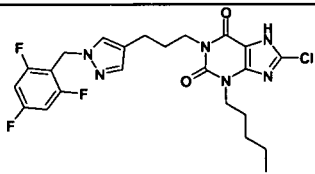
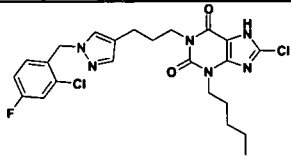
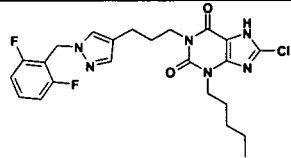


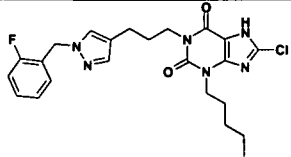
3-Pentyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (5g, 16.86mmol) and 3-(1*H*-pyrazol-4-yl)propan-1-ol (2.12g, 16.8mmol) were stirred in dry THF (150ml) at 3°C. Dibenzyl azodicarboxylate (10.05g, 33.7mmol) was added followed by the dropwise addition of triphenylphosphine (8.83g, 33.7mmol) in dry THF (70ml). The mixture was allowed to warm to rt and stirred for 18h. Water (1ml) was added and the solvents evaporated. The residue was taken up in Et₂O (200ml) from which a white solid, mostly triphenylphosphine oxide, crystallised and was filtered off. The filtrate was concentrated and further by-products crystallised from ether-cyclohexane. The remaining filtrate was concentrated (19.2g) and purified on a Biotage™ system (400g) eluting with EtOAc-cyclohexane (2:1) to afford the title compound as a white solid (2.89g).

LC/MS: *m/z* 405 [MH]⁺, RT 3.19min.

- 15 The following compounds (Table 1) were prepared using a method analogous to that for Example 1, from the corresponding benzyl halides.

Table 1

Example	structure	Yield (mg)	LC/MS:
2	 8-chloro-3-pentyl-1-(3-{1-[(2,4,6-trifluorophenyl)methyl]-1<i>H</i>-pyrazol-4-yl}propyl)-3,7-dihydro-1<i>H</i>-purine-2,6-dione	68	<i>m/z</i> 509 [MH] ⁺ RT 3.58 min
3	 8-chloro-1-(3-{1-[(2-chloro-4-fluorophenyl)methyl]-1<i>H</i>-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1<i>H</i>-purine-2,6-dione	56	<i>m/z</i> 507 [MH] ⁺ RT 3.73 min
4	 8-chloro-1-(3-{1-[(2,6-difluorophenyl)methyl]-1<i>H</i>-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1<i>H</i>-purine-2,6-dione	29	<i>m/z</i> 491 [MH] ⁺ RT 3.53 min

5	 8-chloro-1-(3-{1-[(2-fluorophenyl)methyl]-1H-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	32 ^a	m/z 473 [MH] ⁺ RT 3.55 min
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^a after additional purification by MDAP.

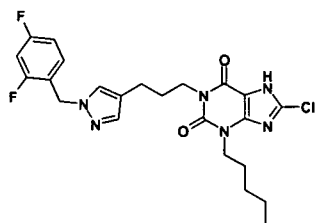
5

NMR details for selected examples from Table 1

Example 2: 8-chloro-3-pentyl-1-(3-{1-[(2,4,6-trifluorophenyl)methyl]-1H-pyrazol-4-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione

¹H NMR (DMSO-d₆) δ: 0.85 (t, 3H, J = 7 Hz), 1.20-1.40 (m, 4H), 1.60-1.70 (m, 2H), 1.70-1.82 (m, 2H), 2.39 (t, 2H, J = 8 Hz), 3.83-3.94 (m, 4H), 5.24 (s, 2H), 7.18-7.30 (m, 3H), 7.57 (s, 1H).

Example 6: 8-Chloro-1-(3-{1-[(2,4-difluorophenyl)methyl]-1H-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione



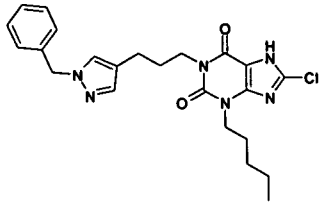
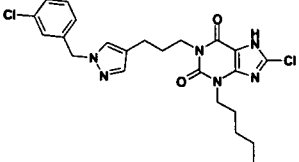
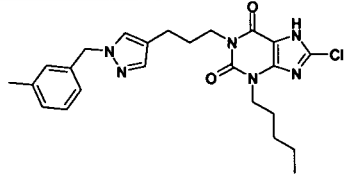
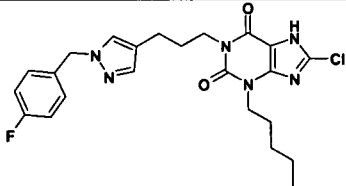
8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1H-pyrazol-4-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione (81mg, 0.2mmol) and sodium carbonate (85mg, 0.8mmol) were stirred in dry DMF (2ml) with 2,4-difluorobenzyl bromide (166mg, 0.8mmol) at 45°C for 18h. The mixture was degassed and stirred with tetrakis(triphenylphosphine)palladium(0) (46mg, 0.04mmol) and morpholine (176mg, 2mmol) at rt for 6h. The reaction was worked up and purified by aminopropyl SPE (5g, washing with THF-MeOH (1:1) then neat MeOH, eluting with DCM-MeOH (1:1) with 5% added AcOH) to yield the title compound (37.7mg) as a solid.

LC/MS: m/z 491 [MH]⁺, RT 3.42min.

The following compounds (Table 1) were prepared using a method analogous to that for Example 6, from the corresponding benzyl halides.

Table 2

Example	Structure	Yield	LC/MS:
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		(mg)	
7	 8-chloro-3-pentyl-1-{3-[1-(phenylmethyl)-1H-pyrazol-4-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	17 ^a	m/z 455 [MH] ⁺ RT 3.52 min
8	 8-chloro-1-(3-{1-[(3-chlorophenyl)methyl]-1H-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	11.6 ^a	m/z 489 [MH] ⁺ RT 3.52 min
9	 8-chloro-1-(3-{1-[(3-methylphenyl)methyl]-1H-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	33	m/z 469 [MH] ⁺ RT 3.54 min
10	 8-chloro-1-(3-{1-[(4-fluorophenyl)methyl]-1H-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	42	m/z 473 [MH] ⁺ RT 3.44 min

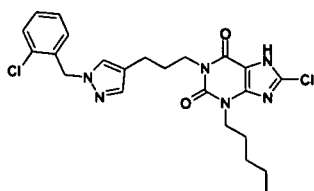
^a after additional purification by MDAP.

NMR details for selected examples from Table 2

- 5 Example 6: ¹H NMR (d⁶ DMSO) 0.85 (3H, t, J = 7Hz), 1.21-1.34 (4H, m), 1.58-1.68 (2H, m), 1.71-1.80 (2H, m), 2.41 (2H, t, J = 8Hz), 3.84-3.93 (4H, m), 5.26 (2H, s), 7.02-7.09 (1H, m), 7.15-7.29 (2H, m), 7.31 (1H, s), 7.61 (1H, s).

- 10 Example 7: 8-chloro-3-pentyl-1-{3-[1-(phenylmethyl)-1H-pyrazol-4-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione; ¹H NMR (DMSO-d₆) δ: 0.87 (t, 3H, J = 7 Hz), 1.20-1.36 (m, 4H), 1.60-1.70 (m, 2H), 1.72-1.85 (m, 2H), 2.42 (t, 2H, J = 8 Hz), 3.83-3.95 (m, 4H), 5.24 (s, 2H), 7.13-7.38 (m, 6H), 7.61 (s, 1H).

- 15 **Example 11: 8-Chloro-1-(3-{1-[(2-chlorophenyl)methyl]-1H-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione**

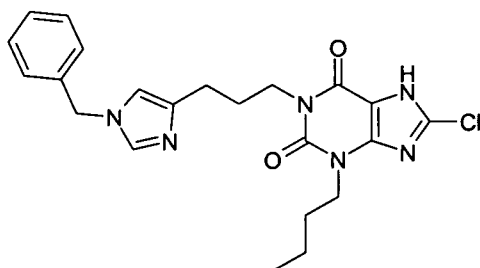


Prepared by the method for 8-chloro-1-(3-{1-[(2,4-difluorophenyl)methyl]-1H-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, Example 6 but from 2-chlorobenzyl bromide (164mg, 0.8mmol). However, in order to complete the deprotection step further tetrakis(triphenylphosphine)palladium(0) (40mg) and morpholine (0.15ml) were added and stirring continued for a further 5.5h. Purification by aminopropyl SPE as above afforded the title compound as a solid (42mg).

LC/MS: m/z 489 [MH]⁺, RT 3.67min.

Example 12: 3-Butyl-8-chloro-1-{3-[1-(phenylmethyl)-1H-imidazol-4-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione

a) 3-Butyl-8-chloro-1-{3-[1-(phenylmethyl)-1H-imidazol-4-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione

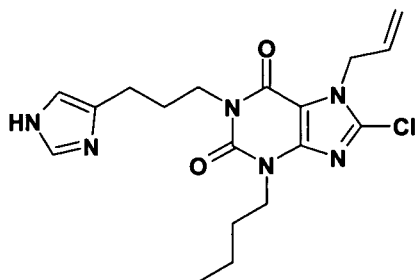


A solution of 3-butyl-8-chloro-1-[4-(1H-imidazol-4-yl)butyl]-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (300mg, 0.77mmol) in anhydrous THF (5ml) was treated with benzyl bromide (144mg, 0.84mmol) and DIPEA (147μl, 0.84mmol). The mixture was left to stir at rt under nitrogen for 4 days. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried (MgSO₄) and concentrated. The crude was purified by a silica SPE column using a 0.5-5% MeOH/DCM gradient. The product fractions were combined and concentrated under high vacuum. The product was dissolved in THF (5ml) then Pd(PPh₃)₄ (88mg, 0.077mmol) and morpholine (670μl, 7.67mmol) were added and the mixture left to stir at rt under nitrogen for 3h. 88mg of Pd(PPh₃)₄ (0.077mmol) was added and the mixture was left to stir at rt under nitrogen for 16h. The mixture was partitioned between EtOAc and H₂O. The organic layer was separated and the aqueous layer was extracted with EtOAc (x2). The organic layers were combined, washed with brine, dried (MgSO₄) and concentrated. The crude product was purified by MDAP to give the title compound as a white solid (9mg, 2%).

LC/MS: m/z 441 [MH]⁺, RT 2.50min.

¹H NMR (DMSO-d₆) δ: 0.89 (t, 3H, J = 7.5 Hz), 1.28 (m, 2H), 1.60 (m, 2H), 1.79 (m, 2H), 2.48 (t overlapping with DMSO, 2H, J = 7.5 Hz), 3.89 (m, 4H), 5.17 (s, 2H), 7.08 (s, 1H), 7.31, (m, 6H), 8.03 (s, 1H).

- 5 b) 3-Butyl-8-chloro-1-[3-(1H-imidazol-4-yl)propyl]-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione

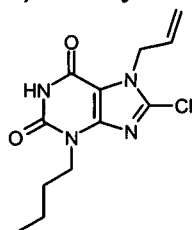


10 A solution of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (2.8g, 9.9mmol) in anhydrous THF (60ml) was treated with 3-(1H-imidazol-4-yl)-1-propanol (1.5g, 12mmol) in anhydrous THF (10ml) and PPh₃ (3.4g, 13mmol). DBAD (2.9g, 13mmol) was added in one portion and the mixture was left to stir at rt, under nitrogen for 18h. The mixture was partitioned between EtOAc and H₂O. The aqueous layer was extracted and washed with EtOAc. The organic layers were combined, washed with
15 brine, dried (MgSO₄) and concentrated. The crude product was purified by a silica SPE cartridge using a MeOH/EtOAc gradient (0.5%-7% MeOH). The product fractions were combined and concentrated by to give the title compound as a white solid (2.16g, 55%).

LC/MS: m/z 391 [MH]⁺, RT 2.40min.

20

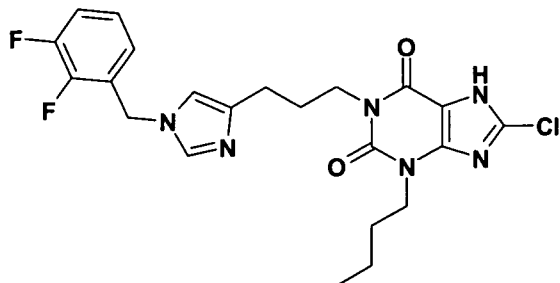
- c) 3-Butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione



25 To a solution of 3-butyl-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (3.34g, 13.4mmol) in anhydrous DMF (19ml) was added NCS (1.97g, 14.8mmol) and left to stir at rt under nitrogen for 22h. The mixture was concentrated *in vacuo* to give a yellow solid which was filtered and washed with MeOH to provide a first crop. The filtrate was concentrated to a solid and washed with MeOH to provide a second crop and repeated a further two occasions to provide the title compound. On the final wash the filtrate was further purified by SPE (Si, 20g) cartridge eluting with EtOAc:cyclohexane (1:1). The
30 combined solids were dried under vacuum to afford the title compound (2.42g, 64%).

LC/MS: m/z 283 [MH]⁺.

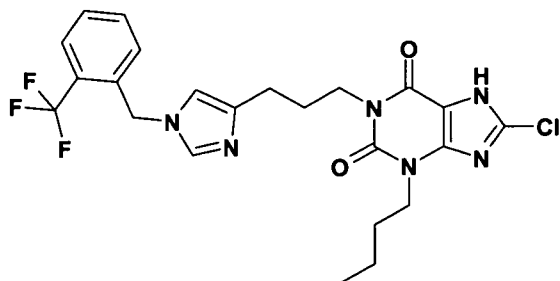
Example 13: 3-Butyl-8-chloro-1-(3-{1-[(2,3-difluorophenyl)methyl]-1H-imidazol-4-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione



A solution of 3-butyl-8-chloro-1-[4-(1H-imidazol-4-yl)butyl]-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (150mg, 0.38mmol) in anhydrous DMF (3ml) was treated with 1-(bromomethyl)-2,4-difluorobenzene (54μl, 0.42mmol) and DIPEA (73μl, 0.42mmol). The mixture was left to stir at rt under nitrogen for 3 days. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried (MgSO₄) and concentrated. The crude product was purified on a silica SPE column using a DCM to load the material onto the column and wash through the impurities then a 0-5% MeOH/DCM gradient to elute the compound. The product fractions were combined and concentrated and the residues dissolved in anhydrous DMF (3ml). The solution was degassed then Pd(PPh₃)₄ (39mg, 0.034mmol) and morpholine (200μl, 2.3mmol) were added and the mixture left to stir at rt under nitrogen for 3h. The crude product was purified by an aminopropyl SPE using MeOH to load the compound onto the column and wash through the impurities then a 0-5% AcOH/MeOH gradient to elute the product. The product fractions were combined and concentrated by high vacuum to leave the title compound as a white solid (14mg, 7%).

LC/MS: m/z 477 [MH]⁺, RT 2.54min.

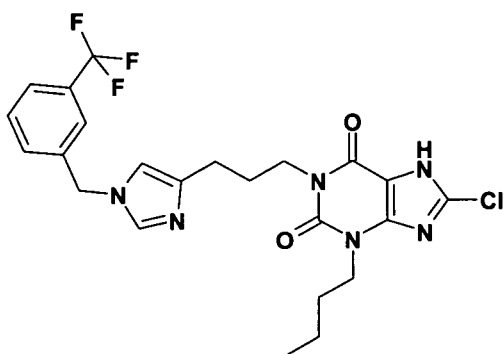
Example 14 : 3-Butyl-8-chloro-1-[3-(1-{[2-(trifluoromethyl)phenyl]methyl}-1H-imidazol-4-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione



A solution of 3-butyl-8-chloro-1-[4-(1H-imidazol-4-yl)butyl]-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (150mg, 0.38mmol) in anhydrous DMF (3ml) was treated with 1-(chloromethyl)-2-(trifluoromethyl)benzene (61μl, 0.42mmol) and DIPEA (73μl,

0.42mmol). The mixture was left to stir at rt under nitrogen for 3 days. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried (MgSO₄) and concentrated. The crude product was purified on a silica SPE column using DCM to load the material onto the column and wash through the impurities then a 0-5% MeOH/DCM gradient to elute the compound. The product fractions were combined and concentrated and the residues dissolved in anhydrous DMF (3ml). The solution was degassed then Pd(PPh₃)₄ (35mg, 0.030mmol) and morpholine (174μl, 2.0mmol) were added and the mixture left to stir at rt under nitrogen for 3h. The crude product was purified by an aminopropyl SPE using MeOH to load the compound onto the column and wash through the impurities then a 0-5% AcOH/MeOH gradient to elute the product. The product fractions were combined and concentrated by high vacuum to leave the title compound as a white solid (50mg, 26%).
LC/MS: m/z 509 [MH]⁺, RT 2.64min.

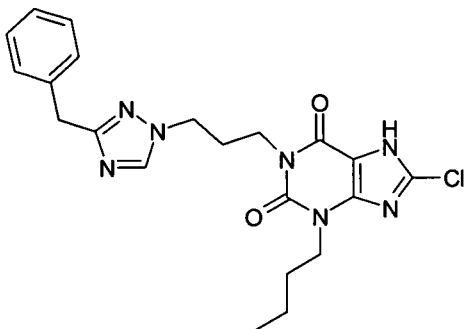
Example 15: 3-Butyl-8-chloro-1-[3-(1-{[3-(trifluoromethyl)phenyl]methyl}-1H-imidazol-4-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione



A solution of 3-butyl-8-chloro-1-[4-(1H-imidazol-4-yl)butyl]-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (150mg, 0.38mmol) in anhydrous DMF (3ml) was treated with 1-(chloromethyl)-3-(trifluoromethyl)benzene (65μl, 0.42mmol) and DIPEA (73μl, 0.42mmol). The mixture was left to stir at rt under nitrogen for 3 days. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried (MgSO₄) and concentrated. The crude product was purified on a silica SPE column using a DCM to load the material onto the column and wash through the impurities then a 0-5% MeOH/DCM gradient to elute the compound. The product fractions were combined and concentrated and the residues dissolved in anhydrous DMF (3ml). The solution was degassed then Pd(PPh₃)₄ (30mg, 0.027mmol) and morpholine (156μl, 1.8mmol) were added and the mixture left to stir at rt under nitrogen for 3h. The crude product was purified by an aminopropyl SPE using MeOH to load the compound onto the column and wash through the impurities then a 0-5% AcOH/MeOH gradient to elute the product. The product fractions were combined and concentrated by high vacuum to leave the title compound as a white solid (18mg, 9%).
LC/MS: m/z 509 [MH]⁺, RT 2.78min.

Example 16 : 3-Butyl-8-chloro-1-{3-[3-(phenylmethyl)-1*H*-1,2,4-triazol-1-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

- 5 a) 3-Butyl-8-chloro-1-{3-[3-(phenylmethyl)-1*H*-1,2,4-triazol-1-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

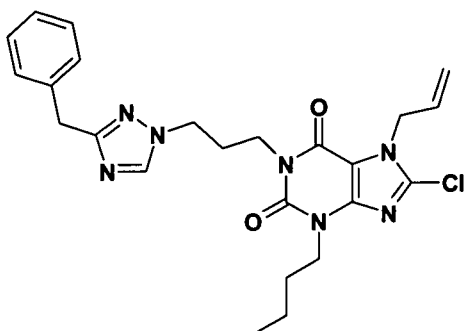


A solution of 3-butyl-8-chloro-1-{3-[3-(phenylmethyl)-1*H*-1,2,4-triazol-1-yl]propyl}-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (669mg, 1.39mmol) in THF (7ml) was degassed by applying a vacuum and then nitrogen was introduced. Pd(PPh₃)₄ (160mg, 0.14mmol) was added and the mixture degassed once more. Morpholine (1.2ml, 13.9mmol) was added and the mixture was stirred under nitrogen for 18h, then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated and the aqueous layer extracted again with EtOAc. The combined extracts were washed with brine, dried (MgSO₄) and concentrated, giving a yellow residue. MeOH was added and then passed down an aminopropyl SPE with the product eluting with 2-3% AcOH/MeOH. The product fractions were combined and concentrated giving a pale yellow solid (380mg). Approximately a quarter of the material was purified by autoprep HPLC and rest was crystallised from MeOH:DMSO (1:1) giving the title compound as a white solid (125mg, 31%).

LC/MS: *m/z* 442 [MH]⁺, RT 3.0min.

¹H NMR (DMSO-*d*₆) δ: 0.89 (t, 3H, *J* = 7Hz), 1.30 (m, 2H), 1.62 (m, 2H), 2.07 (m, 2H), 3.90 (m, 6H), 4.13 (t, 2H, *J* = 7Hz), 7.24 (m, 5H), 8.36 (1H, s), 14.5 (br s, 1H).

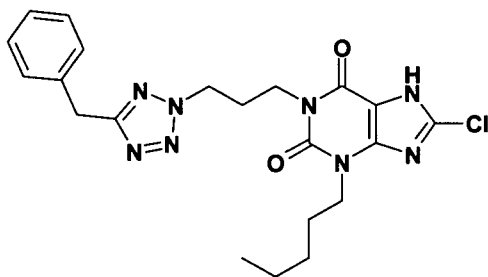
- 25 b) 3-Butyl-8-chloro-1-{3-[3-(phenylmethyl)-1*H*-1,2,4-triazol-1-yl]propyl}-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 3-(phenylmethyl)-1*H*-1,2,4-triazole (2.1g, 13.2mmol) in MeOH (40ml) was treated with 0.5M NaOMe in MeOH (29ml) followed by 1,3-dibromopropane (1.7ml). After stirring for 5h at 50°C the mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried (MgSO₄) and concentrated, giving an oily residue (1.0g). To this was added butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (917mg, 3.2mmol) and Cs₂CO₃ (1.2g, 3.6mmol). DMF (15ml) was added and the mixture was stirred at 50°C for 20h then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried (MgSO₄) and concentrated. The resulting oil (1.52g) was passed down a silica SPE (50g) column eluting with EtOAc/ cyclohexane mixtures. Two isomeric products of the triazole were obtained as a 2:1 mixture, in favour of the title compound, as a yellow paste (697mg, 67% based on ratio of isomers present).

LC/MS: *m/z* 482 [MH]⁺, RT 3.3min.

Example 17 : 8-Chloro-3-pentyl-1-{3-[5-(phenylmethyl)-2*H*-tetrazol-2-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



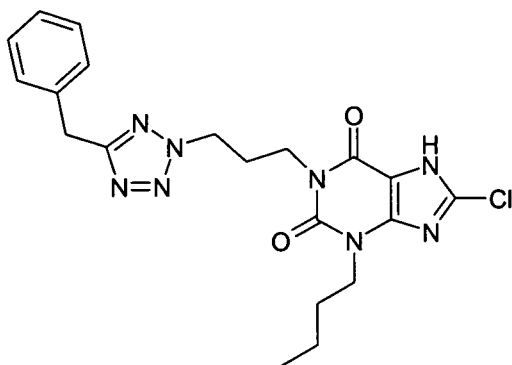
A solution of 5-benzyl-1*H*-tetrazole (1.0g, 6.24mmol) in MeOH (5ml) was treated with 1-chloro-3-iodopropane (1.0ml, 9.36mmol) and a solution of 0.5M NaOMe in MeOH (4.7ml, 9.36mmol). The reaction was heated at reflux for 18h then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated and the aqueous layer extracted once more with EtOAc. The combined extracts were washed with brine, dried (MgSO₄) and concentrated, giving a yellow solid. (796mg). 700mg of this material was reacted with 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (732mg, 2.47mmol) and Cs₂CO₃ (967mg, 3.0mmol) in DMF (20ml) at 75°C for 24h. The reaction was allowed to cool to rt and the mixture was degassed by applying a vacuum and then nitrogen was introduced. Pd(PPh₃)₄ (428mg, 0.37mmol) was added and the

mixture degassed once more. Morpholine (2.1ml, 24.7mmol) was added and the mixture was stirred under nitrogen for 3h, then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated and the aqueous layer extracted once more. The combined extracts were concentrated, giving a yellow residue. MeOH was added and then passed down an aminopropyl SPE, the product eluting with 2-3% AcOH/MeOH. The product fractions were combined and concentrated then purified by the MDAP to give the title compound as a white solid (35mg, 3%).

LC/MS: m/z 457 $[MH]^+$, RT 3.5min.

1H NMR; (DMSO- d_6) δ : 0.85 (t, 3H, $J = 7$ Hz), 1.21-1.34 (m, 4H), 1.62 (m, 2H), 2.22 (m, 2H), 3.88 (t, 2H, $J = 7$ Hz), 3.97 (t, 2H, $J = 7$ Hz), 4.17 (s, 2H), 4.67 (t, 2H, $J = 7$ Hz), 7.20-7.32 (m, 5H), 14.5 (br s, 1H).

Example 18: 3-Butyl-8-chloro-1-{3-[5-(phenylmethyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione



A solution of 5-benzyl-1H-tetrazole (1.8g, 11.2mmol) in MeOH (30ml) was treated with 1,3-dibromopropane (5.7ml, 56.2mmol) and 0.5M NaOMe in MeOH (31.5ml) then stirred at 40°C under nitrogen for 60h. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. Partial purification by SPE (20g silica, cyclohexane/EtOAc mixtures) and by the CompanionTM system (silica SPE, cyclohexane/EtOAc mixtures) gave an oil (1.98g, 62% of a mixture of isomers, 2:1 in favour of 2-(3-bromopropyl)-5-(phenylmethyl)-2H-tetrazole) which was taken on crude in the next step.

A mixture of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (1.74g, 6.1mmol), crude 2-(3-bromopropyl)-5-(phenylmethyl)-2H-tetrazole (1.9g, 6.8mmol), CS_2CO_3 (2.2g, 6.8mmol) and DMF (60ml) was stirred at 45°C under nitrogen for 24h. The mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (705mg, 0.61mmol) was added and the mixture degassed once more. Morpholine (5.4ml, 61.4mmol) was added and the mixture was stirred under nitrogen for 4h, and then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated, giving a yellow residue. MeOH was added and then passed down an aminopropyl column with the product eluting with 2% AcOH/MeOH. The product was further purified by the

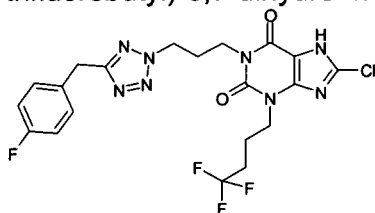
Companion™ system using EtOAc/cyclohexane mixtures. The resulting solid was stirred with boiling Et₂O and filtered after cooling to rt. The title compound was collected as a white solid (1.01g, 37%) and dried at 50°C under vacuum.

LC/MS: m/z 443 [MH]⁺, RT 3.3min.

- 5 ¹H NMR (DMSO-d₆) δ: 0.89 (t, 3H, J = 7Hz), 1.29 (m, 2H), 1.61 (m, 2H), 2.22 (m, 2H), 3.89 (t, 2H, J = 7Hz), 3.97 (t, 2H, J = 7Hz), 4.17 (s, 2H), 4.67 (t, 2H, J = 7Hz), 7.20-7.32 (m, 5H), 14.5 (br s, 1H).

10 **Example 19: 8-Chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione**

a) 8-Chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione



15

5-[(4-Fluorophenyl)methyl]-1H-tetrazole (75mg, 0.4mmol) was treated with potassium carbonate (100mg, 0.7mmol) and DMF (3ml). The mixture was treated with a solution of 3-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-2,3,6,7-tetrahydro-1H-purin-1-yl]propyl methanesulfonate (100mg, 0.2mmol) in DMF (0.5ml). The mixture was stirred and heated at 60°C 3 hours then cooled and evaporated. The residue was partitioned between chloroform (4ml) and water (2cm³). 1cm³ of saturated aqueous sodium bicarbonate (3ml) was added to each. The mixture was separated and the organic phase evaporated. The residue was dissolved in anhydrous THF (3ml) and the mixture degassed by the cautious successive application of vacuum and nitrogen pressure to the mixture. The mixture was treated with tetrakis(triphenylphosphine)palladium(0) (10mg, 0.008mmol) and morpholine (0.2ml, 2.3mmol) and then stirred in a nitrogen atmosphere for 2h. The mixture was evaporated and partitioned between chloroform (4ml) and saturated aqueous ammonium chloride (3ml). The mixture was separated, and the aqueous phase re-extracted with chloroform. The organic phase was evaporated and the residue dissolved in MeOH (3ml). The solution was added to the top of a 2g aminopropyl SPE and washed with MeOH (15ml). The desired product was eluted from the cartridge with a 3% v/v solution of AcOH in MeOH (20ml). Product containing fractions were combined and evaporated and the residue subjected to purification by flash column chromatography (gradient elution from 10:1 cyclohexane/EtOAc to EtOAc). Product-containing fractions were combined and evaporated to yield the product as a colourless oil. Trituration in minimal diethyl ether caused the product to solidify and this was thoroughly dried to yield the title compound as a white solid (18.7mg, 18%).

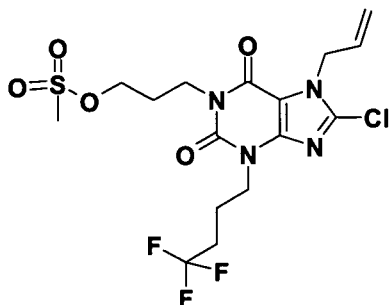
30

35

LC/MS: m/z 515 $[MH]^+$, RT 3.31min.

1H NMR ($CDCl_3$) δ : 2.06 (m, 2H), 2.21 (m, 2H), 2.45 (m, 2H), 4.17 (m, 4H), 4.24 (t, 2H, $J = 7.0Hz$), 4.70 (t, 2H, $J = 7.2Hz$), 6.96 (m, 2H), 7.25 (m, 2H).

- 5 b) 3-[8-Chloro-2,6-dioxo-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-2,3,6,7-tetrahydro-1H-purin-1-yl]propyl methanesulfonate

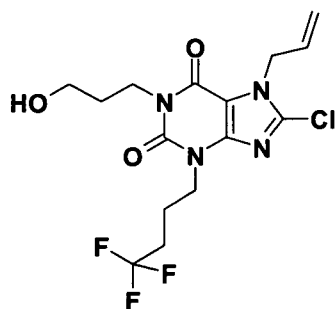


- 10 A solution of 8-chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione (0.82g, 2.1mmol) in DCM (20ml) was treated with triethylamine (0.42ml, 3.1mmol) and methanesulfonic anhydride (0.40g, 2.3mmol). After 1h the mixture was treated with saturated aqueous sodium bicarbonate (20ml). The mixture was separated and the organic phase dried ($MgSO_4$), filtered and evaporated to give the title compound (0.91g), which was used without further purification.

LC/MS: m/z 473 $[MH]^+$, RT 3.17min.

- 15 c) 8-Chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione

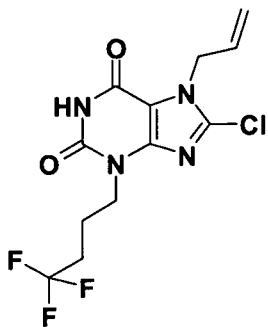
20



- 25 A solution of 8-chloro-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione (1.0g, 3.0mmol) in DMF (15ml) was treated with caesium carbonate (1.16g, 3.6mmol) and 3-bromo-1-propanol (0.3ml, 3.3mmol). The mixture was heated at 60°C for 4h and then cooled and evaporated. The residue was partitioned between EtOAc (50ml) and water (50ml). The organic phase was dried ($MgSO_4$), filtered and evaporated. The product was purified by flash chromatography using a gradient elution from cyclohexane to EtOAc. Product-containing fractions were combined and evaporated to give the title compound as a colourless oil (0.82g, 75%).

LC/MS: m/z 395 [MH]⁺, RT 2.90min.

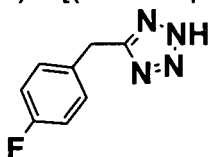
d) 8-Chloro-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione



A solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (2.0g, 8.8mmol) in DMF (20ml) was treated with sodium carbonate (1.15g, 10.8mmol) and 4-bromo-1,1,1-trifluorobutane (1.86g, 9.7mmol). The mixture was stirred at 50°C for 18h then cooled and evaporated. The residue was partitioned between EtOAc (100ml) and saturated aqueous sodium bicarbonate (50ml). The organic phase was dried (MgSO₄), filtered and evaporated. The residue was triturated in a mixture of diethyl ether and cyclohexane then the product filtered off and dried to yield the title compound as a white solid (1.18g, 40%).

LC/MS: m/z 337 [MH]⁺, RT 2.83min.

e) 5-[(4-Fluorophenyl)methyl]-1H-tetrazole



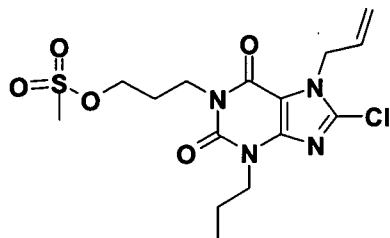
A mixture of triethylammonium chloride (4.14g, 30mmol) and sodium azide (1.95g, 30mmol) was treated with a solution of (4-fluorophenyl)acetonitrile (1.35g, 10mmol) in toluene (14ml) and the mixture was stirred and heated at 100°C for 5h. The cooled mixture was treated with water (10ml) and the mixture separated. The aqueous phase was stirred and treated dropwise with concentrated hydrochloric acid until the product had precipitated from solution. The precipitated product was filtered off, washed with water and dried to yield the title compound as a white solid (1.27g, 72%).

LC/MS: m/z 179 [MH]⁺, RT 2.24min.

The compounds in Table 3 were prepared using a method analogous to that for Example 19: 8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione, with the appropriate methanesulfonate and tetrazole. MDAP was employed to further purify those compounds insufficiently pure following normal phase chromatography.

Methanesulfonates intermediates and their precursor alcohols were prepared according to the following procedures:

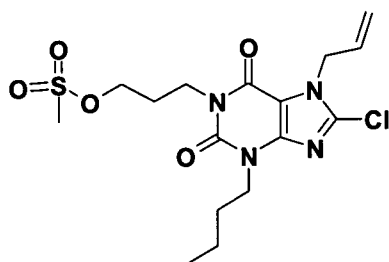
- 5 3-[8-Chloro-2,6-dioxo-7-(2-propen-1-yl)-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl]propyl methanesulfonate



- 10 A solution of 8-chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione (1.99g, 6.1mmol) in DCM (50ml) was treated with triethylamine (1.2ml, 8.6mmol) and methanesulfonic anhydride (1.2g, 6.9mmol). After 1.5h the mixture was treated with water (50ml). The mixture was separated and the aqueous phase extracted with DCM (25ml), the combined organic phases dried (MgSO₄), filtered and
15 evaporated to give the title compound as a pale yellow oil (2.38g), which was used without further purification.

LC/MS: m/z 405 [MH]⁺, RT 2.93min.

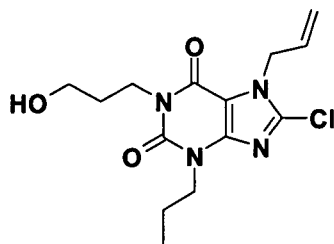
- 20 3-[3-Butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]propyl methanesulfonate



- 25 Prepared according to the method used for 3-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl]propyl methanesulfonate to give the title compound as a pale yellow oil (2.44g).

LC/MS: m/z 419 [MH]⁺, RT 3.14min.

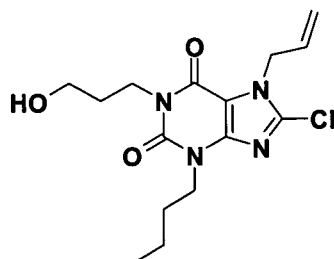
- 30 8-Chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 8-chloro-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione (3.0g, 11.1mmol) in DMF (20ml) was treated with caesium carbonate (3.7g, 11.4mmol) and 3-bromo-1-propanol (1.6g, 11.5mmol). The mixture was heated at 60°C for 4h and then cooled and evaporated. The residue was partitioned between EtOAc (60ml) and saturated aqueous sodium bicarbonate (50ml). The aqueous phase was extracted with EtOAc (60ml), the combined organic phases were dried (MgSO₄), filtered and evaporated. The product was purified using the Companion™ system and a gradient elution from cyclohexane to EtOAc. Product containing fractions were combined and evaporated to give the title compound as a colourless oil (2.6g).

LC/MS: m/z 327 [MH]⁺, RT 2.62min.

3-Butyl-8-chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione



Prepared according to the method used for 8-chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione to give the title compound as a colourless oil (2.3g).

LC/MS: m/z 341 [MH]⁺, RT 2.85min.

Table 3

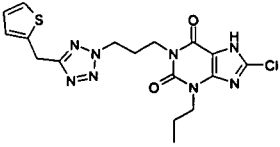
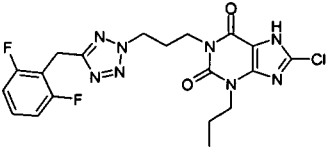
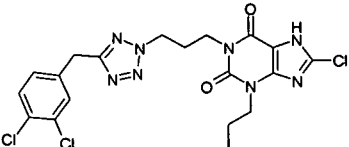
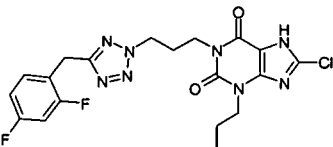
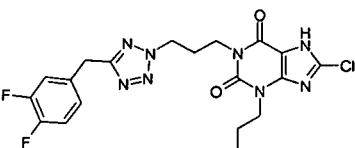
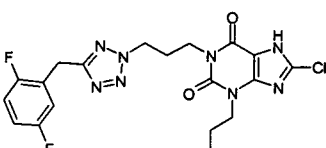
#	Structure	Name	Yield	LC/MS:
20		8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	12.4mg (14%)	m/z 447 [MH] ⁺ RT 3.14 min

21		8-chloro-3-propyl-1-[3-(5-((3-(trifluoromethyl)phenyl)methyl)-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	8.0mg (8%)	m/z 497 [MH] ⁺ RT 3.36 min
22		8-chloro-3-(4,4,4-trifluorobutyl)-1-[3-(5-((3-(trifluoromethyl)phenyl)methyl)-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	21.0mg (19%)	m/z 565 [MH] ⁺ RT 3.34 min
23		8-chloro-3-(4,4,4-trifluorobutyl)-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	17.0mg (15%)	m/z 551 [MH] ⁺ RT 3.27 min
24		8-chloro-1-(3-{5-[(3,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione	19.1mg (18%)	m/z 533 [MH] ⁺ RT 3.36 min
25		3-butyl-8-chloro-1-[3-(5-([2-fluoro-5-(trifluoromethyl)phenyl]methyl)-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	23.9mg (23%)	m/z 529 [MH] ⁺ RT 3.50 min
26		8-chloro-1-(3-{5-[(2-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione	19.8mg (19%)	m/z 515 [MH] ⁺ RT 3.31 min

27		8-chloro-1-(3-{5-[(2,6-dichlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	50.7mg (51%)	m/z 497 [MH] ⁺ RT 3.33 min
28		3-butyl-8-chloro-1-(3-{5-[(2-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	46.4mg (48%)	m/z 461 [MH] ⁺ RT 3.27 min
29		3-butyl-8-chloro-1-(3-{5-[(2-chlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	25.4mg (27%)	m/z 477 [MH] ⁺ RT 3.40 min
30		3-butyl-8-chloro-1-(3-{5-[(3-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	36.8mg (40%)	m/z 461 [MH] ⁺ RT 3.31 min
31		3-butyl-8-chloro-1-(3-{5-[(3-chlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	38.5mg (40%)	m/z 477 [MH] ⁺ RT 3.45 min
32		3-butyl-8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	31.6mg (34%)	m/z 461 [MH] ⁺ RT 3.31 min

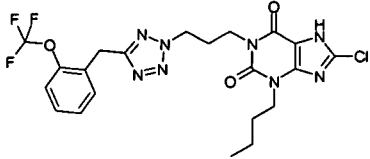
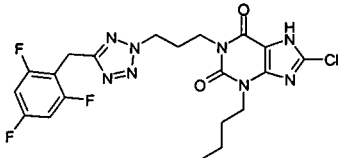
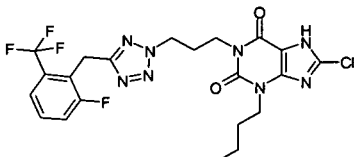
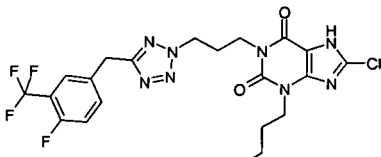
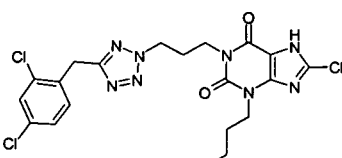
33		3-butyl-8-chloro-1-(3-{5-[(4-chlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	33.1mg (35%)	m/z 477 [MH] ⁺ RT 3.46 min
34		3-butyl-8-chloro-1-(3-{5-[(2-methylphenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	39.5mg (43%)	m/z 457 [MH] ⁺ RT 3.37 min
35		3-butyl-8-chloro-1-(3-{5-[(3-methylphenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	36.5mg (40%)	m/z 457 [MH] ⁺ RT 3.40 min
36		3-butyl-8-chloro-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	43.7mg (43%)	m/z 511 [MH] ⁺ RT 3.50 min
37		3-butyl-8-chloro-1-[3-(5-{[2-(methoxy)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	28.6mg (30%)	m/z 473 [MH] ⁺ RT 3.29 min
38		3-butyl-8-chloro-1-[3-(5-{[2-(thienyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	33.4mg (37%)	m/z 449 [MH] ⁺ RT 3.20 min

39		3-butyl-8-chloro-1-(3-{5-[(2,6-dichlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	36.4mg (36%)	m/z 511 [MH] ⁺ RT 3.49 min
40		8-chloro-1-(3-{5-[(2-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	5.6mg (6%)	m/z 447 [MH] ⁺ RT 3.10 min
41		8-chloro-1-(3-{5-[(3-chlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	5.9mg (6%)	m/z 463 [MH] ⁺ RT 3.29 min
42		8-chloro-1-(3-{5-[(4-chlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	14.9mg (16%)	m/z 463 [MH] ⁺ RT 3.30 min
43		8-chloro-1-(3-{5-[(3-methylphenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	17.5mg (20%)	m/z 443 [MH] ⁺ RT 3.23 min
44		8-chloro-1-(3-{5-[(2-methoxyphenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	14.5mg (16%)	m/z 459 [MH] ⁺ RT 3.12 min

45		8-chloro-3-propyl-1-(3-(5-(2-thienylmethyl)-2H-tetrazol-2-yl)propyl)-3,7-dihydro-1H-purine-2,6-dione	17.0mg (20%)	m/z 435 [MH] ⁺ RT 3.02 min
46		8-chloro-1-(3-(5-((2,6-difluorophenyl)methyl)-2H-tetrazol-2-yl)propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	18.4mg (20%)	m/z 465 [MH] ⁺ RT 3.11 min
47		8-chloro-1-(3-(5-((3,4-dichlorophenyl)methyl)-2H-tetrazol-2-yl)propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	19.4mg (20%)	m/z 497 [MH] ⁺ RT 3.44 min
48		8-chloro-1-(3-(5-((2,4-difluorophenyl)methyl)-2H-tetrazol-2-yl)propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	19.1mg (21%)	m/z 465 [MH] ⁺ RT 3.16 min
49		8-chloro-1-(3-(5-((3,4-difluorophenyl)methyl)-2H-tetrazol-2-yl)propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	21.5mg (23%)	m/z 465 [MH] ⁺ RT 3.19 min
50		8-chloro-1-(3-(5-((2,5-difluorophenyl)methyl)-2H-tetrazol-2-yl)propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	8.5mg (9%)	m/z 465 [MH] ⁺ RT 3.14 min

51		8-chloro-3-propyl-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	17.4mg (18%)	m/z 483 [MH] ⁺ RT 3.09 min
52		8-chloro-1-[3-(5-{[2-fluoro-6-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	22.3mg (22%)	m/z 515 [MH] ⁺ RT 3.28 min
53		8-chloro-1-[3-(5-{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	17.2mg (17%)	m/z 515 [MH] ⁺ RT 3.30 min
54		8-chloro-1-[3-(5-{[2-fluoro-5-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	18.2mg (18%)	m/z 515 [MH] ⁺ RT 3.34 min
55		3-butyl-8-chloro-1-(3-{5-[(2,6-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	18.2mg (19%)	m/z 479 [MH] ⁺ RT 3.29 min
56		3-butyl-8-chloro-1-(3-{5-[(3,4-dichlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	20.1mg (20%)	m/z 511 [MH] ⁺ RT 3.58 min

57		3-butyl-8-chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	19.3mg (20%)	m/z 479 [MH] ⁺ RT 3.33 min
58		3-butyl-8-chloro-1-(3-{5-[(2-chloro-6-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	18.9mg (19%)	m/z 495 [MH] ⁺ RT 3.33 min
59		3-butyl-8-chloro-1-(3-{5-[(3,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	21.7mg (23%)	m/z 479 [MH] ⁺ RT 3.33 min
60		3-butyl-8-chloro-1-[3-(5-{[2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	18.1mg (18%)	m/z 511 [MH] ⁺ RT 3.32 min
61		3-butyl-8-chloro-1-(3-{5-[(2,5-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	24.0mg (25%)	m/z 479 [MH] ⁺ RT 3.31 min
62		3-butyl-8-chloro-1-(3-{5-[(3,5-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	15.9mg (17%)	m/z 479 [MH] ⁺ RT 3.38 min

63		3-butyl-8-chloro-1-(3-((2-((trifluoromethyl)oxy)phenyl)methyl)-2H-tetrazol-2-yl)propyl)-3,7-dihydro-1H-purine-2,6-dione	32.8mg (31%)	m/z 527 [MH] ⁺ RT 3.51 min
64		3-butyl-8-chloro-1-(3-((5-((2,4,6-trifluorophenyl)methyl)-2H-tetrazol-2-yl)propyl)-3,7-dihydro-1H-purine-2,6-dione	20.7mg (21%)	m/z 497 [MH] ⁺ RT 3.35 min
65		3-butyl-8-chloro-1-(3-((5-((2-fluoro-6-(trifluoromethyl)phenyl)methyl)-2H-tetrazol-2-yl)propyl)-3,7-dihydro-1H-purine-2,6-dione	23.9mg (23%)	m/z 529 [MH] ⁺ RT 3.44 min
66		3-butyl-8-chloro-1-(3-((5-((4-fluoro-3-(trifluoromethyl)phenyl)methyl)-2H-tetrazol-2-yl)propyl)-3,7-dihydro-1H-purine-2,6-dione	13.9mg (13%)	m/z 529 [MH] ⁺ RT 3.53 min
67		3-butyl-8-chloro-1-(3-((5-((2,4-dichlorophenyl)methyl)-2H-tetrazol-2-yl)propyl)-3,7-dihydro-1H-purine-2,6-dione	17.5mg (17%)	m/z 511 [MH] ⁺ RT 3.63 min

NMR details for selected examples from Table 3:

Example 20: 8-Chloro-1-(3-((5-((4-fluorophenyl)methyl)-2H-tetrazol-2-yl)propyl)-3,7-dihydro-1H-purine-2,6-dione

5 ¹H NMR (CDCl₃) δ: 0.99 (t, 3H, J = 7.5 Hz), 1.80 (m, 2H), 2.46 (m, 2H), 4.06 (m, 2H), 4.18 (s, 2H), 4.25 (t, 2H, J = 7Hz), 4.70 (t, 2H, J = 7.5Hz), 6.96 (m, 2H), 7.26 (m, 2H), 13.15 (br s, 1H).

Example 23 : 8-Chloro-3-(4,4,4-trifluorobutyl)-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione : ^1H NMR (CDCl_3) δ : 2.07 (m, 2H), 2.21 (m, 2H), 2.44 (m, 2H), 4.18 (t, 2H, J = 7.1Hz), 4.20 (s, 2H), 4.24, (t, 2H, J = 6.8Hz), 4.68 (t, 2H, J = 7.3Hz), 6.67 (t, 2H, J = 8.1Hz), 13.04 (br s, 1H).

5

Example 24: ^1H NMR (CDCl_3): 2.03-2.10 (m, 2H), 2.16-2.28 (m, 2H), 2.43-2.50 (m, 2H), 4.16-4.19 (m, 2H), 4.17 (s, 2H), 4.24 (t, 2H, J=7.1Hz), 4.71(t, 2H, J=7.1Hz), 7.00-7.13 (m, 3H), 13.06 (bs, 1H).

10

Example 27: ^1H NMR (CDCl_3): 0.99 (t, 3H, J=7.5Hz), 1.76-1.86 (m, 2H), 2.40-2.47 (m, 2H), 4.05-4.09 (m, 2H), 4.23-4.26 (m, 2H), 4.54 (s, 2H), 4.65-4.69 (m, 2H), 7.14-7.18 (m, 1H), 7.31-7.33, (m, 2H), 13.18 (bs, 1H).

15

Example 28: ^1H NMR (CDCl_3): 0.97 (t, 3H, J=7.5Hz), 1.36-1.46 (m, 2H), 1.71-1.79 (m, 2H), 2.42-2.49 (m, 2H), 4.08-4.11 (m, 2H), 4.25 (s, 2H), 4.24-4.27 (m, 2H), 4.68-4.71 (m, 2H), 7.02-7.09 (m, 2H), 7.20-7.26, (m, 2H), 13.14 (bs, 1H).

20

Example 29: ^1H NMR (CDCl_3): 0.97 (t, 3H, J=7.5Hz), 1.36-1.45 (m, 2H), 1.71-1.79 (m, 2H), 2.42-2.49 (m, 2H), 4.09 (t, 2H, J=7.5Hz), 4.26 (t, 2H, J=7.5Hz), 4.34 (s, 2H), 4.70 (t, 2H, J=7.3Hz), 7.18-7.21 (m, 2H), 7.25-7.27, (m, 1H), 7.35-7.37, (m, 1H), 13.34 (bs, 1H).

25

Example 30: 3-Butyl-8-chloro-1-(3-{5-[(3-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione

^1H NMR (CDCl_3) δ : 0.97 (t, 3H, J = 7Hz), 1.40 (m, 2H), 1.75 (m, 2H), 2.46 (m, 2H), 4.10 (t, 2H, J = 7.5Hz), 4.21 (s, 2H), 4.26 (t, 2H, J = 6.5Hz), 4.70 (t, 2H, J = 7.5Hz), 6.90 (m, 1H), 6.99 (m, 1H), 7.07 (m, 1H), 7.25 (m, 1H), 13.25 (br s, 1H).

30

Example 31: ^1H NMR (CDCl_3): 0.99 (t, 3H, J=7.5Hz), 1.38-1.48 (m, 2H), 1.73-1.81 (m, 2H), 2.44-2.51 (m, 2H), 4.12 (t, 2H, J=7.5Hz), 4.20 (s, 2H), 4.27 (t, 2H, J=7.5Hz), 4.70 (t, 2H, J=7.3Hz), 6.95-7.00 (m, 2H), 7.26-7.30, (m, 2H), 13.35 (bs, 1H).

35

Example 32: 3-Butyl-8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione

^1H NMR (CDCl_3) δ : 0.99 (t, 3H, J = 7Hz), 1.43 (m, 2H), 1.77 (m, 2H), 2.48 (m, 2H), 4.12 (t, 2H, J = 7.5Hz), 4.20 (s, 2H), 4.27 (t, 2H, J = 7Hz), 4.72 (t, 2H, J = 7.5Hz), 6.98 (m, 2H), 7.27 (m, 2H), 13.35 (br s, 1H).

40

Example 33: 3-Butyl-8-chloro-1-(3-{5-[(4-chlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione

^1H NMR (CDCl_3) δ : 1.02 (t, 3H, J = 7.5Hz), 1.45 (m, 2H), 1.79 (m, 2H), 2.50 (m, 2H), 4.14 (t, 2H, J = 7.5Hz), 4.22 (s, 2H), 4.29 (t, 2H, J = 7Hz), 4.75 (t, 2H, J = 7.5Hz), 7.27 (s, 4H), 13.35 (br s, 1H).

45

Example 48: 8-Chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione

^1H NMR (CDCl_3) δ : 0.99 (t, 3H, J = 7.5 Hz), 1.80 (m, 2H), 2.45 (m, 2H), 4.06 (m, 2H), 4.20 (s, 2H), 4.25 (t, 2H, J = 7Hz), 4.70 (t, 2H, J = 7.5Hz), 6.80 (m, 2H), 7.23 (m, 1H).

50

Example 51: 8-Chloro-3-propyl-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione : ^1H NMR (CDCl_3) δ : 0.99 (t, 3H, $J = 7.3$ Hz), 1.80 (m, 2H), 1.98 (m, 2H), 2.01 (m, 2H), 4.20 (s, 2H), 4.25 (t, 2H, $J = 6.5$ Hz), 4.67 (t, 2H, $J = 7.3$ Hz), 6.68 (t, 2H, $J = 8.1$ Hz).

5

Example 52: ^1H NMR (CDCl_3): 0.99 (t, 3H, $J=7.3$ Hz), 1.76-1.85 (m, 2H), 2.39-2.46 (m, 2H), 4.05-4.08 (m, 2H), 4.24 (t, 2H, $J=7.1$ Hz), 4.39 (s, 2H), 4.64 (t, 2H, $J=7.1$ Hz), 7.29-7.32 (m, 1H), 7.38-7.44, (m, 1H), 7.49-7.51, (m, 1H), 13.17 (bs, 1H).

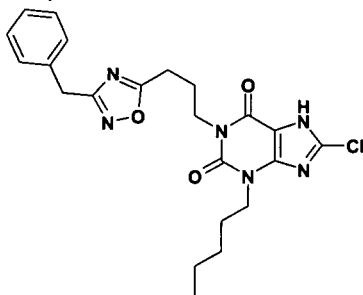
10 Example 59: ^1H NMR (CDCl_3): 0.99 (t, 3H, $J=7.6$ Hz), 1.36-1.45 (m, 2H), 1.71-1.79 (m, 2H), 2.42-2.49 (m, 2H), 4.09 (t, 2H, $J=7.5$ Hz), 4.17 (s, 2H), 4.24 (t, 2H, $J=7.5$ Hz), 4.71 (t, 2H, $J=7.3$ Hz), 7.00-7.14 (m, 3H), 13.07 (bs, 1H).

15 Example: 61: ^1H NMR (CDCl_3): 0.96 (t, 3H, $J=7.2$ Hz), 1.32-1.47 (m, 2H), 1.68-1.80 (m, 2H), 2.40-2.51 (m, 2H), 4.06-4.12 (m, 2H), 4.22 (s, 2H), 4.22-4.27 (m, 2H), 4.67-4.73 (m, 2H), 6.84-7.04 (m, 3H), 13.05 (bs, 1H).

20 Example 64: 3-Butyl-8-chloro-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione : ^1H NMR (CDCl_3) δ : 0.97 (t, 3H, $J = 7.3$ Hz), 1.41 (m, 2H), 1.75 (m, 2H), 2.44 (m, 2H), 4.10 (t, 2H, $J = 7.5$ Hz), 4.20 (s, 2H), 4.25 (t, 2H, $J = 6.5$ Hz), 4.67 (t, 2H, $J = 7.4$ Hz), 6.67 (t, 2H, $J = 8.0$ Hz), 13.25 (br s, 1H).

25 **Example 68 : 8-Chloro-3-pentyl-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione**

a) 8-Chloro-3-pentyl-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione



30 A solution of 3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-propanol (88mg, 0.4mmol) in THF (4ml) was treated with 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (100mg, 0.34mmol) and PPh_3 (115mg, 0.44mmol) under nitrogen. DBAD (101mg, 0.44mmol) was added in one portion and the reaction left to react for 5h. The mixture was degassed by applying a vacuum and then nitrogen was introduced.

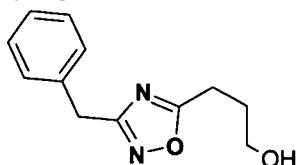
35 $\text{Pd}(\text{PPh}_3)_4$ (39mg, 0.034mmol) was added and the mixture degassed once more. Morpholine (294 μl , 3.4mmol) was added and the mixture was stirred under nitrogen for 3h. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer

was separated, washed with brine, dried (MgSO_4) and concentrated. The title compound was obtained as a white solid after purification by MDAP (64mg, 42%).

LC/MS: m/z 457 $[\text{MH}]^+$, RT 3.4min.

^1H NMR ($\text{DMSO}-d_6$) δ : 0.85 (t, 3H, $J = 7\text{Hz}$), 1.22-1.34 (m, 4H), 1.62 (m, 2H), 2.02 (m, 2H), 2.91 (t, 2H, $J = 7\text{Hz}$), 3.88 (t, 2H, $J = 7\text{Hz}$), 3.95-4.00 (m, 4H), 7.22-7.33 (m, 5H), 14.5 (br s, 1H).

b) 3-[3-(Phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-propanol

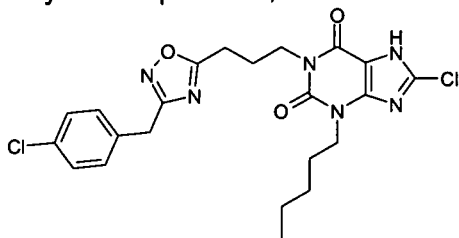


A mixture of γ -butyrolactone (223 μl , 2.9mmol), benzamidine oxime (480mg, 3.2mmol), 21% solution of NaOEt in EtOH (1.3ml) and EtOH (3ml) was heated in the microwave at 140°C for 10min. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried (MgSO_4) and concentrated. The title product was purified over silica using the CompanionTM system to give a pale yellow oil (143mg, 23%).

LC/MS: m/z 219 $[\text{MH}]^+$, RT 2.4min.

Example 69 : 8-Chloro-1-(3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione

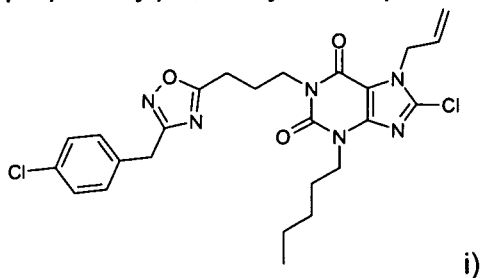
a) 8-Chloro-1-(3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione



A solution of 8-chloro-1-(3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (0.18g, 0.34mmol) in DMF (5ml) was degassed by sequential evacuation of the flask and admission of nitrogen (x3) and morpholine (0.5ml, 5.8mmol), and $\text{Pd}(\text{PPh}_3)_4$ (80mg, 0.068mmol) added. The solution was stirred for 72h then concentrated and the residues loaded onto an aminopropyl SPE (10g) with MeOH. Elution with MeOH followed by 5% AcOH/MeOH provided the title compound as a pale yellow solid, which was washed with ether to yield a white solid (0.053g, 32%).

LC/MS: m/z 491 $[\text{MH}]^+$, RT 3.69min

b) 8-Chloro-1-(3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



5 i) A mixture of γ -butyrolactone (8ml, 104mmol), 4-chlorobenzamidine oxime (3.0g, 16.25mmol), 30% solution of NaOMe in MeOH (5ml) and MeOH (80ml) was refluxed for 30h, cooled and concentrated. The residues were purified by flash chromatography over silica eluting with DCM/EtOH/0.88 aq ammonia (200:8:1) to provide a yellow oil (13g). This material was dissolved in DCM (150ml) and washed with 2M sodium
10 hydroxide (100ml) and the organics separated, dried and concentrated to yield 3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}-1-propanol as a viscous oil (3.95g, 96%) which was used in the next step.

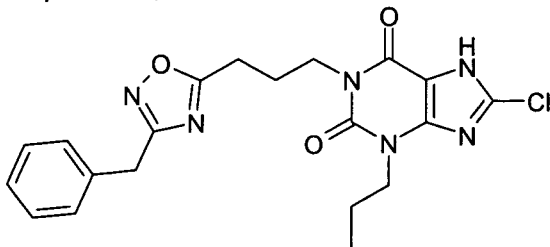
15 ii) To a solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.10g, 0.34mmol), 3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}-1-propanol (0.086g, 0.34mmol) and triphenylphosphine (0.186g, 0.69mmol) in THF (5ml) was added dibenzylazodicarboxylate (0.204g, 0.68mmol) and the solution stirred for 18h. The solution was then concentrated and the residues chromatographed over silica (20g, SPE) eluting with DCM initially then DCM/Et₂O mixtures to yield the title
20 compound contaminated with dibenzylazodicarboxylate by-products (0.18g). Material used crude in deprotection step.

LC/MS: m/z 531 [MH]⁺, RT 3.83min.

25

Example 70 : 8-Chloro-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione

30 a) 8-Chloro-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione

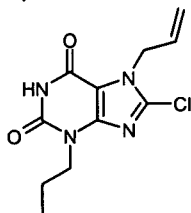


A solution of 8-chloro-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione (200mg, 0.74mmol) in THF (4ml) was treated with 3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-propanol (195mg, 0.89mmol) and PPh₃ (254mg, 0.96mmol). DBAD (223mg, 0.96mmol) was added in one portion and the mixture was left to stir at rt under nitrogen for 18h. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried (MgSO₄) and concentrated. The crude product was purified by a silica SPE column using a 0-70% cyclohexane/EtOAc gradient. The product fractions were combined, concentrated and further purified by a silica SPE column using a 0-60% cyclohexane/EtOAc gradient. The product fractions were combined and concentrated then dissolved in anhydrous THF (4ml). The solution was degassed by high vacuum then Pd(PPh₃)₄ (86mg, 0.074mmol) and morpholine (644μl, 7.4mmol) were added and the mixture left to stir at rt under nitrogen for 1 day. The mixture was partitioned between EtOAc and HCl (aq). The organic layer was separated, washed with brine, dried (MgSO₄) and concentrated by high vacuum. The crude product was purified by an aminopropyl SPE using MeOH to load the compound onto the column and wash through the impurities then a 2-4% AcOH/MeOH gradient to elute the product. The product fractions were combined and concentrated by high vacuum to leave the title compound as a white solid (74mg, 23%).

LC/MS: *m/z* 429 [MH]⁺, RT 3.14min.

¹H NMR; (DMSO-*d*₆) δ: 0.87 (t, 3H, *J* = 7.5 Hz), 1.65 (m, 2H), 2.02 (m, 2H), 2.91 (t, 2H, *J* = 7.5Hz), 3.86 (t, 2H, *J* = 7Hz), 3.97 (s,t overlapping, 4H), 7.27 (m, 5H) 14.46 (s, 1H).

b) 8-Chloro-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione

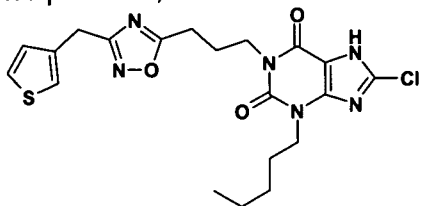


A mixture of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.5g, 6.6mmol), 1-iodopropane (1.2g, 6.9mmol) and sodium carbonate (0.9g, 8.5mmol) in DMF (40ml) was heated at 50°C for 18h. The reaction mixture was concentrated *in vacuo* and the residue treated with water (60ml) and extracted with EtOAc (3x 80ml). The combined organic extracts were dried (MgSO₄) filtered and evaporated. The residue was triturated with ether/cyclohexane, the solid was filtered off and dried to afford the title compound (0.82g, 46%).

LC/MS: *m/z* 269 [MH]⁺.

Example 71: 8-Chloro-3-pentyl-1-{3-[3-(3-thienylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

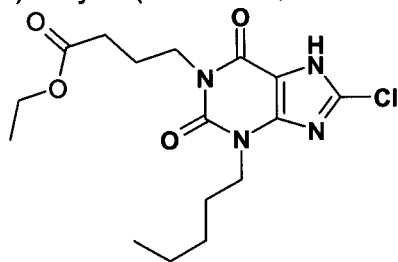
a) 8-Chloro-3-pentyl-1-{3-[3-(3-thienylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



A mixture of ethyl 4-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (70mg, 0.19mmol), *N*-hydroxy-2-(3-thienyl)ethanimidamide (36mg, 0.23mmol), 21% solution of NaOEt in EtOH (78μL, 0.21mmol) and EtOH (1.5ml) was heated in the microwave at 140°C for 10min. After cooling the reaction was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated and the aqueous layer extracted again with EtOAc. The combined extracts were concentrated and purified by MDAP. The title compound was freeze dried from 1,4-dioxane to give a white solid (27mg, 31%).

LC/MS: *m/z* 463 [MH]⁺, RT 3.4min.

b) Ethyl 4-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate

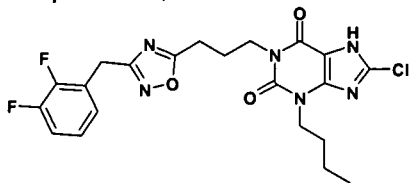


A solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (3.0g, 10.1mmol) in anhydrous DMF (35ml) was treated with Cs₂CO₃ (3.6g, 11.1mmol) and ethyl 4-bromobutyrate (1.6ml, 11.1mmol). The mixture was stirred at rt for 18h then degassed under a gentle vacuum, then nitrogen introduced. This was repeated twice. Pd(PPh₃)₄ (1.17g, 1.0mmol) was added and the mixture degassed once more. Morpholine (8.8ml, 101mmol) was added and left to stir for 3 h at rt. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried (MgSO₄) and concentrated, giving a yellow solid (5.16g). The residue was taken up in MeOH and divided into two equal portions, and then each passed down an aminopropyl SPE (20g), eluting with MeOH followed by 5% AcOH/MeOH. The product fractions were combined and concentrated giving the title compound as a near white solid (3.01g, 80%).

LC/MS: *m/z* 371 [MH]⁺, RT 3.2min.

Example 72 : 3-Butyl-8-chloro-1-{3-[3-(2,3-difluorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

a) 3-Butyl-8-chloro-1-{3-[3-(2,3-difluorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

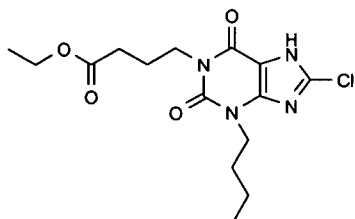


5 2,3-Difluorophenylacetonitrile (23mg, 0.15mmol) was dissolved in EtOH (1ml). Hydroxylamine hydrochloride (14mg, 0.20mmol) was added, followed by water (0.5ml) and potassium carbonate (41mg, 0.3mmol). The mixture was heated at reflux overnight and then cooled and partitioned between EtOAc and brine. The organic phase was evaporated and the crude amidoxime thus obtained was dissolved in EtOH (1ml). Ethyl
10 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (43mg, 0.12mmol) and 21% by wt. ethanolic sodium ethoxide ((0.067ml, 0.18mmol) was added and the mixture heated in the microwave reactor at 140°C for 10min. The mixture was partitioned between EtOAc and 2M HCl, the organic phase evaporated and the product purified by MDAP to provide the title compound as a solid (13mg).

15 LC/MS: m/z 479 $[MH]^+$, RT 3.52min.

1H NMR (MeOH- d_4) δ : 0.96 (t, 3H, J = 7Hz), 1.34-1.45 (m, 2H), 1.65-1.75 (m, 2H), 2.13-2.22 (m, 2H), 2.97 (t, 2H, J = 7Hz), 4.00 (t, 2H, J = 7Hz), 4.05 (s, 2H), 4.12 (t, 2H, J = 7Hz), 7.03-7.25 (m, 3H).

20 b) Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate



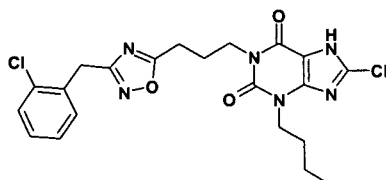
To 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (6.0g, 21.24mmol) in dry DMF (100ml) was added Cs_2CO_3 (7.62g, 23.36mmol) followed by
25 ethyl 4-bromobutyrate (4.556g, 23.36mmol). The mixture was heated at 55°C for 18h and allowed to cool then degassed by repeatedly evacuating and readmitting nitrogen. Morpholine (14.9g, 171mmol) was added followed by tetrakis(triphenylphosphine)palladium(0) (4.0g, 3.46mmol) and the mixture was stirred for 4h. EtOAc (300ml) and 2M HCl (150ml) and water (100ml) were added and the
30 organic phase separated, washed with brine (3 x 100ml) and filtered. The filtrate was dried (Na_2SO_4) and evaporated. The crude product (10g) was purified by aminopropyl SPE (3 x 20g), loading in THF/MeOH (1:1), washing with THF/MeOH (1:1) and neat MeOH and eluting the product with DCM/MeOH (1:1) containing 5% added AcOH to afford the title compound (5.08g).

LC/MS: m/z 357 [MH]⁺, RT 3.06min.

¹H NMR (d⁴ MeOH) 0.96 (3H, t, J = 7Hz), 1.33-1.42 (2H, m), 1.64-1.74 (2H, m), 2.12-2.21 (2H, m), 2.95 (2H, t, J = 8Hz), 3.99 (2H, t, J = 7Hz), 4.03 (2H, s), 4.11 (2H, t, J = 7Hz), 7.03-7.21 (3H, m).

5

Example 73 : 3-Butyl-8-chloro-1-{3-[3-(2-chlorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione



10

Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butanoate (53mg, 0.15mmol) and (1Z)-2-(2-chlorophenyl)-N-hydroxyethanimidamide (30mg, 0.18mmol; Entry 1, table 7) were heated in EtOH (0.75ml) with 21% ethanolic sodium ethoxide (0.083ml, 0.22mmol) at 140°C for 10min. The mixture was then partitioned between EtOAc and 2M HCl and the organic phase evaporated. The product was purified by MDAP to yield the title compound as a solid (34.8mg).

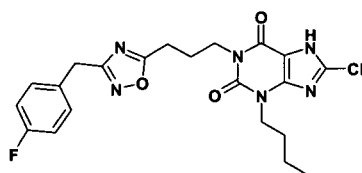
15

LC/MS: m/z 477 [MH]⁺, RT 3.59min.

¹H NMR (d⁶ DMSO) 0.89 (3H, t, J = 8Hz), 1.24-1.34 (2H, m), 1.56-1.65 (2H, m), 1.98-2.07 (2H, m), 2.92 (2H, t, J = 7Hz), 3.89 (2H, t, J = 7Hz), 3.98 (2H, t, J = 7Hz), 4.09 (2H, s), 7.28-7.48 (4H, m).

20

Example 74 : 3-Butyl-8-chloro-1-{3-[3-(4-fluorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione



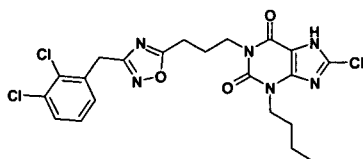
25

Starting from (1Z)-2-(4-fluorophenyl)-N-hydroxyethanimidamide (28mg, 0.18mmol; Entry 2, Table 7) was similarly obtained the title compound as a solid (10.0mg).

LC/MS: m/z 461 [MH]⁺, RT 3.49min.

30

Example 75 : 3-Butyl-8-chloro-1-{3-[3-(2,3-dichlorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione



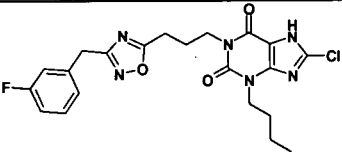
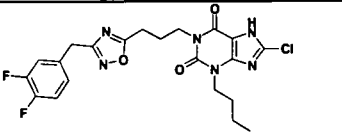
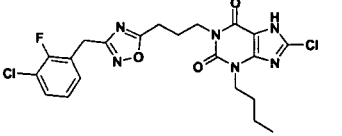
Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (53mg, 0.15mmol) and (1*Z*)-2-(2,3-dichlorophenyl)-*N*-hydroxyethanimidamide (36mg, 0.165mmol; Entry 3, Table 7) and 21% ethanolic sodium ethoxide (0.083ml, 0.22mmol) were heated together in EtOH (0.75ml) in the microwave reactor at 140°C for 10min.

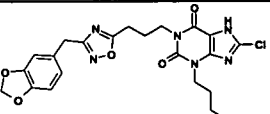
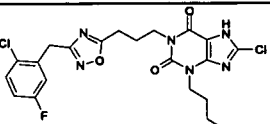
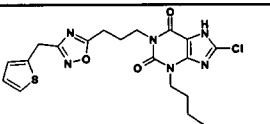
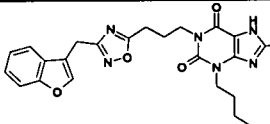
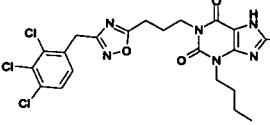
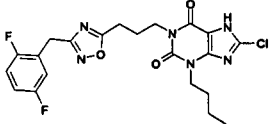
- 5 The mixture was then partitioned between EtOAc and 2M HCl, the organic phase separated, evaporated and the product purified by MDAP to give the title compound as a solid (42.1mg).

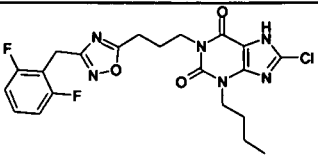
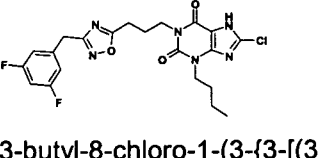
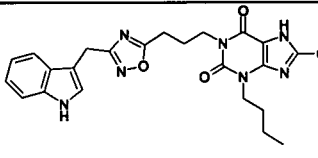
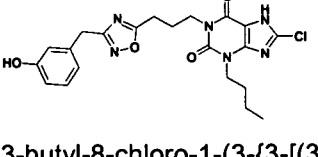
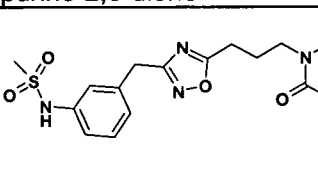
LC/MS: *m/z* 511, 513, 515 (isotopes) [MH]⁺, RT 3.66min.

- 10 The following compounds (Table 4) were prepared using a method analogous to that for Example 75, using the appropriate amidoxime, (with the exceptions that for Example 87 (Table 4) during workup the pH was adjusted to 5 prior to extraction with EtOAc; and in the case of Example 88 (Table 4) the crude product was stirred for 18h with EtOH (1ml) and 2M NaOH (0.5ml) and Example 89 (Table 4) was stirred for 18h with EtOH (0.75ml) and 2M NaOH (0.5ml) prior to repeat workup and purification by MDAP).

Table 4

Example	Structure	Amidoxime (see table 7)	Wt of amidoxime Mg	Yield mg	LC/MS :
76	 3-butyl-8-chloro-1-{3-[3-(3-fluorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1<i>H</i>-purine-2,6-dione	4	28	32.4	<i>m/z</i> 461 [MH] ⁺ RT 3.41 min
77	 3-butyl-8-chloro-1-{3-[3-(3,4-difluorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1<i>H</i>-purine-2,6-dione	5	31	28.3	<i>m/z</i> 479 [MH] ⁺ RT 3.46 min
78	 3-butyl-8-chloro-1-{3-[3-(3-chloro-2-fluorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1<i>H</i>-purine-2,6-dione	6	33	32.3	<i>m/z</i> 495 [MH] ⁺ RT 3.55 min

	yl}propyl}-3,7-dihydro-1 <i>H</i> -purine-2,6-dione				
79	 1-{3-[3-(1,3-benzodioxol-5-ylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3-butyl-8-chloro-3,7-dihydro-1<i>H</i>-purine-2,6-dione	10	32	30.5	m/z 487 [MH] ⁺ RT 3.27 min
80	 3-butyl-8-chloro-1-(3-{3-[(2-chloro-5-fluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1<i>H</i>-purine-2,6-dione	19	33	26.2	m/z 495 [MH] ⁺ RT 3.47 min
81	 3-butyl-8-chloro-1-{3-[3-(2-thienylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1<i>H</i>-purine-2,6-dione	21	26	33.4	m/z 449 [MH] ⁺ RT 3.23 min
82	 1-{3-[3-(1-benzofuran-3-ylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3-butyl-8-chloro-3,7-dihydro-1<i>H</i>-purine-2,6-dione	22	31	27.3	m/z 483 [MH] ⁺ RT 3.47 min
83	 3-butyl-8-chloro-1-(3-{3-[(2,3,4-trichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1<i>H</i>-purine-2,6-dione	15	42	29.8	m/z 545 [MH] ⁺ RT 3.79 min
84	 3-butyl-8-chloro-1-(3-{3-[(2,5-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1<i>H</i>-purine-2,6-dione	16	31	34.8	m/z 479 [MH] ⁺ RT 3.35 min

	dione				
85	 3-butyl-8-chloro-1-(3-{3-[(2,6-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	17	31	38.2	m/z 479 [MH] ⁺ RT 3.31 min
86	 3-butyl-8-chloro-1-(3-{3-[(3,5-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	18	31	35.4	m/z 479 [MH] ⁺ RT 3.39 min
87	 3-butyl-8-chloro-1-(3-{3-[(1H-indol-3-yl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	20	31	16.1	m/z 482 [MH] ⁺ RT 3.31 min
88	 3-butyl-8-chloro-1-(3-{3-[(3-hydroxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	7	28	10	m/z 459 [MH] ⁺ RT 3.07 min
89	 N-[3-({5-[3-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-1,2,4-oxadiazol-3-yl}methyl)phenyl]methanesulfonamide	25	40	28.4	m/z 536 [MH] ⁺ RT 3.03 min

NMR details for selected examples from Table 4:

Example 76: 3-butyl-8-chloro-1-{3-[3-(3-fluorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

¹H NMR (DMSO-*d*₆) δ: 0.90 (t, 3H, J = 7 Hz), 1.25-1.36 (m, 2H), 1.56-1.67 (m, 2H), 2.0-2.1 (m, 2H), 2.94 (t, 2H, J = 7 Hz), 3.90 (t, 2H, J = 7 Hz), 3.98 (t, 2H, J = 7 Hz), 4.02 (s, 2H), 7.05-7.15 (m, 3H), 7.32-7.40 (m, 1H).

Example 77: 3-Butyl-8-chloro-1-{3-[3-(3,4-difluorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

¹H NMR (DMSO-*d*₆) δ: 0.89 (t, 3H, J = 7.5 Hz), 1.25-1.34 (m, 2H), 1.56-1.65 (m, 2H), 1.99-2.07 (m, 2H), 2.92 (t, 2H, J = 7 Hz), 3.89 (t, 2H, J = 7 Hz), 3.98 (t, 2H, J = 7 Hz), 4.02 (s, 2H), 7.10-7.15 (m, 1H), 7.32-7.39 (m, 2H), 14.45 (br s, 1H).

Example 79: 1-{3-[3-(1,3-benzodioxol-5-ylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione

¹H NMR (DMSO-*d*₆) δ: 0.90 (t, 3H, J = 7 Hz), 1.25-1.36 (m, 2H), 1.58-1.68 (m, 2H), 1.98-2.09 (m, 2H), 2.92 (t, 2H, J = 7 Hz), 3.88-3.95 (m, 4H), 3.99 (t, 2H, J = 7 Hz), 5.98 (s, 2H), 6.70-6.86 (m, 3H).

Example 87: 3-butyl-8-chloro-1-{3-[3-(1*H*-indol-3-ylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

¹H NMR (DMSO-*d*₆) δ: 0.89 (t, 3H, J = 7 Hz), 1.23-1.36 (m, 2H), 1.56-1.67 (m, 2H), 1.96-2.08 (m, 2H), 2.90 (t, 2H, J = 7 Hz), 3.90 (t, 2H, J = 7 Hz), 3.99 (t, 2H, J = 7 Hz), 4.04 (s, 2H), 6.92-7.50 (m, 5H), 10.95 (s, 1H).

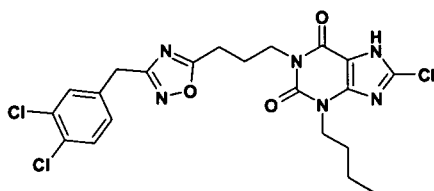
Example 88: 3-butyl-8-chloro-1-(3-{3-[(3-hydroxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione

¹H NMR (DMSO-*d*₆) δ: 0.90 (t, 3H, J = 7 Hz), 1.25-1.38 (m, 2H), 1.57-1.68 (m, 2H), 1.96-2.07 (m, 2H), 2.92 (t, 2H, J = 7 Hz), 3.86 (s, 2H), 3.89 (t, 2H, J = 7 Hz), 3.99 (t, 2H, J = 7 Hz), 6.58-6.68 (m, 3H), 7.08 (m, 1H), 9.40 (s, 1H).

Example 89: *N*-[3-({5-[3-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]-1,2,4-oxadiazol-3-yl)methyl]phenyl]methanesulfonamide

¹H NMR (DMSO-*d*₆) δ: 0.89 (t, 3H, J = 7.5 Hz), 1.24-1.34 (m, 2H), 1.56-1.65 (m, 2H), 1.97-2.06 (m, 2H), 2.91 (t, 2H, J = 7.5 Hz), 2.97 (s, 3H), 3.90 (t, 2H, J = 7.5 Hz), 3.96 (s, 2H), 3.97 (t, 2H, J = 7 Hz), 6.96-6.99 (m, 1H), 7.06-7.13 (m, 2H), 7.26 (t, 1H, J = 8 Hz), 9.75 (s, 1H), 14.45 (br s, 1H).

Example 90: 3-Butyl-8-chloro-1-(3-{3-[(3,4-dichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione

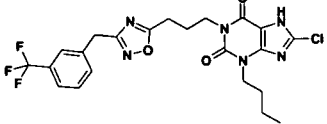
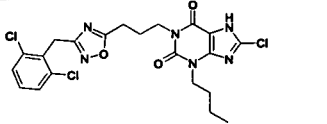
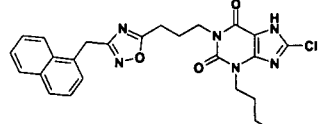


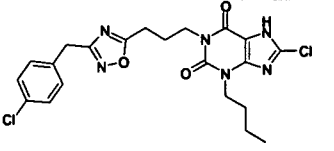
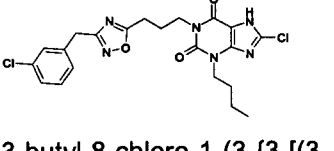
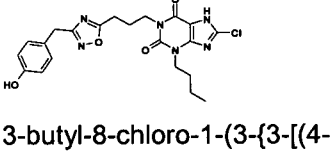
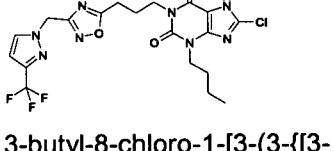
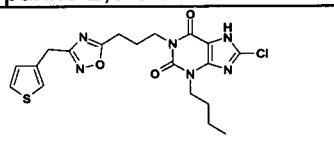
Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butanoate (71mg, 0.2mmol), (1Z)-2-(3,4-dichlorophenyl)-N-hydroxyethanimidamide (48mg, 0.22mmol) and 21% by wt. ethanolic sodium ethoxide (0.111ml, 0.3mmol) were heated together in EtOH (1ml) in the microwave reactor at 140°C for 10min. The mixture was then

- 5 partitioned between EtOAc and 2M HCl, the organic phase separated and evaporated, and the crude product was purified by MDAP to give the title compound as a solid (48.8mg).
LC/MS: m/z 511, 513 [MH]⁺, RT 3.65min.

- 10 The following compounds (Table 5) were prepared using a method analogous to that for Example 90, using the appropriate amidoxime (with the exception that for Example 91, 0.185ml, (0.5mmol) of 21% sodium ethoxide was added in order to allow for the amidoximes being the hydrochloride salts).

15 Table 5

Example	Structure	Amidoxime	Wt of amidoxime mg	Yield mg	LC/MS:
91	 3-butyl-8-chloro-1-[3-(3-((3-(trifluoromethyl)phenyl)methyl)-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	(1Z)-N-hydroxy-2-[3-(trifluoromethyl)phenyl]ethanimidamide hydrochloride	56	46.5	m/z 511 [MH] ⁺ RT 3.63 min
92	 3-butyl-8-chloro-1-(3-(3-((2,6-dichlorophenyl)methyl)-1,2,4-oxadiazol-5-yl)propyl)-3,7-dihydro-1H-purine-2,6-dione	(1Z)-2-(2,6-dichlorophenyl)-N-hydroxyethanimidamide	48	53.8	m/z 511 [MH] ⁺ RT 3.64 min
93	 3-butyl-8-chloro-1-(3-(3-(1-naphthalenylmethyl)-1,2,4-oxadiazol-5-yl)propyl)-3,7-dihydro-1H-purine-2,6-dione	(1Z)-N-hydroxy-2-(1-naphthalenyl)ethanimidamide	44	48.6	m/z 493 [MH] ⁺ RT 3.67 min

94	 3-butyl-8-chloro-1-(3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	(1Z)-2-(4-chlorophenyl)-N-hydroxyethanimidamide	41	35.6	m/z 477 [MH] ⁺ RT 3.60 min
95	 3-butyl-8-chloro-1-(3-{3-[(3-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	(1Z)-2-(3-chlorophenyl)-N-hydroxyethanimidamide	41	39.4	m/z 477 [MH] ⁺ RT 3.64 min
96	 3-butyl-8-chloro-1-(3-{3-[(4-hydroxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	(1Z)-N-hydroxy-2-(4-hydroxyphenyl)ethanimidamide	36	53.5	m/z 459 [MH] ⁺ RT 3.08 min
97	 3-butyl-8-chloro-1-[3-(3-{[3-(trifluoromethyl)-1H-pyrazol-1-yl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	(1Z)-N-hydroxy-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]ethanimidamide	46	58.1	m/z 501 [MH] ⁺ RT 3.33 min
98	 3-butyl-8-chloro-1-(3-{3-[(3-thienyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	(1Z)-N-hydroxy-2-(3-thienyl)ethanimidamide	34	32.6	m/z 449 [MH] ⁺ RT 3.31 min

NMR details for selected examples from Table 5

Example 91: ¹H NMR (d⁶ DMSO) 0.88 (3H, t, J = 7Hz), 1.24-1.33 (2H, m), 1.56-1.65 (2H, m), 1.98-2.06 (2H, m), 2.92 (2H, t, J = 7Hz), 3.89 (2H, t, J = 7Hz), 3.97 (2H, t, J = 7Hz), 4.14 (2H, s), 7.52-7.70 (4H, m).

Example 94: 3-butyl-8-chloro-1-(3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione

¹H NMR (DMSO-d₆) δ: 0.89 (t, 3H, J = 7Hz), 1.23-1.37 (m, 2H), 1.55-1.67 (m, 2H), 1.97-2.09 (m, 2H), 2.90 (t, 2H, J = 7Hz), 3.88 (t, 2H, J = 7Hz), 3.97 (t, 2H, J = 7Hz), 4.00 (s, 2H), 7.27-7.40 (m, 4H).

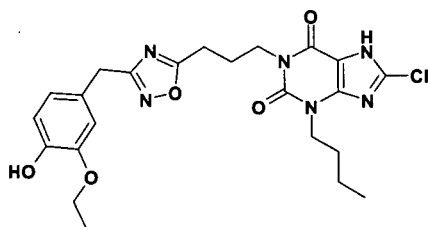
Example 96: 3-butyl-8-chloro-1-(3-{3-[(4-hydroxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione

¹H NMR (DMSO-d₆) δ: 0.90 (t, 3H, J = 7Hz), 1.23-1.37 (m, 2H), 1.57-1.68 (m, 2H), 1.96-2.08 (m, 2H), 2.90 (t, 2H, J = 7Hz), 3.82 (s, 2H), 3.90 (t, 2H, J = 7Hz), 3.98 (t, 2H, J = 7Hz), 6.68 (d, 2H, J = 9Hz), 7.04 (d, 2H, J = 9Hz), 9.32 (s, 1H).

Example 97: 3-butyl-8-chloro-1-[3-(3-{3-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl]-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione

¹H NMR (DMSO-d₆) δ: 0.90 (t, 3H, J = 7Hz), 1.23-1.36 (m, 2H), 1.57-1.69 (m, 2H), 1.95-2.08 (m, 2H), 2.95 (t, 2H, J = 7Hz), 3.91 (t, 2H, J = 7Hz), 3.97 (t, 2H, J = 7Hz), 5.62 (s, 2H), 6.79 (s, 1H), 8.10 (s, 1H).

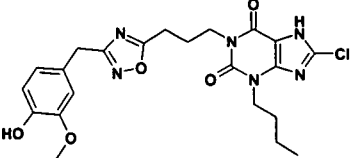
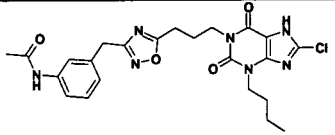
Example 99 : 3-Butyl-8-chloro-1-[3-(3-{[3-(ethyloxy)-4-hydroxyphenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione



Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (53mg, 0.15mmol) and (1*Z*)-2-[3-(ethyloxy)-4-hydroxyphenyl]-*N*-hydroxyethanimidamide (35mg, 0.165mmol; entry 11, Table 7) were mixed in EtOH (0.75ml). Ethanolic sodium ethoxide (21% by wt., 0.083ml, 0.22mmol) was added and the mixture was heated in the microwave at 140°C for 10min. A further 0.055ml (0.15mmol) of NaOEt solution was then added and the mixture heated for a further 10min period at 140°C. The mixture was partitioned between EtOAc and 2M HCl and the organic phase evaporated and purified by MDAP to give the title compound as a solid (29.6mg).
LC/MS: m/z 503 [MH]⁺, RT 3.15min.

The following compounds (Table 6) were prepared using a method analogous to that for Example 99, using the appropriate amidoxime (with the exception that for Example 100 (Table 6), the crude product after workup was stirred with EtOH (1ml) and 2M NaOH (0.5ml) overnight in order to hydrolyse residual starting ester, prior to repeat HCl workup and purification by MDAP).

Table 6

Example	Structure	Amidoxime (see table 7)	Wt of aldoxime mg	Yield mg	LC/MS:
100	 3-butyl-8-chloro-1-[3-(3-((4-hydroxy-3-methoxyphenyl)methyl)-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	12	32	19.3	m/z 489 [MH] ⁺ RT 2.98 min
101	 <i>N</i>-[3-((5-[3-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-1,2,4-oxadiazol-3-yl)methyl)phenyl]acetamide	14	34	23.6	m/z 500 [MH] ⁺ RT 2.94 min

NMR details for selected examples from Table 6

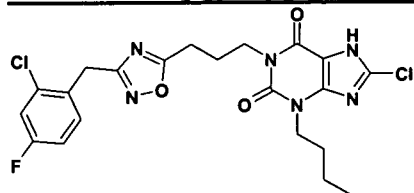
5

Example 101: *N*-[3-((5-[3-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-1,2,4-oxadiazol-3-yl)methyl)phenyl]acetamide

¹H NMR (DMSO-*d*₆) δ: 0.90 (t, 3H, J = 7Hz), 1.25-1.38 (m, 2H), 1.57-1.68 (m, 2H), 1.95-2.07 (m, 5H), 2.92 (t, 2H, J = 7Hz), 3.91 (t, 2H, J = 7Hz), 3.94 (s, 2H), 3.98 (m, 2H), 6.88-7.50 (m, 4H), 9.90 (s, 1H).

10

Example 102: 3-Butyl-8-chloro-1-(3-(3-((2-chloro-4-fluorophenyl)methyl)-1,2,4-oxadiazol-5-yl)propyl)-3,7-dihydro-1H-purine-2,6-dione

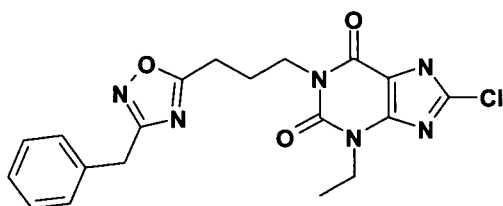


15 Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butanoate (100mg, 0.28mmol) and (1*Z*)-2-(2-chloro-4-fluorophenyl)-*N*-hydroxyethanimidamide (62.4mg, 0.308mmol) and 21% by wt. ethanolic sodium ethoxide (0.157ml, 0.42mmol) were heated together in a microwave reactor in EtOH (1.5ml) at 140°C for 10min. The

mixture was worked up by partitioning between EtOAc and 2M HCl. The organic phase was evaporated and purified by MDAP to afford the title compound as a solid (73mg). LC/MS: m/z 495 $[MH]^+$, RT 3.55min.

5 **Example 103 : 8-Chloro-3-ethyl-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione**

10 **a) 8-Chloro-3-ethyl-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione**

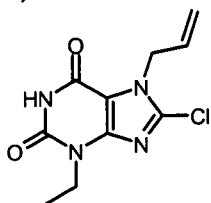


15 A solution of 8-chloro-3-ethyl-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (150mg, 0.59mmol) in anhydrous THF (4ml) was treated with 3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-propanol (154mg, 0.71mmol) and triphenylphosphine (200mg, 0.76mmol). DBAD (162mg, 0.71mmol) was added in one portion and the mixture was left to stir at rt, under nitrogen for 18h. The mixture was degassed by high vacuum then Pd(PPh₃)₄ (68mg, 0.059mmol) and morpholine (515μl, 5.9mmol) were added. The mixture was left to stir at rt, under nitrogen, for 3h. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried (MgSO₄) and concentrated by high vacuum. The crude material was purified by an aminopropyl SPE using MeOH to load the compound onto the column and wash through the impurities, then with 2% AcOH/MeOH to elute the compound. The UV active fractions were combined and concentrated by high vacuum. The product was further purified by MDAP. The product fractions were combined and concentrated to give the title compound as a white solid (61mg, 25%).

LC/MS: m/z 415 $[MH]^+$, RT 3.01min

30 ¹H NMR; (DMSO-d₆) δ : 1.19 (t, 3H, J = 7Hz), 2.93 (m, 2H), 2.91 (t, 2H, J = 7.5Hz), 3.96 (m, 6H), 7.27 (m, 5H) 14.46 (s, 1H).

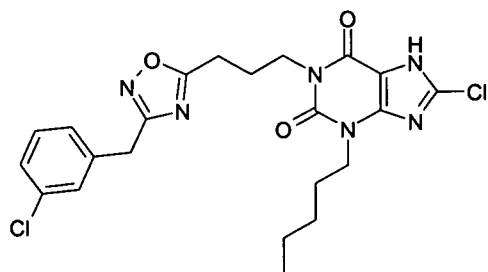
b) 8-Chloro-3-ethyl-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione



A solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (10g, 0.044mol) in anhydrous DMF (100ml) was treated with iodoethane (5.4ml, 0.068mol) and Na₂CO₃ (4.9g, 0.046mol). The reaction mixture was left to stir at rt under nitrogen for 2 days. Iodoethane (0.35ml, 0.0044mol) was added and the mixture was left to stir at rt for 1 day. The mixture was partitioned between EtOAc and 2M HCl. The organic layer was separated, washed sequentially with saturated sodium sulphite solution and brine, dried (MgSO₄) and concentrated. The crude solid was washed with Et₂O to give the title compound as a white solid (8.37g, 75%).

LC/MS: m/z 255 [MH]⁺, RT 2.35min.

Example 104 : 8-Chloro-1-(3-{3-[(3-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione

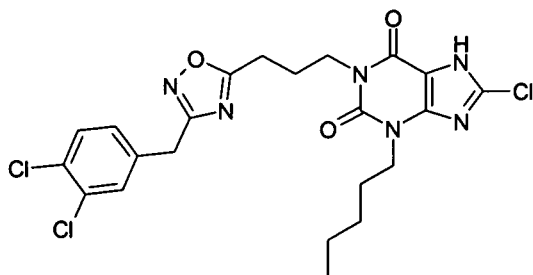


Ethyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (70mg, 0.19mmol) was dissolved in EtOH. The solution was treated with a 21% solution of NaOEt in EtOH (78μl, 0.21mmol) and (1*Z*)-2-(3-chlorophenyl)-*N*-hydroxyethanimidamide (38mg, 0.21mmol). The reaction was heated in the microwave at 140°C for 10min. The mixture was partitioned between EtOH and 2M HCl (aq). The organic layer was decanted off and concentrated. The crude product was purified on the MDAP. The product fractions were combined and concentrated to give the title compound as a white solid (46mg, 49%).

LC/MS: m/z 491 [MH]⁺, RT 3.64min.

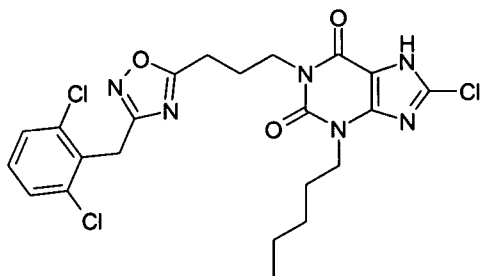
¹H NMR (DMSO-*d*₆) δ: 0.85 (t, 3H, J = 7Hz), 1.27 (m, 4H), 1.62 (m, 2H), 2.02 (m, 2H), 2.92 (t, 2H, J = 7.5Hz), 3.88 (t, 2H, J=7 Hz), 3.97 (t, 2H, J = 6.5Hz), 4.02 (s, 2H), 7.23 (d, 1H, J = 7Hz), 7.34 (m, 3H).

Example 105: 8-Chloro-1-(3-{3-[(3,4-dichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



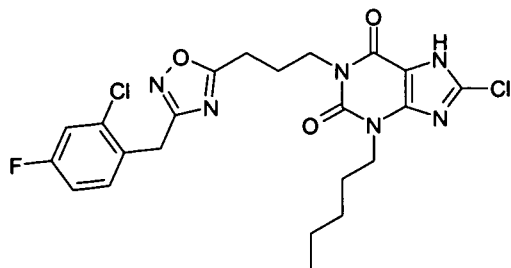
Ethyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (70mg, 0.19mmol) was dissolved in EtOH. The solution was treated with a 21% solution of NaOEt in EtOH (78μl, 0.21mmol) and (1*Z*)-2-(3,4-dichlorophenyl)-*N*-hydroxyethanimidamide (46mg, 0.21mmol). The reaction was heated in the microwave at 140°C for 10min. The mixture was partitioned between EtOH and 2M HCl (aq). The organic layer was decanted off and concentrated. The crude product was purified on the MDAP. The product fractions were combined and concentrated to give the title compound as a white solid (66mg, 66%).
LC/MS: *m/z* 527 [MH]⁺, RT 3.80min.

Example 106 : 8-Chloro-1-(3-{3-[(2,6-dichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



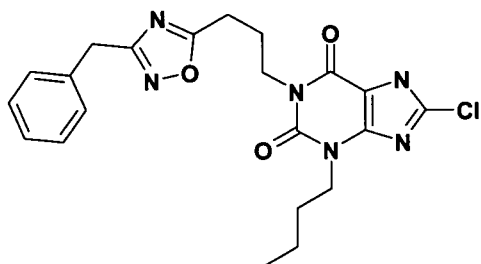
Ethyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (70mg, 0.19mmol) was dissolved in EtOH. The solution was treated with a 21% solution of NaOEt in EtOH (78μl, 0.21mmol) and (1*Z*)-2-(2,6-dichlorophenyl)-*N*-hydroxyethanimidamide (46mg, 0.21mmol). The reaction was heated in the microwave at 140°C for 10min. The mixture was partitioned between EtOH and 2M HCl (aq). The organic layer was decanted off and concentrated by nitrogen blowdown. The crude product was purified on the MDAP. The product fractions were combined and concentrated to give the title compound as a white solid (80mg, 80%).
LC/MS: *m/z* 526 [MH]⁺, RT 3.6 min.

Example 107 : 8-Chloro-1-(3-{3-[(2-chloro-4-fluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



Ethyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoate (70mg, 0.19mmol) was dissolved in EtOH. The solution was treated with a 21% solution of NaOEt in EtOH (78μl, 0.21mmol) and (1Z)-2-(2-chloro-4-fluorophenyl)-N-hydroxyethanimidamide (42mg, 0.21mmol). The reaction was heated in the microwave at 140°C for 10min. The mixture was partitioned between EtOH and 2M HCl (aq). The organic layer was decanted off and concentrated. The crude product was purified on the MDAP. The product fractions were combined and concentrated to give the title compound as a white solid (65mg, 67%).
 LC/MS: m/z 509 [MH]⁺, RT 3.63min.

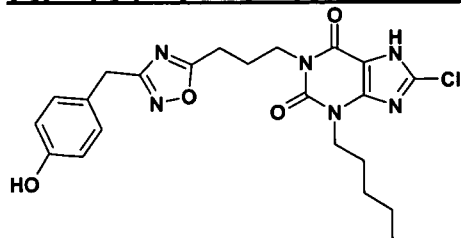
Example 108 : 3-Butyl-8-chloro-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione



A solution of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (205mg, 0.73mmol) in anhydrous THF (4ml) was treated with 3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-propanol (190mg, 0.87mmol) and PPh₃ (247mg, 0.94mmol). DBAD (217mg, 0.94mmol) was added in one portion and the mixture was stirred at rt under nitrogen for 18h. The mixture was degassed by high vacuum then Pd(PPh₃)₄ (84mg, 0.073mmol) and morpholine (636μl, 7.3mmol) were added. The mixture was stirred at rt under nitrogen for 3h. The mixture was partitioned between EtOAc and 2M HCl (aq) and the organic layer separated, washed with brine, dried (MgSO₄) and concentrated. The crude material was purified by an aminopropyl column using MeOH to load the compound onto the column and wash through the impurities, then with 2-4% AcOH/MeOH gradient to remove the compound from the column. Further purification was effected by MDAP to give the title compound as a white solid (75mg, 23%).
 LC/MS: m/z 443 [MH]⁺, RT 3.37min.

¹H NMR; (DMSO-d₆) δ: 0.89 (t, 3H, J = 7.5 Hz), 1.29 (m, 2H), 1.61 (m, 2H), 2.02 (m, 2H), 2.91 (t, 2H, J = 7.5Hz), 3.89 (t, 2H, J = 7Hz), 3.97 (m, 4H), 7.27 (m, 5H) 14.46 (s, 1H).

5 **Example 109: 8-Chloro-1-(3-{3-[(4-hydroxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione**

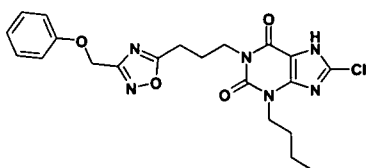


10 Ethyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoate (29mg, 0.078mmol) and (1Z)-N-hydroxy-2-(4-hydroxyphenyl)ethanimidamide (14mg, 0.084mmol) were heated in EtOH (1ml) with 21% ethanolic sodium ethoxide (0.043ml, 0.117mmol) under microwave irradiation at 140°C for 10min. The mixture was partitioned between EtOAc and 2M HCl and the organic phase evaporated. This material was stirred with EtOH (1ml) and 2M NaOH (0.5ml) for 18h, before being worked up again by partition between EtOAc and 2M HCl. Purification by MDAP
15 afforded the title compound (6.5mg).

LC/MS: m/z 473 [MH]⁺, RT 3.34min.

¹H NMR (MeOH-d₄) δ: 0.92 (t, 3H, J = 7Hz), 1.25-1.45 (m, 4H), 1.68-1.78 (m, 2H), 2.11-2.21 (m, 2H), 2.93 (t, 2H, J = 7Hz), 3.82 (s, 2H), 3.98 (t, 2H, J = 7Hz), 4.10 (t, 2H, J = 7Hz), 6.70 (d, 2H, J = 10Hz), 7.02 (d, 2H, J = 10Hz).

20 **Example 110: 3-Butyl-8-chloro-1-(3-{3-[(phenyloxy)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione**

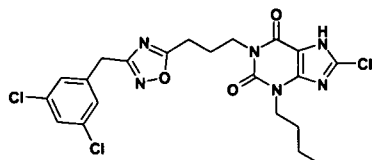


25 To ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butanoate (26mg, 0.073mmol) and (1Z)-N-hydroxy-2-(phenyloxy)ethanimidamide hydrochloride (16mg, 0.079mmol) in EtOH (1ml) was added 21%wt. ethanolic sodium ethoxide solution (0.068 ml, 0.183mmol) and the mixture was heated under microwave irradiation at 140°C for 10min. The mixture was partitioned between EtOAc and 2M
30 HCl, the organic phase dried (Na₂SO₄) evaporated and purified by MDAP to give title compound as a gum which solidified upon trituration with ether (5.9mg).

LC/MS: m/z 459 [MH]⁺, RT 3.39min.

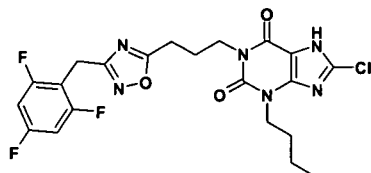
¹H NMR (DMSO-d₆) δ: 0.90 (t, 3H, J = 8Hz), 1.22-1.36 (m, 2H), 1.57-1.68 (m, 2H), 2.02-2.14 (m, 2H), 3.00 (t, 2H, J = 8Hz), 3.90 (t, 2H, J = 7Hz), 4.00 (t, 2H, J = 7Hz), 5.18 (s, 2H), 6.95-7.35 (m, 5H).

5 Example 111: 3-Butyl-8-chloro-1-(3-{3-[(3,5-dichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione



To ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butanoate (185mg, 0.52mmol) and (1Z)-2-(3,5-dichlorophenyl)-N-hydroxyethanimidamide (126mg, 0.58mmol; Entry 23, Table 7) in dry EtOH (2ml) was added 21%wt. ethanolic sodium ethoxide solution (0.29ml, 0.78mmol) and the mixture was heated by microwaves at 140°C for 10min. The reaction was worked up by partition between EtOAc and 2M HCl and evaporating the organic phase. Purification by MDAP afforded the title compound as a solid (135mg).
LC/MS: m/z 511 [MH]⁺, RT 3.71min.

20 Example 112: 3-Butyl-8-chloro-1-(3-{3-[(2,4,6-trifluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione



Similarly prepared starting from (1Z)-N-hydroxy-2-(2,4,6-trifluorophenyl)ethanimidamide (119mg, 0.58mmol; Entry 24, Table 7) in a yield of 135mg.

25 LC/MS: m/z 497 [MH]⁺, RT 3.39min.

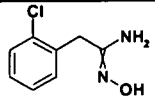
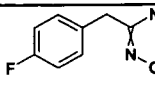
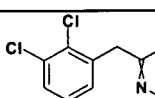
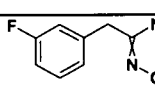
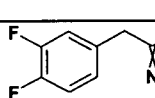
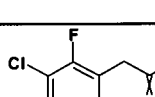
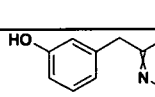
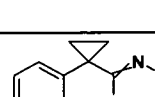
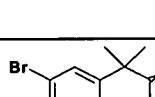
¹H NMR (DMSO-d₆) δ: 0.90 (t, 3H, J = 7Hz), 1.24-1.36 (m, 2H), 1.55-1.66 (m, 2H), 1.96-2.06 (m, 2H), 2.91 (t, 2H, J = 8Hz), 3.91 (t, 2H, J = 8 Hz), 3.94 – 4.02 (m, 4H), 7.18-7.28 (m, 2H).

30 Amidoximes:

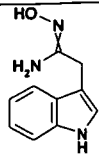
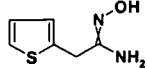
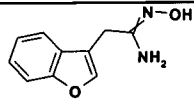
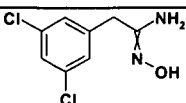
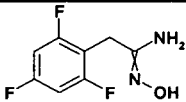
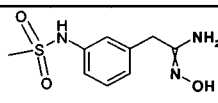
These are available by the methods detailed below and exemplified by analogues in Table 7.

35

Table 7 (Intermediates)

Entry	Structure	Name	Method	Yield mg	LC/MS:
1		(1Z)-2-(2-chlorophenyl)-N-hydroxyethanimidamide	G	38	m/z 185 [MH] ⁺ RT 1.04 min
2		(1Z)-2-(4-fluorophenyl)-N-hydroxyethanimidamide	G	42	m/z 169 [MH] ⁺ RT 0.72 min
3		(1Z)-2-(2,3-dichlorophenyl)-N-hydroxyethanimidamide	B	64	m/z 219 [MH] ⁺ RT 1.83 min
4		(1Z)-2-(3-fluorophenyl)-N-hydroxyethanimidamide	A	78	m/z 169 [MH] ⁺ RT 0.62 min
5		(1Z)-2-(3,4-difluorophenyl)-N-hydroxyethanimidamide	A	88	m/z 187 [MH] ⁺ RT 0.74min
6		(1Z)-2-(3-chloro-2-fluorophenyl)-N-hydroxyethanimidamide	A	92	m/z 203 [MH] ⁺ RT 1.40 min
7		(1Z)-N-hydroxy-2-(3-hydroxyphenyl)ethanimidamide	A	67	m/z 167 [MH] ⁺ RT 0.46 min
8		N-hydroxy-1-phenylcyclopropanecarboximide	C	75	m/z 177 [MH] ⁺ RT 1.06 min
9		(1Z)-2-(3-bromophenyl)-N-hydroxy-2-methylpropanimidamide	D	74	m/z 257 [MH] ⁺ RT 2.04 min

10		(1Z)-2-(1,3-benzodioxol-5-yl)- N-hydroxyethanimidamide	C	98	m/z 195 [MH] ⁺ RT 0.73 min
11		(1Z)-2-[3-(ethoxy)-4- hydroxyphenyl]-N- hydroxyethanimidamide	C	109	m/z 211 [MH] ⁺ RT 0.76 min
12		(1Z)-N-hydroxy-2-[4-hydroxy- 3- (methoxy)phenyl]ethanimida mide	C	98	m/z 197 [MH] ⁺ RT 0.50 min
13		(1Z)-N-hydroxy-2-(4- hydroxyphenyl)-2- methylpropanimidamide	D	66	m/z 195 [MH] ⁺ RT 0.85 min
14		N-{3-[(2Z)-2-(hydroxyamino)-2- iminoethyl]phenyl}acetamide	C	91	m/z 208 [MH] ⁺ RT 0.73 min
15		(1Z)-N-hydroxy-2-(2,3,4- trichlorophenyl)ethanimidami de	C	124	m/z 253 [MH] ⁺ RT 2.29 min
16		(1Z)-2-(2,5-difluorophenyl)-N- hydroxyethanimidamide	C	89	m/z 187 [MH] ⁺ RT 0.66 min
17		(1Z)-2-(2,6-difluorophenyl)-N- hydroxyethanimidamide	C	86	m/z 187 [MH] ⁺ RT 0.62 min
18		(1Z)-2-(3,5-difluorophenyl)-N- hydroxyethanimidamide	C	96	m/z 187 [MH] ⁺ RT 0.80 min
19		(1Z)-2-(2-chloro-5- fluorophenyl)-N- hydroxyethanimidamide	C	97	m/z 203 [MH] ⁺ RT 0.90 min

20		(1Z)-N-hydroxy-2-(1H-indol-3-yl)ethanimidamide	C	95	m/z 190 [MH] ⁺ RT 0.90 min
21		(1Z)-N-hydroxy-2-(2-thienyl)ethanimidamide	C	74	m/z 157 [MH] ⁺ RT 0.38 min
22		(1Z)-2-(1-benzofuran-3-yl)-N-hydroxyethanimidamide	C	87	m/z 191 [MH] ⁺ RT 1.46 min
23		(1Z)-2-(3,5-dichlorophenyl)-N-hydroxyethanimidamide	E	165	m/z 219 [MH] ⁺ RT 2.03 min
24		(1Z)-N-hydroxy-2-(2,4,6-trifluorophenyl)ethanimidamide	F	297	m/z 205 [MH] ⁺ RT 0.66 min
25		(1Z)-N-hydroxy-2-{3-[(methylsulfonyl)amino]phenyl}ethanimidamide	C	125	m/z 244 [MH] ⁺ RT 0.63 min

It should be noted that  as used herein represents a double bond of undefined geometry.

5 Method A

The corresponding nitrile (0.5mmol) was stirred in EtOH (1.5ml) with 50% aqueous hydroxylamine solution (0.08ml, 1.3mmol) and heated at 65°C for 4.5h. After cooling the crude reaction mixture was loaded onto an SCX SPE cartridge (2g) and washed with MeOH, then the amidoxime product was eluted with 2M ammonia in MeOH.

10

Method B

Similar to Method A except that the product crystallised out from the crude reaction mixture and was isolated by filtration instead of by SCX.

15 Method C

Similar to Method A except that the product was purified on a 5g SCX cartridge.

Method D

Similar to Method C except that the heating period was 18h.

Method E

- 5 Similar to Method C except that the scale was 0.753mmol of nitrile.

Method F

Similar to Method A except that the scale was 1.5mmol of nitrile and purification was on a 10g SCX cartridge.

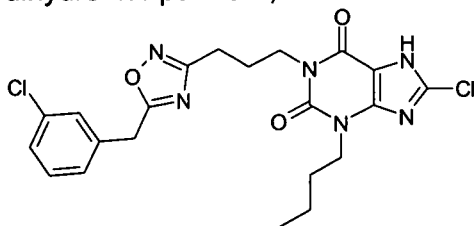
10

Method G

Similar to Method A except that the heating time was 2.75h and the scale was 0.25mmol of nitrile.

- 15 **Example 113: 3-Butyl-8-chloro-1-(3-{5-[(3-chlorophenyl)methyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione**

a) 3-Butyl-8-chloro-1-(3-{5-[(3-chlorophenyl)methyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione



20

(3-Chlorophenyl)acetic acid (0.1mmol), *N*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide hydrochloride (21mg, 0.11mmol) and 1*H*-1,2,3-benzotriazol-1-ol (15mg, 0.11mmol) were stirred in 1-methyl-2-pyrrolidinone (1ml). To this was added (1*Z*)-4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxybutanimidamide (34mg, 0.1mmol) and the mixture stirred at rt for 17h and then at 80°C for 24h. The reaction mixture was purified, without further modification, by preparative HPLC (auto prep) to give the title compound (13mg, 27%).

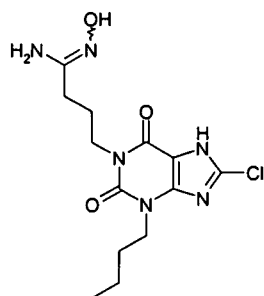
25

LC/MS: *m/z* 477, 479 [MH]⁺, RT 3.5min.

¹H NMR (CDCl₃) δ: 0.96 (t, 3H, *J* = 7Hz), 1.32-1.47 (m, 2H), 1.68-1.80 (m, 2H), 2.12-2.24 (m, 2H), 2.83 (t, 2H, *J* = 7.5Hz), 4.05-4.24 (m, 6H), 7.16-7.30 (m, 4H).

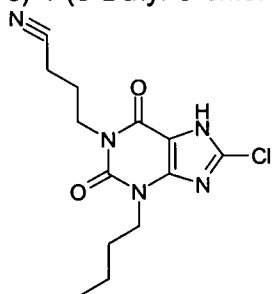
30

b) (1*Z*)-4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxybutanimidamide



4-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butanenitrile (1g, 0.0032mol) was stirred in EtOH (3.5ml) and water (1.8ml). Hydroxylamine hydrochloride (344mg, 0.0049mol) and potassium carbonate (652mg, 0.0049mol) were added and the mixture heated at 80°C for 3 days. After cooling the crude reaction mixture was evaporated. The crude product was dissolved in water, neutralised to pH7 with HCl, and loaded onto an OasisTM cartridge (2g). This was eluted with water to remove the salts and then with MeOH, to give the title compound (957mg, 86%).
LC/MS: m/z 343, 345 [MH]⁺, RT 2.04min.

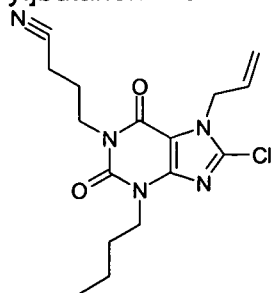
c) 4-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butanenitrile



4-[3-Butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1H-purin-1-yl]butanenitrile (2.1g, 6mmol) was stirred in a mixture of nitrogen degassed DCM (20ml) and AcOH (2ml). Tetrakis(triphenylphosphine)palladium (675mg, 0.6mmol) and phenyl silane (7.4ml, 60mmol) were added and the mixture stirred at rt for 2d. This was then evaporated and the residue triturated with a mixture of diethylether:cyclohexane (1:1) to afford the title compound (1.47g, 60%) as a white solid.

LC/MS: m/z 310 [MH]⁺, RT 2.66min.

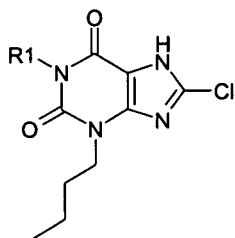
d) 4-[3-Butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1H-purin-1-yl]butanenitrile



3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2.0g, 0.0072mol) in dry MeCN (20ml) was added Cs₂CO₃ (4.68g, 0.0144mol) followed by bromobutyronitrile (1.38g, 0.0094mol). The mixture was heated at 80°C for 18h and then allowed to cool. The reaction mixture was evaporated and the crude product partitioned between EtOAc and HCl (2N). The organic phase was separated and washed with brine, dried (MgSO₄) and evaporated to give the crude product. This was purified by silica SPE (50g), eluting with cyclohexane:ethylacetate (2:1 to 1:1) to afford the title compound as a clear oil (2.1g, 85%).

LC/MS: m/z 350 [MH]⁺, RT 3.10min.

The following compounds (Table 8) were prepared using a method analogous to that for Example 113, from the corresponding acids and (1*Z*)-4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxybutanimidamide.



Where * is used in the examples herein it indicates the attachment point of the R group to the xanthine core.

Table 8

Example	Compound: R1 =	Yield %	LC/MS:
114	3-butyl-8-chloro-1-[3-(5-[[3-(methoxy)phenyl]methyl]-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	22	m/z 473 [MH] ⁺ RT 3.3 min
115	3-butyl-8-chloro-1-[3-(5-[[3-(trifluoromethyl)phenyl]methyl]-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	23	m/z 511 [MH] ⁺ RT 3.5 min
116	3-butyl-8-chloro-1-[3-(5-[[2-chloro-4-fluorophenyl]methyl]-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	28	m/z 495 [MH] ⁺ RT 3.5 min

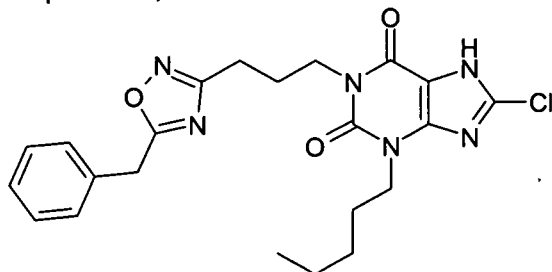
Example		Compound: R1 =	Yield %	LC/MS:
117	1-{3-[5-(1,3-benzodioxol-5-ylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione		27	m/z 487 [MH] ⁺ RT 3.3 min
118	3-butyl-8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione		28	m/z 461 [MH] ⁺ RT 3.3 min
119	3-butyl-8-chloro-1-[3-(5-{[2-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione		21	m/z 473 [MH] ⁺ RT 3.3 min
120	1-{3-[5-(1-benzofuran-4-ylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione		24	m/z 483 [MH] ⁺ RT 3.4 min

NMR details for selected examples from Table 8

Example 115: ¹H NMR (CDCl₃) 0.96 (3H, t, J = 7.5Hz), 1.32-1.47 (2H, m), 1.65-1.81 (2H, m), 2.12-2.25 (2H, m), 2.84 (2H, t, J = 7.5 Hz), 4.02 (2H, t, 7.5Hz), 4.22 (2H, t, 7Hz), 4.24 (2H, s), 7.40-7.62 (4H, m).

Example 121: 8-Chloro-3-pentyl-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione

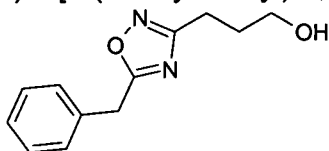
a) 8-Chloro-3-pentyl-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione



To a stirred solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (0.20, 0.67mmol) in THF (5ml) was added 3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]-1-propanol (0.162g, 0.74mmol), DBAD (0.186g, 0.81mmol) and triphenylphosphine

(0.212g, 0.81mmol) and the solution stirred for 18h. To the solution was added Pd(PPh₃)₄ (75mg, 0.067mmol) and morpholine (600μl, 6.7mmol) were added and stirred for at rt under nitrogen for a further 3h. 75mg of Pd(PPh₃)₄ was added and the mixture left to stir for another 3h. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried (MgSO₄) and concentrated. The crude material was purified by an aminopropyl SPE using MeOH to load the compound onto the column and wash through the impurities, then with 2-4% AcOH/MeOH to elute the compound. The product fractions were combined and concentrated then further purified by MDAP. The product fractions were combined and concentrated give the title compound as a white solid (51mg, 20%).
LC/MS: m/z 457 [MH]⁺, RT 3.54min.

b) 3-[5-(Phenylmethyl)-1,2,4-oxadiazol-3-yl]-1-propanol



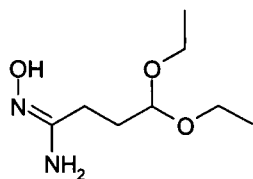
A mixture of (1*E*)-4,4-bis(ethyloxy)-*N*-hydroxybutanimidamide (3.2g, 16.8mmol), ethyl phenylacetate (2.3ml, 14.4mmol) and sodium ethoxide (21% solution in EtOH, 6.4ml) was heated in a microwave at 140°C for 10min. The material was combined with that from a second reaction (using 1.2g of (1*E*)-4,4-bis(ethyloxy)-*N*-hydroxybutanimidamide and conducted as above) and partitioned between 1M HCl solution and EtOAc. The organic layer was separated, washed with brine, dried and concentrated to provide 5-[3,3-bis(ethyloxy)propyl]-5-(phenylmethyl)-1,2,4-oxadiazole which was used without purification in the next stage.

Crude 3-[3,3-bis(ethyloxy)propyl]-5-(phenylmethyl)-1,2,4-oxadiazole (5.63g, 19.4mmol) in EtOH (75ml) was stirred with *p*-toluenesulphonic acid (0.738g, 3.9mmol) for 21h and the mixture partitioned between EtOAc and water. The organics were isolated washed with water and brine, dried and concentrated to a red oil. This material contained significant amounts of acetal, therefore the oil was dissolved in THF (15ml) and treated with 2M HCl solution for 2h then partitioned between EtOAc and water. The organics were isolated washed with brine, dried and concentrated to yield 3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propanal as a red/brown oil (3.77g) which was used crude in the next stage.

A solution of crude 3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propanal (3.76g, 17.4mmol) in MeOH (60ml) was cooled to 0°C and sodium borohydride (0.724g, 19.1mmol) added portionwise over 30min. The cooling bath was removed and the solution stirred for a further 1h then partitioned between 1M HCl and EtOAc. The organic layer was separated and the aqueous extracted with EtOAc. The combined extracts were washed with brine, dried and concentrated to an orange liquid. This was purified on a 50g silica SPE eluting with cyclohexane/EtOAc (20% to 80% gradient elution) to provide the title compound as a yellow oil (2.24g).

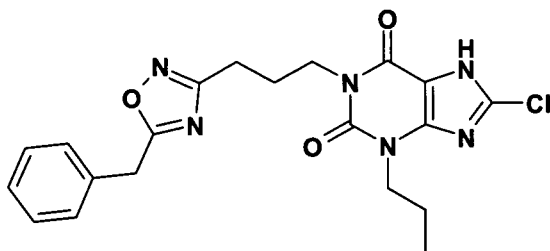
LC/MS: m/z 210 $[MH]^+$.

c) (1*E*)-4,4-bis(ethoxy)-*N*-hydroxybutanimidamide



- 5 A mixture of 3-cynopropionaldehyde diethylacetal (6.12g, 39mmol), hydroxylamine hydrochloride (4.06g, 58.4mmol), potassium carbonate (10.76g, 77.9mmol) in water (20ml) and EtOH (40ml) was refluxed for 24h. The mixture was allowed to cool and then partitioned between water and EtOAc. The organic layer was separated and the aqueous extracted with EtOAc. The combined organic fractions were washed with
- 10 brine, dried and concentrated to provide the title compound as a colourless oil contaminated with ~20% starting nitrile (6.03g, 81%).
LC/MS: m/z 191 $[MH]^+$.

15 **Example 122 : 8-Chloro-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione**



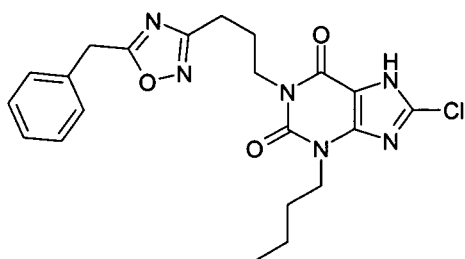
- A solution of 8-chloro-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione (200mg, 0.74mmol) in THF (4ml) was treated with 3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]-1-propanol (195mg, 0.89mmol) and PPh_3 (254mg, 0.96mmol). DBAD (223mg, 0.96mmol) was added in one portion and the mixture was left to stir at rt under nitrogen for 18h. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated by high
- 20 vacuum. The crude product was purified on a silica SPE column using a 0-70% cyclohexane/EtOAc gradient. The product fractions were combined, concentrated by high vacuum and purified on a silica SPE column using a 0-60% cyclohexane/EtOAc gradient. The product fractions were combined and concentrated then dissolved in anhydrous THF (4ml). The solution was degassed by high vacuum then $Pd(PPh_3)_4$ (61mg, 0.053mmol) and morpholine (460 μ l, 5.3mmol) were added and the mixture left to stir at rt under nitrogen for 1 day. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated by high vacuum. The crude product was purified by an aminopropyl SPE
- 25
- 30

using MeOH to load the compound onto the column and wash through the impurities then a 2-4% AcOH/MeOH gradient to elute the product. The product fractions were combined and concentrated to leave the title compound as a white solid (36mg, 11%).

LC/MS: m/z 429 $[MH]^+$, RT 3.14min.

- 5 1H NMR (DMSO- d_6) δ : 0.86 (t, 3H, J = 7.5Hz), 1.65 (m, 2H), 1.93 (m, 2H), 2.70 (t, 2H, J = 7.5Hz), 3.86 (t, 2H, J = 7Hz), 3.96 (t, 2H, J = 7Hz), 4.28 (s, 2H), 7.32 (m, 5H).

Example 123 : 3-Butyl-8-chloro-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione

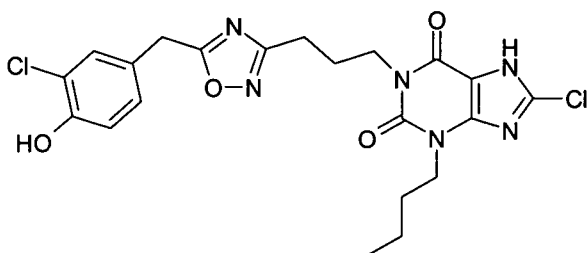


A solution of 3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]-1-propanol (594mg, 2.7mmol) in THF (25ml) was treated with 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (700mg, 2.48mmol) and PPh_3 (779mg, 2.97mmol) under nitrogen. DBAD (684mg, 2.97mmol) was added in one portion and the reaction left to react for 60h. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. MeOH was added to the residue and then passed down an aminopropyl column with the product eluting with 2-4% AcOH/MeOH. Product fractions were combined and concentrated. The off-white residue was recrystallised from EtOAc:cyclohexane (1:1), giving the title compound as a white solid (696mg, 63%).

LC/MS: m/z 443 $[MH]^+$, RT 3.4min.

1H NMR (DMSO- d_6) δ : 0.89 (t, 3H, J = 7Hz), 1.29 (m, 2H), 1.61 (m, 2H), 1.93 (m, 2H), 2.70 (t, 2H, J = 7.5Hz), 3.90 (t, 2H, J = 7Hz), 3.96 (t, 2H, J = 7Hz), 4.28 (2H, s), 7.31 (m, 5H), 14.4 (br s, 1H).

Example 124 : 3-Butyl-8-chloro-1-(3-{5-[(3-chloro-4-hydroxyphenyl)methyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione

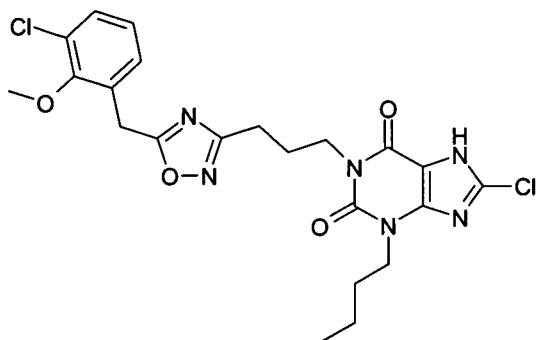


A solution of 3-chloro-4-hydroxyphenylacetic acid (24mg, 0.13mmol) in DMSO (1ml) was treated with CDI (21mg, 0.13mmol) and left to react for 30min. (1Z)-4-(3-Butyl-8-

chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxybutanimidamide (50mg, 0.15mmol) was added and the mixture heated in the microwave at 120°C for 15min. The solution was directly purified by MDAP to obtain the title compound as a white solid (12mg, 17%).

5 LC/MS: *m/z* 493 [MH]⁺, RT 3.2min.

Example 125 : 3-Butyl-8-chloro-1-[3-(5-{[3-chloro-2-(methoxy)phenyl]methyl}-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione



10

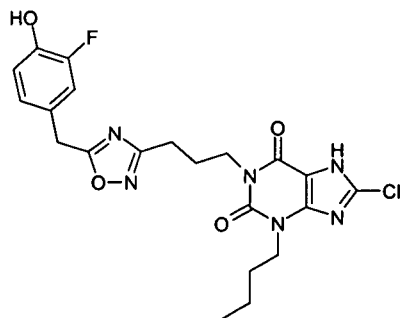
A mixture of [3-chloro-2-(methoxy)phenyl]acetic acid (32mg, 0.16mmol) in DMF (1.5ml) was treated with CDI (26mg, 0.16mmol) and left to react for 45min. (1*Z*)-4-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxybutanimidamide (60mg, 0.18mmol) was added and the mixture heated in the microwave at 140°C for 15min. After cooling, the reaction was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated then concentrated and purified by the MDAP. The title compound was obtained as a white solid (25mg, 28%).

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LC/MS: *m/z* 507 [MH]⁺, RT 3.5min.

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Example 126 : 3-Butyl-8-chloro-1-(3-{5-[(3-fluoro-4-hydroxyphenyl)methyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



25

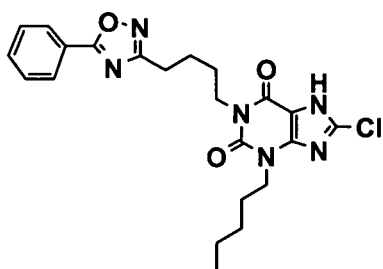
A mixture of (3-fluoro-4-hydroxyphenyl)acetic acid (27mg, 0.16mmol) in DMF (1.5ml) was treated with CDI (26mg, 0.16mmol) and left to react for 45min. (1*Z*)-4-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxybutanimidamide (60mg, 0.18mmol) was added and the mixture heated in the microwave at 140°C for 15min. After cooling, the reaction was partitioned between 2M HCl (aq) and EtOAc. The

organic layer was separated then concentrated and purified by MDAP. The title compound was obtained as a white solid (10mg, 12%).

LC/MS: m/z 477 $[MH]^+$, RT 3.2min.

5 **Example 127 : 8-chloro-3-pentyl-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione**

a) Preparation of 8-chloro-3-pentyl-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione

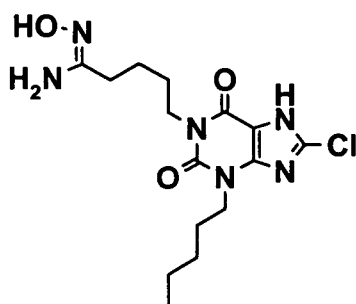


Benzoic acid (18mg, 0.15mmol) was treated with a solution of 1H-1,2,3-benzotriazol-1-ol hydrate (25mg, 0.19mmol) in DMSO (0.3ml). To this was added a solution/suspension of N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (29mg, 0.15mmol) in DMSO (0.3ml) followed by a solution of 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (55mg, 0.15mmol) in DMSO (0.3ml). The mixture was heated at 40°C for 1h, then at 80°C for 5h and then cooled. The mixture was subjected to purification by MDAP. Product-containing fractions were blown to dryness by a stream of nitrogen to yield the title compound as a white solid (17.2mg, 25%).

LC/MS: m/z 457 $[MH]^+$, RT 3.67min.

1H NMR ($CDCl_3$) δ : 0.90 (t, 3H, J = 6.8Hz), 1.35 (m, 4H), 1.76 (m, 2H), 1.89 (m, 4H), 2.88 (t, 2H, J = 7.2Hz), 4.08 (t, 2H, J = 7.5Hz), 4.17 (t, 2H, J = 6.7Hz), 7.50 (m, 2H), 7.57 (m, 1H), 8.08, (d, 2H, J = 7.3Hz).

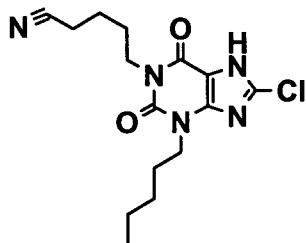
b) 5-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide



A solution of 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanenitrile (3.0g, 8.9mmol) in EtOH (30ml) was treated with water (15ml), potassium carbonate (1.48g, 10.7mmol) and hydroxylamine hydrochloride (0.74g, 10.7mmol) and then heated at 70°C overnight. A further potassium carbonate (1.5g, 10.9mmol) and hydroxylamine hydrochloride (1.0g, 14.5mmol) were cautiously added to the mixture which was then heated to 90°C for 24h. The mixture was cooled and concentrated *in vacuo* to remove most of the EtOH. The residual mixture was treated with water (30ml) and acidified to pH 7 by the cautious addition of 2M aqueous hydrochloric acid. The precipitated solid was filtered off, washed with water, then with diethyl ether and thoroughly dried to yield the title compound as a white solid (2.80g, 85%).

LC/MS: m/z 371 [MH]⁺, RT 2.27min.

c) 5-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanenitrile



A solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (4.0g, 13.5mmol) in DMF (100ml) was treated with caesium carbonate (4.83g, 14.8mmol) and 5-bromopentanenitrile (1.73ml, 14.8mmol). The mixture was heated at 50°C in a nitrogen atmosphere for 19h and then cooled. The mixture was then degassed by the repeated successive application of a vacuum and then nitrogen pressure. The mixture was then treated with tetrakis(triphenylphosphine)palladium(0) (1.1g, 0.94mmol) and morpholine (11.8ml, 136mmol). The mixture was stirred in a nitrogen atmosphere for 3h and then partitioned between EtOAc and 2M aqueous hydrochloric acid. The organic layer was separated, washed with brine, dried (MgSO₄) and concentrated to reveal a yellow, oily residue. This was dissolved in MeOH, divided equally into four portions and each portion applied to a 20g aminopropyl SPE which was then washed through with MeOH. The desired product was eluted from the cartridge with a 5% v/v solution of AcOH in MeOH. The product-containing fractions were combined and concentrated to yield the title compound as a pale yellow solid (4.03g, 88%).

LC/MS: m/z 338 [MH]⁺, RT 3.05min.

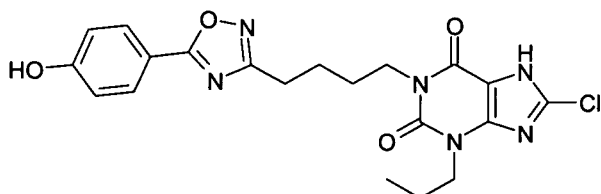
The following compounds were prepared using a method analogous to that for Example 127 (8-chloro-3-pentyl-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione) from the corresponding acids:

Table 9

#	Structure	Name	Yield	LC/MS:
128		8-chloro-3-pentyl-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	7.3mg (11%)	m/z 458 [MH] ⁺ RT 3.21 min
139		8-chloro-1-{4-[5-(2-chlorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	12.8mg (17%)	m/z 491 [MH] ⁺ RT 3.77 min
130		8-chloro-1-{4-[5-(2-methoxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	21.7mg (30%)	m/z 487 [MH] ⁺ RT 3.54 min
131		8-chloro-1-{4-[5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	16.6mg (23%)	m/z 475 [MH] ⁺ RT 3.62 min

In addition Example 128, 8-chloro-3-pentyl-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione has the following spectral data: ¹H NMR (CDCl₃) δ: 0.89 (t, 3H, J = 6.9Hz), 1.75 (m, 4H), 1.89 (m, 6H), 2.92 (t, 2H, J = 7.1Hz), 4.07 (t, 2H, J = 7.4Hz), 4.16 (t, 2H, J = 6.9Hz), 7.52 (m, 1H), 7.92 (m, 1H), 8.18 (m, 1H), 8.83 (m, 1H), 13.40 (br s, 1H).

Example 132: 8-Chloro-1-{4-[5-(4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-propyl-3,7-dihydro-1H-purine-2,6-dione



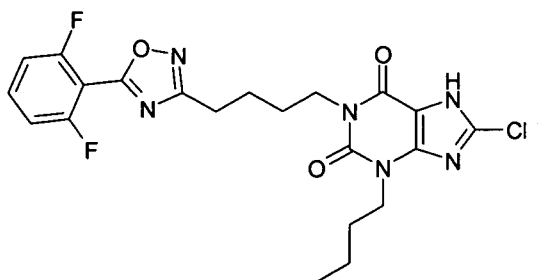
4-Hydroxybenzoic acid (18mg, 0.13mmol) and CDI (24mg, 0.15mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1Z)-5-(8-Chloro-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (50mg, 0.15mmol; prepared in a manner similar to (1Z)-5-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide as described in Example 128(b)) was added and the

mixture was stirred at 90°C for 2h. The reaction mixture was purified by MDAP. The product fraction was combined and concentrated under high vacuum to give the title compound as a white solid (7mg, 11%).

LC/MS: m/z 443 [MH]⁺, RT 3.28min.

5

Example 133 : 3-Butyl-8-chloro-1-{4-[5-(2,6-difluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione



10

2,6-Difluorobenzoic acid (40mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1Z)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (100mg, 0.28mmol) was added and the mixture was stirred at 90°C for 16h. The reaction mixture was purified by

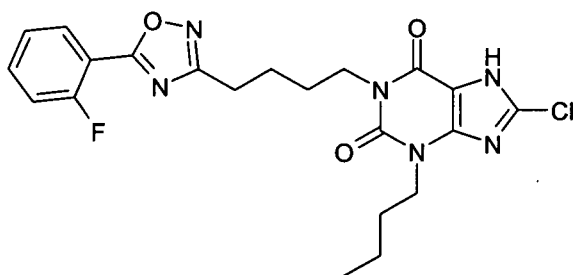
15

MDAP. The product fraction was combined and concentrated to give the title compound as a white solid (18mg, 15%).

LC/MS: m/z 479 [MH]⁺, RT 3.40min.

Example 134 : 3-Butyl-8-chloro-1-{4-[5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione

20



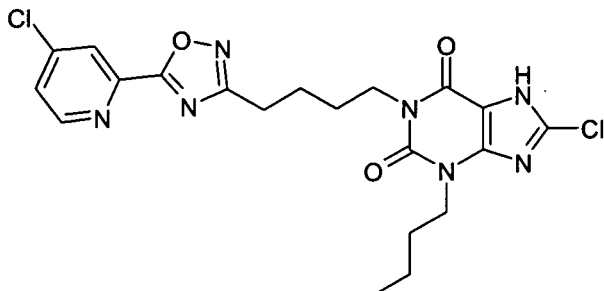
2-Fluorobenzoic acid (36mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1Z)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (100mg, 0.28mmol) was added and the mixture was stirred at 90°C for 16h. The mixture was purified by MDAP. The product fraction was combined and concentrated to give the title compound as a white solid (33mg, 29%).

25

LC/MS: m/z 461 [MH]⁺, RT 3.44min.

30

Example 135 : 3-Butyl-8-chloro-1-{4-[5-(4-chloro-2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione

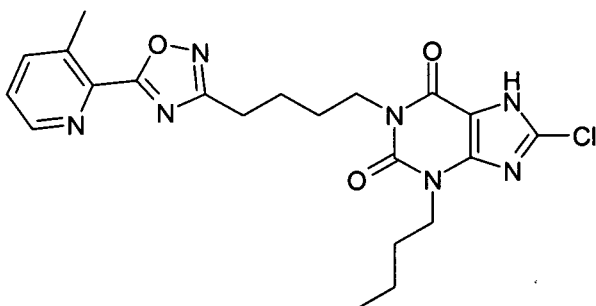


5 4-Chloro-2-pyridinecarboxylic acid (40mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1Z)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (100mg, 0.28mmol) was added and the mixture was stirred at 90°C for 16h. The reaction mixture was purified by MDAP. The product fraction was combined and concentrated to give the title
10 compound as a white solid (13mg, 11%).

LC/MS: m/z 478 [MH]⁺, RT 3.31min.

¹H NMR (DMSO-d₆) δ_H 14.4 (br. s, 1H), 8.79 (d, 1H, J=6Hz), 8.24 (d, 1H, J=2Hz), 7.88 (dd, 1H, J=6Hz & 2Hz), 3.91 (m, 4H), 2.85 (t, 2H, J=7.5Hz), 1.56-1.76 (m, 6H), 1.28 (m, 2H), 0.87 (t, 3H, J=7.5Hz) ppm.

Example 136 : 3-Butyl-8-chloro-1-{4-[5-(3-methyl-2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione

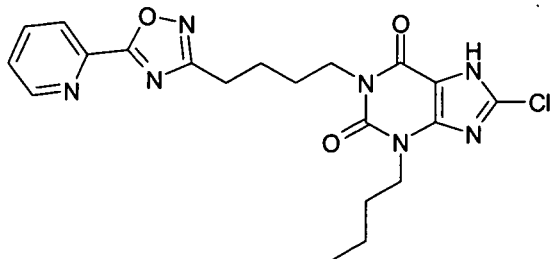


20 3-Methyl-2-pyridinecarboxylic acid (35mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1Z)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (100mg, 0.28mmol) was added and the mixture was stirred at 90°C for 16h. The reaction mixture was purified by MDAP. The product fraction was combined and concentrated to give the title
25 compound as a white solid 14mg, 12%).

LC/MS: m/z 458 [MH]⁺, RT 3.13min.

Example 137 : 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione

Method A

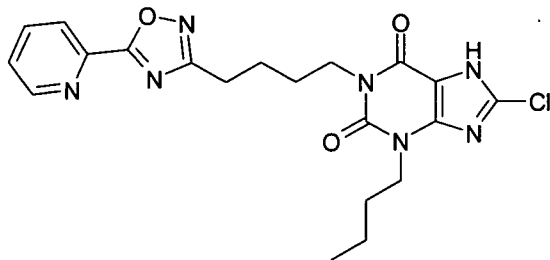


2-Pyridinecarboxylic acid (31mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.5ml) at rt for 1h. A solution of (1Z)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (100mg, 0.28mmol) in DMSO (0.4ml) was added and the mixture was stirred at 90°C for 16h. The reaction mixture was purified directly by MDAP. The product fractions were combined and concentrated to give the title compound as a white solid (14mg, 12%).

LC/MS: m/z 444 [MH]⁺, RT 3.01min.

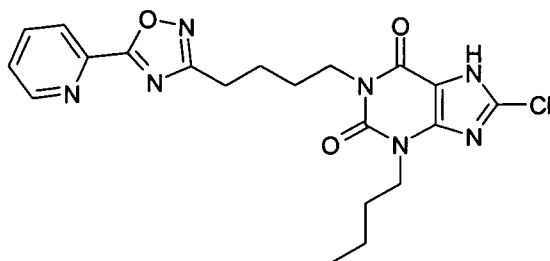
¹H NMR (DMSO-d₆) δ: 0.87 (t, 3H, J = 7 Hz), 1.27 (m, 2H), 1.65 (m, 6H), 2.84 (t, 2H, J = 7 Hz), 3.91 (m, 4H), 7.70 (dd 1H, J = 5 & 7Hz), 8.07 (m, 1H), 8.19 (d, 1H, J = 8Hz), 8.81 (d, 1H, J = 5Hz), 14.5 (br. s, 1H).

Method B



2-Pyridinecarboxylic acid (675mg, 5.3mmol) and CDI (909mg, 5.6mmol) were stirred in anhydrous DMF (30ml) at rt under nitrogen for 90mins. (1Z)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (2.0g, 5.6mmol) and DMF (10ml) were added and the mixture was stirred at 100°C for 20h. The reaction mixture was cooled to rt then partitioned between sat. NH₄Cl(aq) solution and EtOAc. The organic layer was separated, and the aqueous solution extracted with EtOAc. The combined extracts were washed with brine, dried MgSO₄ and concentrated giving an orange liquid. This was purified using the CompanionTM system giving two identical white solids (649mg; 240mg).

LC/MS: m/z 444 [MH]⁺, RT 3.04min.

Method C

- 5 A 12-L, round-bottom flask was equipped with an overhead, mechanical stirrer, a temperature probe with a J-KEM temperature controller, a condenser and a nitrogen inlet adapter. The flask was charged with picolinic acid (0.180 kg, 1.46 mol), MIBK (4.0 L), 1,1'-carbonyldiimidazole (0.23 kg, 1.42 mol,) and more MIBK (0.66 L). The mixture was stirred and warmed to 50 °C over approximately 1 hour, and the temperature
- 10 overshot to 56 °C. The solids dissolved during the heat up to 50 °C and carbon dioxide was generated. After 1 hour at 50 °C, (1Z)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (0.467 kg, 1.31 mol) was added to the reaction. The mixture was then warmed to 90 °C over 1 hour. HPLC analysis of the reaction after heating at 90 °C for 5.5 hours indicated that the reaction was
- 15 complete. The heat was turned off, and 1.0 N hydrochloric acid solution (2.33 L) was added. The temperature dropped to 61 °C. After stirring overnight, the product precipitated and was filtered. The filtercake was washed with water (1 x 2.23 L, 1 x 2.43 L) and heptanes (1.40 L). The wet cake was dried in a vacuum oven at 50 °C for 22 hours to give 396 g of product (68%) HPLC analysis 97.7% (AUC) t_R = 18.6 min.

20

Methods A, B and C of Example 137 produce substantially crystalline 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione Form 2.

Method D

- 25 **Formation of 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione Form 1**

- The reaction vessel was charged with 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione (1wt), acetone (20vol) and water (0.6vol). The mixture was stirred and warmed to 50-60 °C and agitated for a minimum
- 30 of 1 hour. A solution was formed which is clarified at this temperature by filtration through a 1micron filter into a 2nd reaction vessel. The solution was cooled over approximately 3 hours to 33-38°C and seeded at this temperature with 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione
- 35 (Form 1, 0.01wt). The thin suspension was agitated at this temperature for a minimum of 1hour then cooled to 20-25°C and held at this temperature for a minimum of 12hours. The suspension thus formed was cooled to 13-17°C and held at this

temperature for a minimum of 1 hour. The suspension was then sampled*, and the solid collected by filtration in the laboratory. The solid was dried and analysed by xrpD/DSC to check form. If the form is as required (Form 1) the batch is filtered, washed (2x3vol acetone) and dried in a vacuum oven at 50°C. The batch is offloaded once analysis

5 shows solvent levels (acetone, water) to be at acceptable.

Expected yield (75-80%w/w).

If the form of the sample taken at * is shown to be other than pure Form 1, then **the batch is reheated to 35-45°C and agitated at this temperature for a minimum of 1 hour. The thin suspension is then cooled to 20-25°C and held at this temperature for a minimum of 12 hours. The suspension thus formed is then cooled to 13-17°C and held at this temperature for a minimum of 1 hour. The suspension is then sampled, and the solid collected by filtration in the laboratory. The solid is dried and analysed by

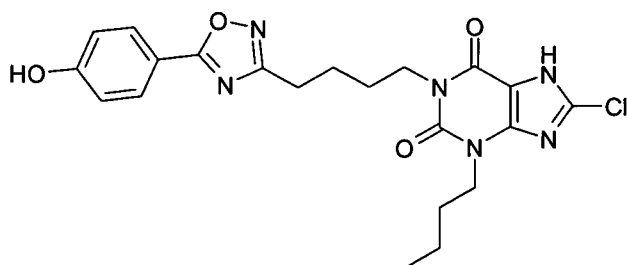
10 xrpD/DSC to check form. If the form is as required (Form 1) the batch is filtered, washed and dried as described previously. If the form is not pure Form 1, then the cycle from ** is repeated until a satisfactory result is obtained.

X-Ray Powder Diffraction (XRPD)

X-ray powder diffraction (XRPD) data are shown in Figures 1-3. The data were acquired on a PANalytical X'Pert Pro powder diffractometer, model PW3040/60, serial number DY1850 using an X'Celerator detector. The acquisition conditions were: radiation: Cu K α , generator tension: 40 kV, generator current: 45 mA, start angle: 2.0°2 θ , end angle: 40.0°2 θ , step size: 0.0167 °2 θ , time per step: 31.75 seconds. The

20 samples were prepared by mounting a few milligrams of sample on a Si wafer (zero background) plates, resulting in a thin layer of powder.

Example 138: 3-Butyl-8-chloro-1-{4-[5-(4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione



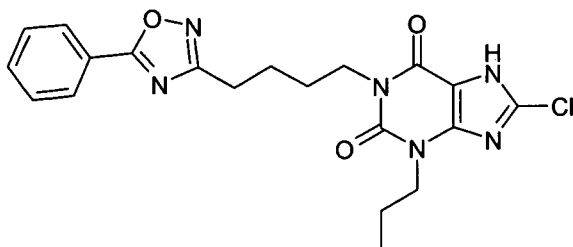
4-Hydroxybenzoic acid (35mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1Z)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (100mg, 0.28mmol) was added

35

and the mixture was stirred at 90°C for 16h. The mixture was purified by MDAP to give the title compound as a white solid (5mg, 4%).

LC/MS: m/z 459 [MH]⁺, RT 3.24min.

5 **Example 139 : 8-Chloro-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione**

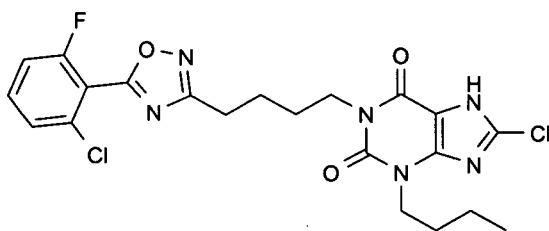


10 Benzoic acid (9mg, 0.074mmol) and CDI (13mg, 0.081mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1Z)-5-(8-Chloro-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (28mg, 0.081mmol) was added and the mixture was stirred at 80°C for 4h. The mixture was purified by MDAP to give the title compound as a white solid (0.6mg, 2%).

LC/MS: m/z 429 [MH]⁺, RT 3.21min.

15 ¹H NMR (MeOH-d₄) δ: 0.93 (t, 3H, J = 7.5Hz), 1.74 (m, 4H), 1.84 (m, 2H), 2.84 (t, 2H, J = 7Hz), 3.97 (t, 2H, J = 7.5Hz), 4.08 (t, 2H, J = 7Hz), 7.57 (dd, 2H, J = 7 & 7.5Hz), 7.65 (dd, 1H, J = 7 & 7.5Hz), 8.08 (d, 2H, J = 7.5Hz).

20 **Example 140: 3-Butyl-8-chloro-1-[4-[5-(2-chloro-6-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl]-3,7-dihydro-1H-purine-2,6-dione**

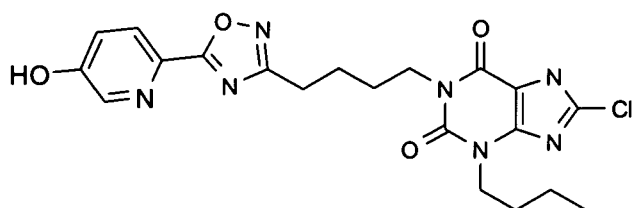


25 2-Chloro-6-fluorobenzoic acid (44mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1Z)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (100mg, 0.28mmol) was added and the mixture was stirred at 90°C for 16h. The mixture was purified by MDAP. The product fraction was combined and concentrated to give the title compound as a white solid (6.4mg, 5%).

LC/MS: m/z 495 [MH]⁺, RT 3.58min.

30

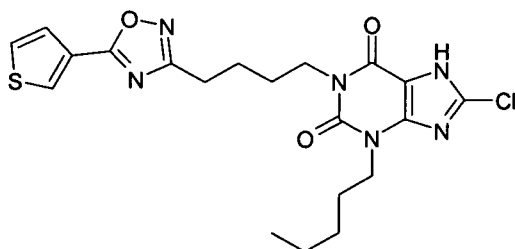
Example 141: 3-Butyl-8-chloro-1-[4-[5-(5-hydroxy-2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl]-3,7-dihydro-1H-purine-2,6-dione



5-Hydroxy-2-pyridinecarboxylic acid (24mg, 0.17mmol) and CDI (31mg, 0.19mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1Z)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (68mg, 0.19mmol) was added and the mixture was stirred at 90°C for 16h. The mixture was purified by MDAP and the product fractions concentrated to give the title compound as a white solid (19mg, 24%).

LC/MS: m/z 459 [MH]⁺, RT 3.03min.

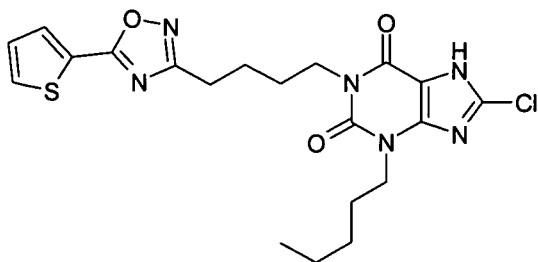
Example 142: 8-Chloro-3-pentyl-1-{4-[5-(3-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione



A solution of (1Z)-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (50mg, 0.13mmol) in EtOH (1ml) was treated with a 21% solution of NaOEt in EtOH (55μl, 0.21mmol) and ethyl 3-thiophenecarboxylate (18μl, 0.13mmol). The mixture was heated in the microwave at 150°C for 10min. After cooling, the reaction was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated and the aqueous extracted again with EtOAc. The combined extracts were concentrated and purified by the MDAP. The title compound was obtained as an off-white solid (20mg, 32%).

LC/MS: m/z 463 [MH]⁺, RT 3.6min.

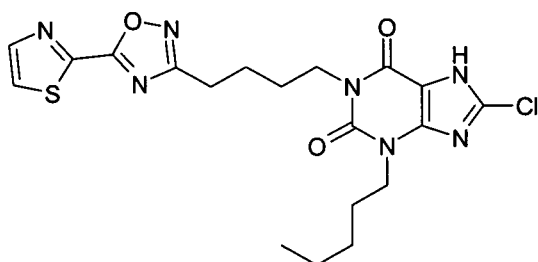
Example 143 : 8-Chloro-3-pentyl-1-{4-[5-(2-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione



2-Thiophenecarboxylic acid (14mg, 0.11mmol) was dissolved in NMP (0.9ml) and treated with CDI (18mg, 0.11mmol). After 1h, (1Z)-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (50mg, 0.13mmol) was added and the mixture heated in the microwave at 150°C for 15min. The solution was directly purified by MDAP to obtain the title compound which was then freeze dried from 1,4-dioxane to give the title compound as a white solid (19mg, 31%).

LC/MS: m/z 463 [MH]⁺, RT 3.5min.

Example 144: 8-Chloro-3-pentyl-1-{4-[5-(1,3-thiazol-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione



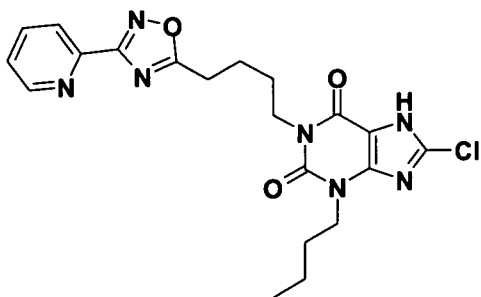
A solution of (1Z)-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (50mg, 0.13mmol) in EtOH (1.5ml) was treated with a 21% solution of NaOEt in EtOH (50μl, 0.13mmol) and ethyl 1,3-thiazole-2-carboxylate (18mg, 0.11mmol). The mixture was heated in the microwave at 170°C for 10min. After cooling, the reaction was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated then concentrated and purified by the MDAP. The title compound was obtained as a white solid (13mg, 21%).

LC/MS: m/z 464 [MH]⁺, RT 3.3min.

¹H NMR (DMSO-d₆) δ: 0.83 (t, 3H, J = 7Hz), 1.21-1.32 (m, 4H), 1.60-1.77 (m, 6H), 2.84 (t, 2H, J = 7Hz), 3.91 (m, 4H), 8.23 (d, 1H, J = 3Hz), 8.27 (d, 1H, J = 3Hz), 14.4 (br s, 1H).

Example 145: 3-butyl-8-chloro-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione

a) Preparation of 3-butyl-8-chloro-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione

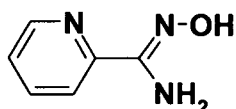


To a mixture of ethyl 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoate (120mg, 0.32mmol) and of N-hydroxy-2-pyridinecarboximidamide (50mg, 0.36mmol) in EtOH (2ml) was added a 21% (w/v) solution of sodium ethoxide in EtOH (0.225ml, 0.62mmol) and then heated in a sealed vial in a microwave oven at 140°C for 10min. The cooled mixture was evaporated to dryness and the residue partitioned between chloroform (5ml) and saturated aqueous ammonium chloride (5ml). The organic phase was evaporated to dryness and the crude product subjected to purification by MDAP. Product containing fractions were combined and evaporated to dryness. The product was triturated to a solid in a small amount of diethyl ether then dried to reveal the title compound as a white solid (44mg, 31%).

LC/MS: m/z 444 [MH]⁺, RT 3.03min.

¹H NMR (CDCl₃) δ: 0.96 (t, 3H, J = 7.3Hz), 1.40 (m, 2H), 1.74 (m, 2H), 1.88 (m, 2H), 1.99 (m, 2H), 3.07 (t, 2H, J = 7.5Hz), 4.09 (t, 2H, J = 7.5Hz), 4.17 (t, 2H, J = 7.0Hz), 7.43 (m, 1H), 7.64 (m, 1H), 8.10 (m, 1H), 8.79 (m, 1H).

b) Preparation of N-hydroxy-2-pyridinecarboximidamide



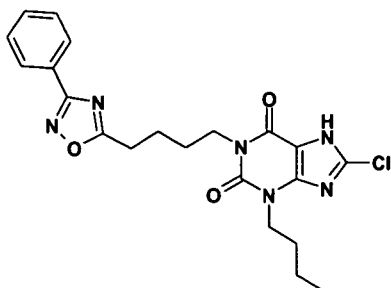
To a mixture of 2-pyridinecarbonitrile (3g, 29mmol) and potassium carbonate (4.1g, 30mmol) in EtOH (30ml) was added water (15ml) and, cautiously, hydroxylamine hydrochloride (2.9g, 42mmol) and then heated at reflux for 6h, cooled and evaporated to dryness. The residue was treated with water (100ml) and the suspended solid product filtered off, washed with water and dried to yield the title compound as a white solid (2.28g, 57%).

¹H NMR (DMSO-d₆) δ: 5.85 (br s, 2H), 7.40 (m, 1H), 7.79 (m, 1H), 7.86 (m, 1H), 8.55 (m, 1H), 9.92 (s, 1H)

Example 146: 3-Butyl-8-chloro-1-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione

Method A

a) 3-Butyl-8-chloro-1-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione

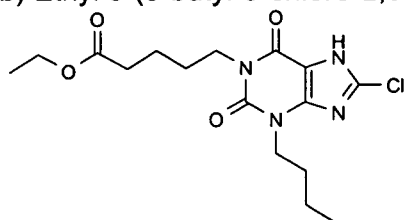


Ethyl 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (74mg, 0.2mmol) and benzamidoxime (30mg, 0.22mmol) were suspended in dry EtOH (1ml) and ethanolic sodium ethoxide (21% by wt., 0.111ml, 0.3mmol) was added. The mixture was gently warmed until solids were dissolved and then heated in the microwave reactor at 140°C for 10min. The mixture was then partitioned between EtOAc and 2M HCl and the organic phase dried (Na₂SO₄) and evaporated. MDAP afforded the pure title compound (40.7mg).

LC/MS: m/z 443 [MH]⁺, RT 3.67min.

¹H NMR (DMSO-d₆) δ: 0.89 (t, 3H, J = 7Hz), 1.22-1.34 (m, 2H), 1.57-1.75 (m, 4H), 1.75-1.86 (m, 2H), 3.05 (t, 2H, J = 7 Hz), 3.88-3.98 (m, 4H), 7.52-7.63 (m, 3H), 7.95-8.0 (m, 2H).

b) Ethyl 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate

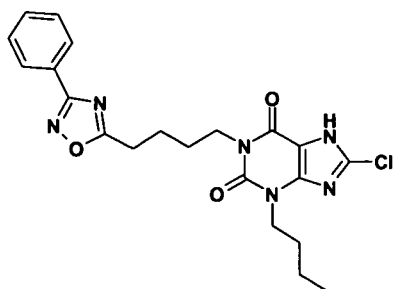


To 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.5g, 5.31mmol) in dry DMF (25ml) was added Cs₂CO₃ (1.905g, 5.84mmol), followed by ethyl 5-bromovalerate (1.46g, 6.99mmol). The mixture was heated at 55°C for 18h then allowed to cool. It was degassed by repeatedly evacuating and readmitting nitrogen, then morpholine (3.70ml, 42.5mmol) and tetrakis(triphenylphosphine)palladium(0) (1.0g, 0.865mmol) were added and the mixture stirred for 5h. EtOAc (75ml), 2M HCl (40ml) and water (20ml) were added and the organic phase was separated, washed with brine (3 x 25ml), filtered to remove some insoluble yellow solid, dried (Na₂SO₄) and evaporated. The residue (2.5g) was purified by aminopropyl SPE (20g), loading in THF-MeOH (1:1), washing with MeOH and eluting the product with DCM-MeOH (1:1) containing 5% added AcOH to afford the title compound (1.53g).

LC/MS: m/z 371 MH⁺, RT 3.18min

Method B

a) 3-Butyl-8-chloro-1-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione

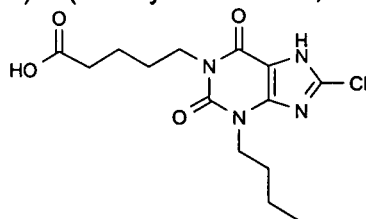


CDI (0.98g, 6.1mmol) was added to a solution of 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoic acid (1.89g, 5.5mmol) in DMF (15ml) and stirred under nitrogen for 1.5h. Benzamidoxime (0.91g, 6.1mmol) was added and the mixture stirred at 110°C overnight. The reaction mixture was partitioned between EtOAc and 2M HCl. The organic layer was separated, washed with brine, dried (MgSO₄) and evaporated. The crude product was crystallised from methanol and then further purified using the Companion™ system and a gradient elution from cyclohexane to EtOAc. Product containing fractions were combined and evaporated to give the title compound as a white solid (850mg).

LC/MS: m/z 443 [MH]⁺, RT 3.52min.

¹H NMR (MeOH-d₄) δ: 0.94 (t, 3H, J = 7.5Hz), 1.31-1.41 (m, 2H), 1.65-1.73 (m, 2H), 1.75-1.83 (m, 2H), 1.87-1.96 (m, 2H), 3.04 (t, 2H, J = 7.5Hz), 4.01 (t, 2H, J = 7.5Hz), 4.06 (t, 2H, J = 7Hz), 7.46-7.55 (m, 3H), 7.98-8.02 (m, 2H).

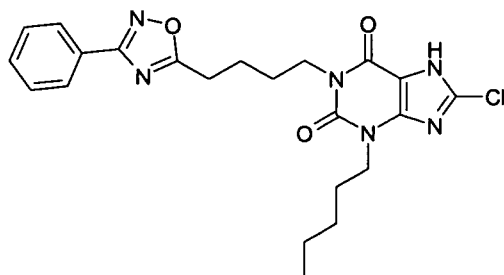
b) 5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoic acid



A mixture of ethyl 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoate (2.8g, 7.55mmol), LiOH (542mg, 22.7mmol), water (2.5ml) and methanol (50ml) was stirred at rt for 60h. The mixture was portioned between water and EtOAc and the pH of the aqueous phase adjusted to pH 4-5. The organic layer was separated, washed with brine, dried (MgSO₄) and evaporated to give the title compound as a white solid (2.18g).

LC/MS: m/z 343 [MH]⁺, RT 2.69min.

Example 147 : 8-Chloro-3-pentyl-1-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione

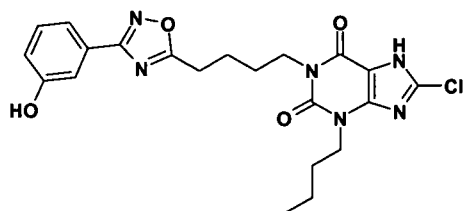


A mixture of methyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoate (50mg, 0.13mmol), benzamidine oxime (20mg, 0.15mmol) and a 21% solution of NaOEt in EtOH (76μl, 0.20mmol) in EtOH (1.5ml) was heated in the microwave at 140°C for 10min. After cooling the reaction was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, dried (MgSO₄) and concentrated. Purification by the MDAP gave the title compound as a white solid (25mg, 41%).

LC/MS: m/z 457 [MH]⁺, RT 3.7min.

¹H NMR (DMSO-d₆) δ: 0.82 (t, 3H, J = 7 Hz), 1.25 (m, 4H), 1.66 (m, 4H), 1.79 (m, 2H), 3.04 (t, 2H, J = 7Hz), 3.92 (4H,m), 7.57 (m, 3H), 7.97 (m, 2H), 14.5 (br s, 1H).

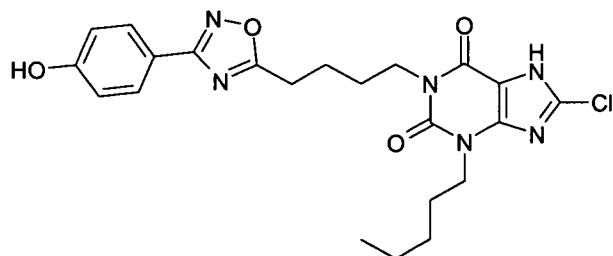
Example 148: 3-Butyl-8-chloro-1-{4-[3-(3-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione



A mixture of ethyl 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoate (50mg, 0.13mmol), N,3-dihydroxybenzenecarboximidamide (25mg, 0.16mmol), 21% solution of NaOEt in EtOH (55μl, 0.15mmol) and EtOH (1.5ml) was heated in the microwave at 180°C for 10min. Another aliquot of 21% solution of NaOEt in EtOH (55μl, 0.21mmol) was added and the mixture heated in the microwave at 175°C for 30min. After cooling the reaction was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, concentrated and purified by the MDAP. The title compound was obtained as an off-white solid (20mg, 32%).

LC/MS: m/z 459 [MH]⁺, RT 3.3min.

Example 149: 8-Chloro-1-{4-[3-(4-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione

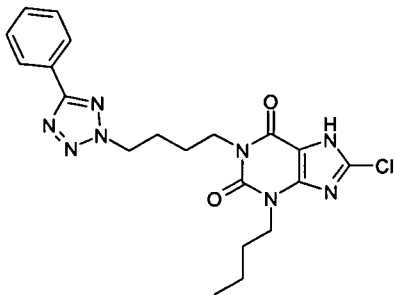


A solution of 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoic acid (50mg, 0.14mmol) in DMF (2ml) was treated with CDI (23mg, 0.14mmol) and stirred at rt for 30min. N,4-dihydroxybenzenecarboximidamide (26mg, 0.17mmol) was

added and the mixture heated in the microwave at 120°C for 15min. After cooling the reaction was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, concentrated and purified by the MDAP. The title compound was obtained as an off-white solid (17mg, 26%).

5 LC/MS: m/z 473 [MH]⁺, RT 3.5min.

Example 150: 3-Butyl-8-chloro-1-[4-(5-phenyl-2H-tetrazol-2-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione

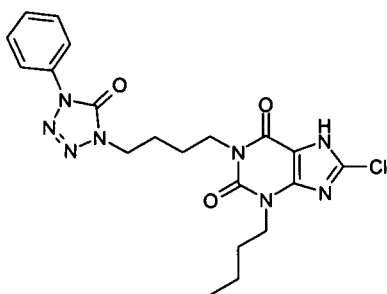


10 A mixture of 4-[3-butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1H-purin-1-yl]butyl methanesulfonate (50mg, 0.12mmol), Cs₂CO₃ (45mg, 0.14mmol) and DMF (3ml) was treated with 5-phenyl-1H-tetrazole (20mg, 0.14mmol) and stirred for 60h at 50°C. After cooling, the mixture was degassed by applying a vacuum and then
15 nitrogen was introduced. Pd(PPh₃)₄ (20mg, 0.017mmol) was added and the mixture degassed once more. Morpholine (150μl, 1.7mmol) was added and the mixture was stirred under nitrogen for 18h, then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated and the aqueous layer extracted again with EtOAc. The combined extracts were concentrated, giving a yellow residue. MeOH was added and
20 then passed down an NH₂-propyl column with the product eluting with 2% AcOH/MeOH. Further purification by MDAP gave the title compound as an off-white solid (15mg, 29%).

LC/MS: m/z 443 [MH]⁺, RT 3.4min.

¹H NMR (DMSO-d₆) δ: 0.86 (t, 3H, J = 7Hz), 1.26 (m, 2H), 1.59 (m, 4H), 1.97 (m, 2H),
25 3.90 (m, 4H), 4.76 (t, 2H, J = 7Hz), 7.54 (m, 3H), 8.02 (m, 2H), 14.4 (br s, 1H).

Example 151: 3-Butyl-8-chloro-1-[4-(5-oxo-4-phenyl-4,5-dihydro-1H-tetrazol-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione

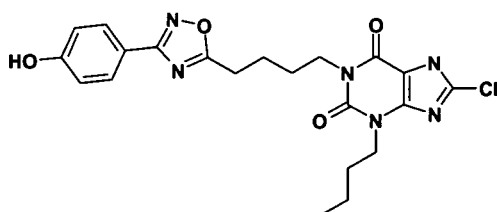


A mixture of 4-[3-butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1H-purin-1-yl]butyl methanesulfonate (50mg, 0.12mmol), Cs₂CO₃ (45mg, 0.14mmol) and DMF (3ml) was treated with 1-phenyl-1,2-dihydro-5H-tetrazol-5-one (23mg, 0.14mmol) and stirred for 60h at 50°C. After cooling, the mixture was degassed by applying a vacuum and then nitrogen was introduced. Pd(PPh₃)₄ (20mg, 0.017mmol) was added and the mixture degassed once more. Morpholine (150μl, 1.7mmol) was added and the mixture was stirred under nitrogen for 18h, then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated and the aqueous layer extracted again with EtOAc. The combined extracts were concentrated, giving a yellow residue. MeOH was added and then passed down an aminopropyl column with the product eluting with 2% AcOH/MeOH. Further purification by MDAP gave the title compound as an off-white solid (27mg, 51%). NB. ca. 10% O-alkylated material present.

LC/MS: m/z 459 [MH]⁺, RT 3.1min.

¹H NMR (DMSO-d₆) δ: 0.88 (t, 3H, J = 7Hz), 1.28 (m, 2H), 1.62 (m, 4H), 1.79 (m, 2H), 3.91 (m, 4H), 4.03 (m, 2H), 7.44 (m, 1H), 7.57 (m, 2H), 7.85 (m, 2H), 14.5 (br s, 1H).

Example 152: 3-butyl-8-chloro-1-{4-[3-(4-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione

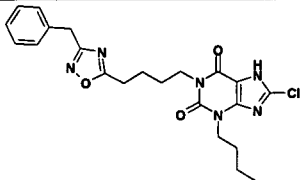
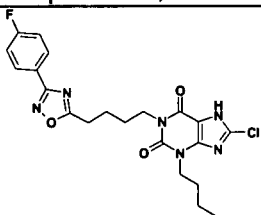
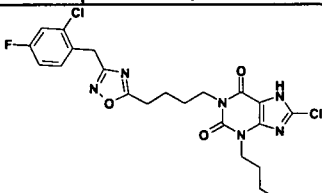


A stirred solution of 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoic acid (100mg, 0.29mmol) in DMF (4ml) was treated with CDI (52mg, 0.32mmol). After 1h, N,4-dihydroxybenzenecarboximidamide was added and the mixture heated at 100°C for 6h. On cooling, the reaction mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried (MgSO₄) and concentrated. Purification by MDAP afforded the title compound as a pale grey solid (72mg).

LC/MS: m/z 459 [MH]⁺, RT 3.27min.

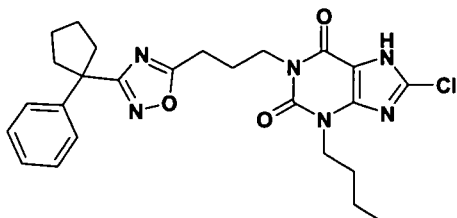
The following compounds (**Table 10**) were prepared using a method analogous to that for **Example 146**, using the appropriate amidoxime.

Table 10

Example	Structure	Yield (mg)	LC/MS
153	 3-butyl-8-chloro-1-{4-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	48.4	m/z 457 [MH] ⁺ RT 3.56min
154	 3-butyl-8-chloro-1-{4-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	35.8	m/z 461 [MH] ⁺ RT 3.74min
155	 3-butyl-8-chloro-1-(4-{3-[(2-chloro-4-fluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	48.2	m/z 509 [MH] ⁺ RT 3.74min

5

Comparative Example A: 3-Butyl-8-chloro-1-{3-[3-(1-phenylcyclopentyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione



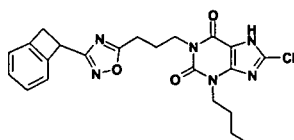
- 10 Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butanoate (53mg, 0.15mmol), *N*-hydroxy-1-phenylcyclopentanecarboximidamide (34mg, 0.165mmol) and sodium methoxide (20mg, 0.37mmol) in dry MeOH (0.75ml) were heated at 140°C in

the microwave reactor for 10min. The mixture was then partitioned between ethyl acetate and 2M HCl, the organic phase evaporated and the product purified by MDAP to give the title compound as a solid (29.1mg).

LC/MS: m/z 497 [MH]⁺, RT 3.76min.

5

Example 156: 1-[3-(3-bicyclo[4.2.0]octa-1,3,5-trien-7-yl-1,2,4-oxadiazol-5-yl)propyl]-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione



10

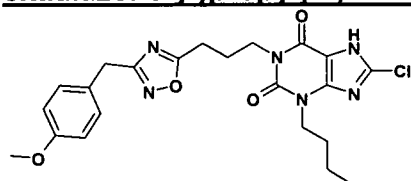
This compound was prepared using a method analogous to that for comparative example A, using the appropriate amidoxime.

Yield (mg): 28.8

LC/MS: m/z 455 [MH]⁺, RT 3.43min.

15

Example 157: 3-Butyl-8-chloro-1-[3-(3-[4-(methyloxy)phenyl]methyl)-1,2,4-oxadiazol-5-yl]propyl]-3,7-dihydro-1H-purine-2,6-dione



20

Prepared using a method analogous to that used for **Example 93**, except an additional final purification step using HPLC was employed. Yield 6.0mg.

LC/MS: m/z 473 [MH]⁺, RT 3.27min.

25

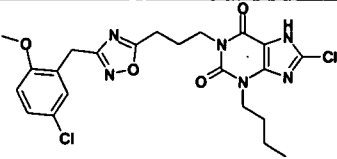
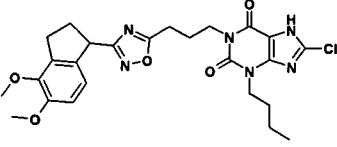
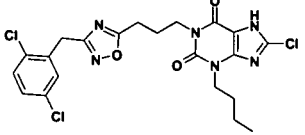
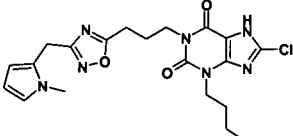
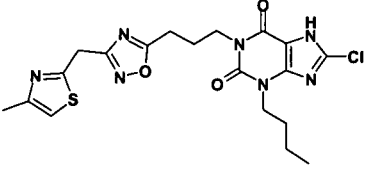
The following compounds (**Table 11**) were prepared using a method analogous to that for **Example 75**, using the appropriate amidoxime [with the exception that for **Example 162** the crude product was stirred in EtOH (0.75ml) with 2M NaOH (0.5ml) overnight prior to the usual EtOAc/HCl workup and MDAP; **Example 164** was isolated as an impurity from the preparation of **Example 165** and was separated from it by HPLC; for **Examples 166**, and **167** the pH during aqueous workup was adjusted to approximately 5 prior to extraction; additionally **Example 167** was further purified by silica SPE (2g, DCM-MeOH 40:1 then 20:1) after MDAP].

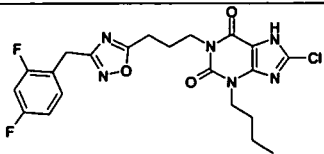
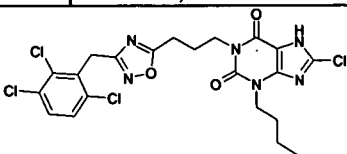
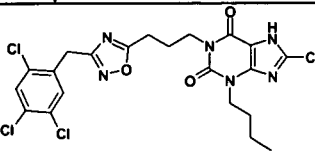
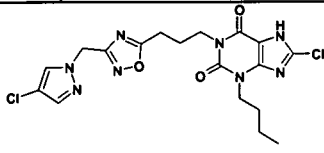
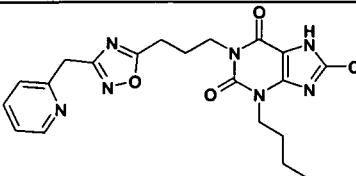
30

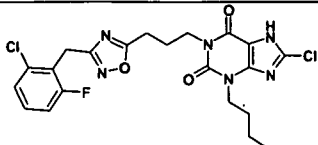
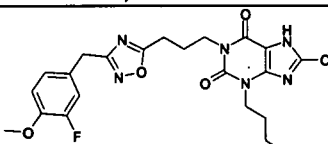
Table 11

35

Example	Structure	Yield	LC/MS
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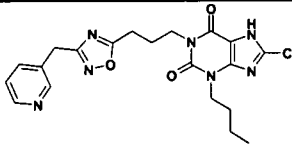
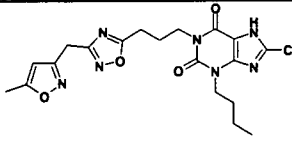
		(mg)	
158	 3-butyl-8-chloro-1-[3-(3-{[5-chloro-2-(methoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	39.5	m/z 507 [MH] ⁺ RT 3.58min
169	 1-(3-{3-[4,5-bis(methoxy)-2,3-dihydro-1H-inden-1-yl]-1,2,4-oxadiazol-5-yl}propyl)-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione	35.8	m/z 529 [MH] ⁺ RT 3.41min
160	 3-butyl-8-chloro-1-(3-{3-[(2,5-dichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	9.7	m/z 511 [MH] ⁺ RT 3.63min
161	 3-butyl-8-chloro-1-(3-{3-[(1-methyl-1H-pyrrol-2-yl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	18.0	m/z 446 [MH] ⁺ RT 3.15min
162	 3-butyl-8-chloro-1-(3-{3-[(4-methyl-1,3-thiazol-2-yl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	15.5	m/z 464 [MH] ⁺ RT 2.94min

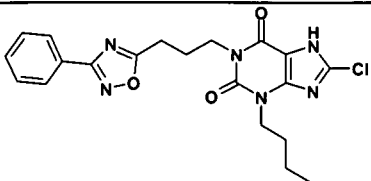
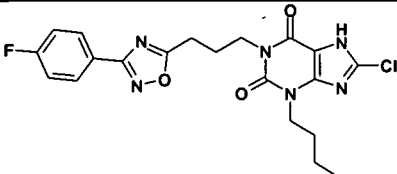
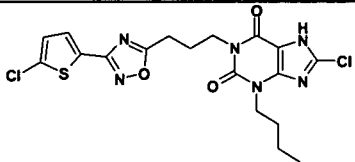
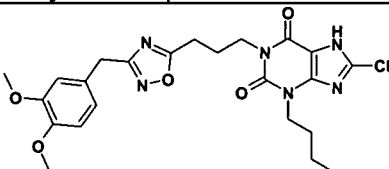
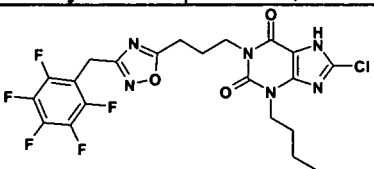
163	 3-butyl-8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	33.5	m/z 479 [MH] ⁺ RT 3.35min
164	 3-butyl-8-chloro-1-(3-{3-[(2,3,6-trichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	4.6	m/z 545 [MH] ⁺ RT 3.71min
165	 3-butyl-8-chloro-1-(3-{3-[(2,4,5-trichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	17.7	m/z 545 [MH] ⁺ RT 3.79min
166	 3-butyl-8-chloro-1-(3-{3-[(4-chloro-1H-pyrazol-1-yl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	39.2	m/z 467 [MH] ⁺ RT 3.24min
167	 3-butyl-8-chloro-1-(3-{3-(2-pyridinylmethyl)-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	23.6	m/z 444 [MH] ⁺ RT 2.92min

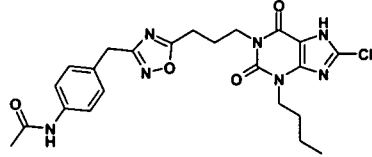
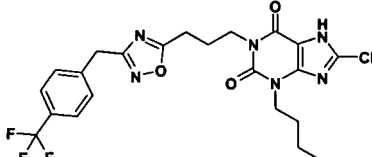
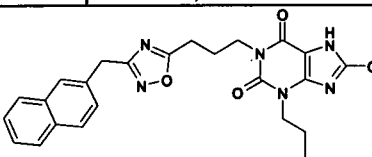
168	 3-butyl-8-chloro-1-(3-{3-[(2-chloro-6-fluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	38.8	m/z 495[MH] ⁺ RT 3.43min
169	 3-butyl-8-chloro-1-(3-{3-[(3-fluoro-4-methoxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	27	m/z 491[MH] ⁺ RT 3.31min

The following compounds (**Table 12**) were prepared using a method analogous to that for **Example 90**, using the appropriate amidoxime [with the exception that **Example 170** was conducted on half the scale of **Example 90** and during workup the aqueous phase was neutralised prior to extraction; **Example 171** was conducted on half the scale of **Example 90** and the crude product stirred with 2M NaOH (0.5ml) in EtOH (1ml) for 5h prior to workup and MDAP; for **Example 175** 0.185ml (0.5mmol) of 21% NaOEt was used].

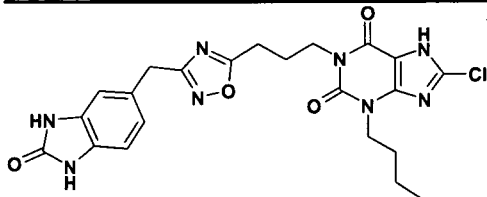
10 **Table 12**

Example	Structure	Yield (mg)	LC/MS
170	 3-butyl-8-chloro-1-(3-{3-(3-pyridinylmethyl)-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	20	m/z 444 [MH] ⁺ RT 2.74min
171	 3-butyl-8-chloro-1-(3-{3-[(5-methyl-3-isoxazolyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	7.2	m/z 448 [MH] ⁺ RT 3.13min

	dione		
172	 3-butyl-8-chloro-1-[3-(3-phenyl-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	36.7	m/z 429 [MH] ⁺ RT 3.36min
173	 3-butyl-8-chloro-1-{3-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	41.1	m/z 447 [MH] ⁺ RT 3.42min
174	 3-butyl-8-chloro-1-{3-[3-(5-chloro-2-thienyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	36.7	m/z 469 [MH] ⁺ RT 3.60min
175	 1-[3-(3-{[3,4-bis(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione	47.0	m/z 503 [MH] ⁺ RT 3.14min
176	 3-butyl-8-chloro-1-(3-{3-[(pentafluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	29.2	m/z 533 [MH] ⁺ RT 3.62min

177	 <i>N</i>-[4-({5-[3-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1<i>H</i>-purin-1-yl)propyl]-1,2,4-oxadiazol-3-yl)methyl}phenyl]acetamide	29.8	<i>m/z</i> 500 [MH] ⁺ RT 3.01min
178	 3-butyl-8-chloro-1-[3-(3-{4-(trifluoromethyl)phenyl}methyl)-1,2,4-oxadiazol-5-yl]propyl]-3,7-dihydro-1<i>H</i>-purine-2,6-dione	37.7	<i>m/z</i> 511 [MH] ⁺ RT 3.65min
179	 3-butyl-8-chloro-1-[3-[3-(2-naphthalenylmethyl)-1,2,4-oxadiazol-5-yl]propyl]-3,7-dihydro-1<i>H</i>-purine-2,6-dione	47.5	<i>m/z</i> 493 [MH] ⁺ RT 3.69min

Example 180: 3-Butyl-8-chloro-1-[3-[3-[(2-oxo-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]-1,2,4-oxadiazol-5-yl]propyl]-3,7-dihydro-1*H*-purine-2,6-dione



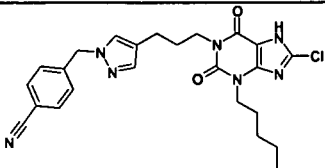
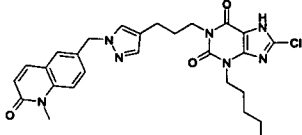
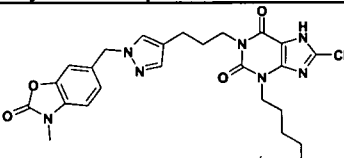
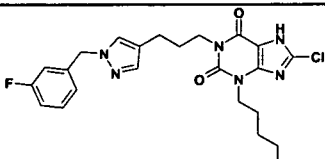
- 5 Synthesised by a method analogous to that for **Example 99** with the exception that a further 2 equivalents of 21% sodium ethoxide (0.11ml) was used, the extra heating time was 20min. and the product was isolated by filtration followed by trituration with hot MeOH. Yield 14.5mg.
LC/MS: *m/z* 499 [MH]⁺, RT 2.78min.

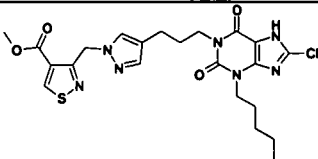
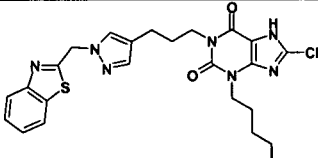
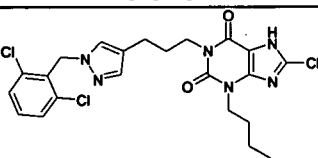
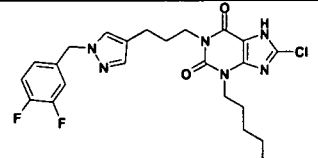
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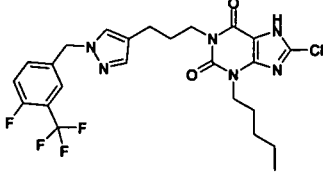
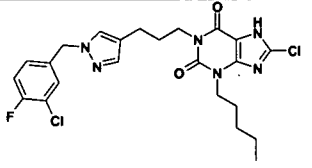
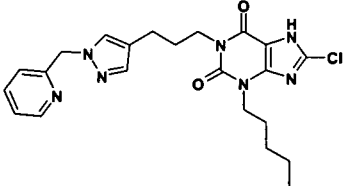
The following compounds (**Table 13**) were prepared by a method analogous to that for **Example 1** [with the exception that **Examples 181-186** were all synthesised on a scale starting from 50mg of 8-chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione; **Examples 184, 186, 188, 189 and 190** were

additionally purified by MDAP following aminopropyl SPE; **Example 185** was additionally purified by recrystallisation from MeOH following aminopropyl SPE; for **Example 191**, 128mg (1.2mmol) of sodium carbonate was used; during workup the aqueous phase was adjusted to pH6 prior to extraction; and the product was purified by MDAP then by further HPLC; for **Example 184** solids which precipitated during workup were combined with the EtOAc extracts prior to SPE].

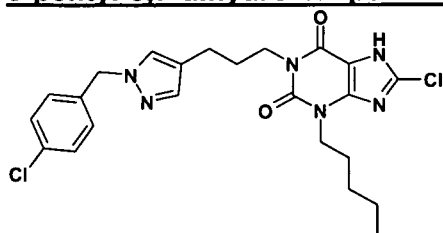
Table 13

Example	Structure	Yield (mg)	LC/MS
181	 4-((4-{3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl}-1H-pyrazol-1-yl)methyl)benzonitrile	36.0	m/z 480 [MH] ⁺ RT 3.24min
182	 8-chloro-1-(3-{1-[(1-methyl-2-oxo-1,2-dihydro-6-quinolinyl)methyl]-1H-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	7.6	m/z 536 [MH] ⁺ RT 3.03min
183	 8-chloro-1-(3-{1-[(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)methyl]-1H-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	34.0	m/z 526 [MH] ⁺ RT 3.11min
184	 8-chloro-1-(3-{1-[(3-(4-fluorophenyl)-1H-pyrazol-1-yl)methyl]-1H-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	26.2	m/z 473 [MH] ⁺ RT 3.38min

	fluorophenyl)methyl]-1 <i>H</i> -pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1 <i>H</i> -purine-2,6-dione		
185	 methyl 3-({4-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1<i>H</i>-purin-1-yl)propyl]-1<i>H</i>-pyrazol-1-yl}methyl)-4-isothiazolecarboxylate	16.2	m/z 520 [MH] ⁺ RT 3.12min
186	 1-{3-[1-(1,3-benzothiazol-2-ylmethyl)-1<i>H</i>-pyrazol-4-yl]propyl}-8-chloro-3-pentyl-3,7-dihydro-1<i>H</i>-purine-2,6-dione	21.0	m/z 512 [MH] ⁺ RT 3.36min
187	 8-chloro-1-(3-{1-[(2,6-dichlorophenyl)methyl]-1<i>H</i>-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1<i>H</i>-purine-2,6-dione	65.0	m/z 523, 525 [Cl isotopes MH ⁺] RT 3.77min
188	 8-chloro-1-(3-{1-[(3,4-difluorophenyl)methyl]-1<i>H</i>-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1<i>H</i>-purine-2,6-dione	35.0	m/z 491 [MH] ⁺ RT 3.61min

189	 8-chloro-1-[3-(1-([4-fluoro-3-(trifluoromethyl)phenyl)methyl]-1<i>H</i>-pyrazol-4-yl)propyl]-3-pentyl-3,7-dihydro-1<i>H</i>-purine-2,6-dione	17.0	m/z 541 [MH] ⁺ RT 3.76min
190	 8-chloro-1-(3-{1-[(3-chloro-4-fluorophenyl)methyl]-1<i>H</i>-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1<i>H</i>-purine-2,6-dione	27.0	m/z 507 [MH] ⁺ RT 3.73min
191	 8-chloro-3-pentyl-1-{3-[1-(2-pyridinylmethyl)-1<i>H</i>-pyrazol-4-yl]propyl}-3,7-dihydro-1<i>H</i>-purine-2,6-dione	11.4	m/z 456 [MH] ⁺ RT 3.13min

Example 192: 8-Chloro-1-(3-{1-[(4-chlorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



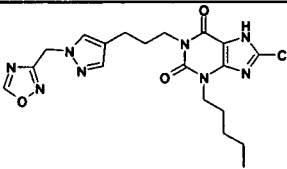
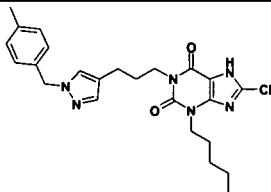
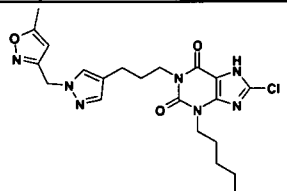
- 5 8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-
purine-2,6-dione (50mg, 0.123mmol) in dry DMF (1.5ml) was stirred with sodium
carbonate (75mg, 0.708mmol) and 4-chlorobenzyl bromide (150mg, 0.73mmol) at 40°C
for 18h. The mixture was partitioned between EtOAc and water, the organic phase
washed with brine, dried and evaporated. The product was purified by normal phase
10 chromatography on silica (Companion System, EtOAc – cyclohexane gradient) giving

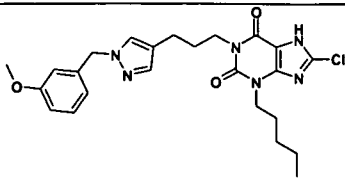
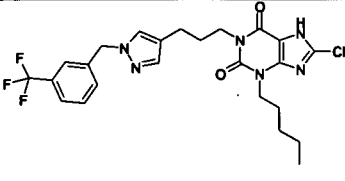
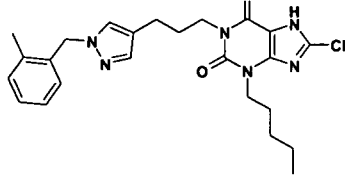
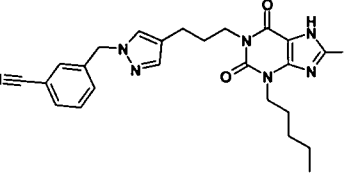
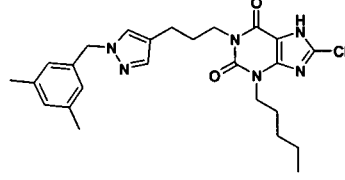
an oil (44mg). This was stirred in degassed, dry DMF (1ml) with tetrakis(triphenylphosphine)palladium(0) (19mg) and morpholine (0.072ml) under nitrogen for 6h. The mixture was partitioned between EtOAc and 2M HCl and the organic phase evaporated and purified by the usual aminopropyl SPE procedure. Yield 21.0mg.

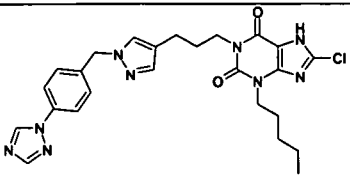
LC/MS: m/z 489 [MH⁺], RT 3.59min.

The following compounds (**Table 14**) were prepared by a method analogous to that for **Example 6** [with the exception that for **Example 193** a second portion of Pd(PPh₃)₄ was added after 5h, stirring was continued overnight, and final purification was achieved by HPLC; for **Example 195** required additional purification by MDAP; **Example 200** required additional purification by recrystallisation from MeOH; **Example 201** required additional purification by trituration with MeOH].

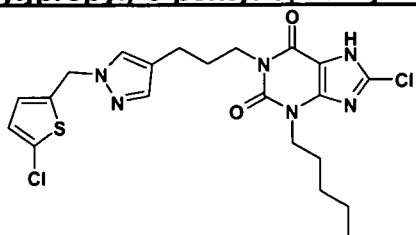
Table 14

Example	Structure	Yield (mg)	LC/MS
193	 8-chloro-1-{3-[1-(1,2,4-oxadiazol-3-ylmethyl)-1H-pyrazol-4-yl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	7.3	m/z 447 [MH] ⁺ RT 3.06min
194	 8-chloro-1-(3-{1-[(4-methylphenyl)methyl]-1H-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	23.7	m/z 469 [MH] ⁺ RT 3.49min
195	 8-chloro-1-(3-{1-[(5-methyl-3-isoxazolyl)methyl]-1H-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	29.0	m/z 460 [MH] ⁺ RT 3.10min

196	 8-chloro-1-[3-(1-([3-(methoxy)phenyl]methyl)-1H-pyrazol-4-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	56.0	m/z 485 [MH] ⁺ RT 3.41min
197	 8-chloro-3-pentyl-1-[3-(1-([3-(trifluoromethyl)phenyl]methyl)-1H-pyrazol-4-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	47.0	m/z 523 [MH] ⁺ RT 3.61min
198	 8-chloro-1-(3-{1-[(2-methylphenyl)methyl]-1H-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	44.0	m/z 469 [MH] ⁺ RT 3.54min
199	 3-({4-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-1H-pyrazol-1-yl}methyl)benzonitrile	51.0	m/z 480 [MH] ⁺ RT 3.32min
200	 8-chloro-1-(3-{1-[(3,5-dimethylphenyl)methyl]-1H-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	36.7	m/z 483 [MH] ⁺ RT 3.66min

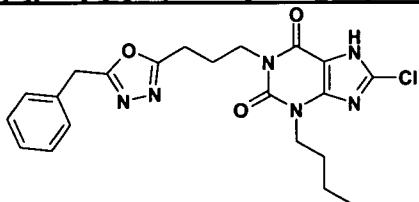
201	 8-chloro-3-pentyl-1-[3-(1-((4-(1H-1,2,4-triazol-1-yl)phenyl)methyl)-1H-pyrazol-4-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	21.2	m/z 522 [MH]⁺ RT 3.09min
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Example 202 : 8-Chloro-1-(3-(1-((5-chloro-2-thienyl)methyl)-1H-pyrazol-4-yl)propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione



- 5 To 8-chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1H-pyrazol-4-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione (61mg, 0.15mmol) in dry THF (1ml) at -78°C, under nitrogen, was added potassium t-butoxide (1M in THF, 0.15ml), followed by 2-chloro-5-(chloromethyl)thiophene (25mg, 0.15mmol). Stirring was continued at -78°C for 15min, then at room temperature for 1h and finally at 60°C for 18h. The solution was degassed
- 10 and morpholine (0.13ml) and tetrakis(triphenylphosphine)palladium(0) (35mg) added and stirring continued for 6h. Further quantities (0.2ml morpholine, 50mg Pd(PPh₃)₄) were added and stirring continued overnight. Worked up by partition between EtOAc and 2M HCl, the organic phase evaporated and purified by the standard aminopropyl SPE procedure followed by MDAP yielding title compound as a white solid (5.1mg).
- 15 LC/MS: m/z 495 [MH]⁺, RT 3.68min.

Example 203: 3-Butyl-8-chloro-1-[3-[5-(phenylmethyl)-1,3,4-oxadiazol-2-yl]propyl]-3,7-dihydro-1H-purine-2,6-dione

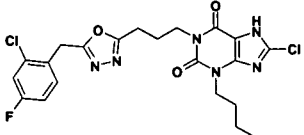
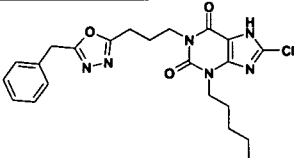
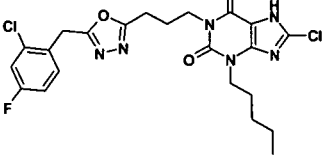


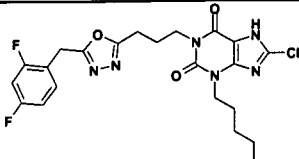
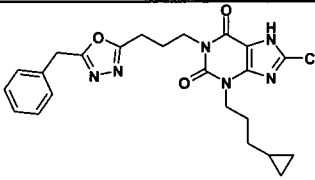
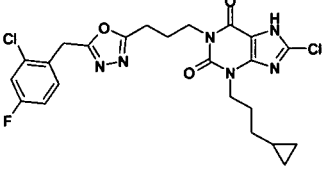
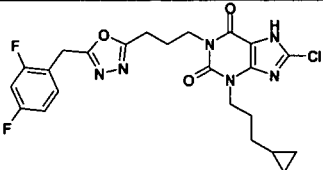
- 20 To 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (99mg, 0.35mmol) in dry DMF (2ml) was added cesium carbonate (137mg, 0.42mmol) followed by a solution in dry DMF (1ml) of 2-(3-chloropropyl)-5-(phenylmethyl)-1,3,4-oxadiazole (99mg, 0.42mmol). The mixture was stirred under nitrogen and heated at 55°C for 2.5h then stirred at room temperature overnight. The mixture was degassed by repeatedly
- 25 evacuating and admitting nitrogen and then tetrakis(triphenylphosphine)palladium(0)

(81mg, 0.07mmol) and morpholine (0.305ml, 3.5mmol) were added and stirring was continued for 5h EtOAc and 2M HCl were added and the mixture stirred for 20min then filtered. The organic phase was separated and evaporated, and the product was purified by aminopropyl SPE (5g) washing with THF-MeOH (1:1) then with MeOH and eluting the acidic product with DCM-MeOH (1:1) containing 5% added AcOH. The product thus obtained was purified further by MDAP to yield the title compound (92mg). LC/MS: m/z 443 [MH]⁺, RT 3.18min.

The following compounds (**Table 15**) were prepared by a method analogous to that for **Example 203**, with the exception that **Example 211** was further purified by HPLC.

Table 18

Example	Product structure	Xanthine precursor	Alkylating agent	Yield (mg)	LC/MS
204	 3-butyl-8-chloro-1-(3-{5-[(2-chloro-4-fluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (99mg)	2-[(2-chloro-4-fluorophenyl)methyl]-5-(3-chloropropyl)-1,3,4-oxadiazole (121mg)	90	m/z 495 [MH] ⁺ RT 3.34 min
205	 8-chloro-3-pentyl-1-(3-{5-(phenylmethyl)-1,3,4-oxadiazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (104mg)	2-(3-chloropropyl)-5-(phenylmethyl)-1,3,4-oxadiazole (99mg)	98	m/z 457 [MH] ⁺ RT 3.35 min
206	 8-chloro-1-(3-{5-[(2-chloro-4-fluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (104mg)	2-[(2-chloro-4-fluorophenyl)methyl]-5-(3-chloropropyl)-1,3,4-oxadiazole (121mg)	98	m/z 509 [MH] ⁺ RT 3.52 min

	yl}propyl)-3-pentyl-3,7-dihydro-1 <i>H</i> -purine-2,6-dione				
207	 8-chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3-pentyl-3,7-dihydro-1<i>H</i>-purine-2,6-dione	8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1 <i>H</i> -purine-2,6-dione (104mg)	2-(3-chloropropyl)-5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazole (111mg)	43	m/z 493 [MH] ⁺ RT 3.40 min
208	 8-chloro-3-(3-cyclopropylpropyl)-1-{3-[5-(phenylmethyl)-1,3,4-oxadiazol-2-yl]propyl}-3,7-dihydro-1<i>H</i>-purine-2,6-dione	8-chloro-3-(3-cyclopropylpropyl)-7-(2-propen-1-yl)-3,7-dihydro-1 <i>H</i> -purine-2,6-dione (108mg)	2-(3-chloropropyl)-5-(phenylmethyl)-1,3,4-oxadiazole (99mg)	95	m/z 469 [MH] ⁺ RT 3.34 min
209	 8-chloro-1-(3-{5-[(2-chloro-4-fluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3-(3-cyclopropylpropyl)-3,7-dihydro-1<i>H</i>-purine-2,6-dione	8-chloro-3-(3-cyclopropylpropyl)-7-(2-propen-1-yl)-3,7-dihydro-1 <i>H</i> -purine-2,6-dione (108mg)	2-[(2-chloro-4-fluorophenyl)methyl]-5-(3-chloropropyl)-1,3,4-oxadiazole (121mg)	99	m/z 521 [MH] ⁺ RT 3.51 min
210	 8-chloro-3-(3-cyclopropylpropyl)-1-(3-{5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3,7-dihydro-1<i>H</i>-purine-2,6-dione	8-chloro-3-(3-cyclopropylpropyl)-7-(2-propen-1-yl)-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	2-(3-chloropropyl)-5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazole	49	m/z 505 [MH] ⁺ RT 3.40 min

	{5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	dione (108mg)	(111mg)		min
211	 3-butyl-8-chloro-1-((3-{5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3,7-dihydro-1 <i>H</i> -purine-2,6-dione)	3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1 <i>H</i> -purine-2,6-dione (99mg)	2-(3-chloropropyl)-5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazole (111mg)	38.9	m/z 479 [MH] ⁺ RT 3.31 min

Synthesis of chloropropyl 1,3,4-oxadiazole intermediates from Table 15:

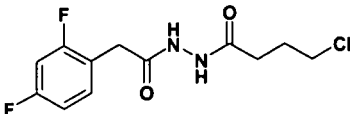
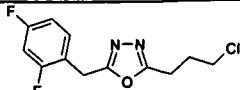
2-[(2-chloro-4-fluorophenyl)methyl]-5-(3-chloropropyl)-1,3,4-oxadiazole

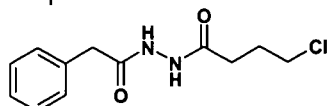
5 2-(3-chloropropyl)-5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazole

2-(3-chloropropyl)-5-(phenylmethyl)-1,3,4-oxadiazole

Diacyl hydrazines (500mg, synthesis below) were stirred in dry toluene (4ml) and phosphorus oxychloride (4ml) was added. The mixtures were heated at 90°C for 2h then allowed to cool and the solvents evaporated. The residues were dissolved in dry toluene, evaporated and then partitioned between EtOAc and aqueous NaHCO₃. The organic phases were washed with brine, dried over Na₂SO₄ and evaporated to give the required oxadiazoles as colourless oils. These were not purified further but reacted directly with the xanthines as above.

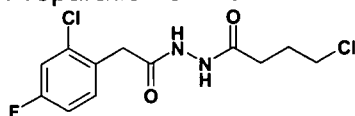
Diacyl hydrazine	Oxadiazole product	Yield (mg)	LC/MS
 4-chloro- <i>N</i> -(phenylacetyl)butanohydrazide	 2-(3-chloropropyl)-5-(phenylmethyl)-1,3,4-oxadiazole	446	m/z 237 [MH] ⁺ RT 2.94min
 4-chloro- <i>N</i> -[(2-chloro-4-fluorophenyl)acetyl]butanohydrazide	 2-[(2-chloro-4-fluorophenyl)methyl]-5-(3-chloropropyl)-1,3,4-oxadiazole	405	m/z 289 [MH] ⁺ RT 3.17min

	(3-chloropropyl)-1,3,4-oxadiazole		
 4-chloro-<i>N'</i>-[(2,4-difluorophenyl)acetyl]butanohydrazide	 2-(3-chloropropyl)-5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazole	333	m/z 273 [MH] ⁺ RT 3.03min

Preparation of 4-chloro-*N'*-(phenylacetyl)butanohydrazide

To 4-chlorobutyl chloride (1.12ml, 10mmol) in dry DCM (10ml) was added, dropwise, over 40min, a mixture of phenylacetic hydrazide (1.5g, 10mmol) and DIPEA (1.77ml, 10.2mmol) in dry DCM (40ml) at room temperature. A dense white precipitate formed. After a further 20min. 2M HCl (30ml) was added and the title compound (white solid) was filtered off, washed with water and dried (2.24g).

LC/MS: m/z 255 [MH]⁺, RT 2.20min.

Preparation of 4-chloro-*N'*-[(2-chloro-4-fluorophenyl)acetyl]butanohydrazide

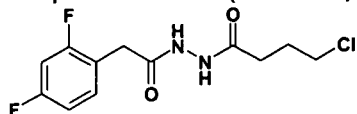
(i) A solution of 2-chloro-4-fluorophenylacetyl chloride (10mmol) in dry DCM (15ml) was added over 20min to a mixture of *t*-butyl carbazate (1.32g, 10mmol) and DIPEA (1.77ml, 10.2mmol) in dry DCM (20ml). After stirring for a further 2h, the mixture was washed with 1M HCl then with aqueous NaHCO₃. A white solid precipitated at this point, which was filtered off, washed with water and DCM then dried to yield 1,1-dimethylethyl 2-[(2-chloro-4-fluorophenyl)acetyl]hydrazinecarboxylate (1.94g).

(ii) This compound (1.92g, 6.34mmol) was suspended in dioxan (2ml) and 4M HCl in dioxan (5ml) was added. A dense white precipitate formed. After 1h the mixture was partitioned between EtOAc and saturated aqueous NaHCO₃ and the organic phase washed with brine, dried (Na₂SO₄) and evaporated giving 2-(2-chloro-4-fluorophenyl)acetohydrazide as a white solid (1.07g).

(iii) A mixture of 2-(2-chloro-4-fluorophenyl)acetohydrazide (909mg, 4.5mmol) and DIPEA (0.817ml, 4.7mmol) in dry DCM (65ml) was added over 20min to 4-chlorobutyl chloride (0.505ml, 4.5mmol) in dry DCM (5ml). After 1.5h, 2M HCl was added and the precipitated 4-chloro-*N'*-[(2-chloro-4-fluorophenyl)acetyl]butanohydrazide was filtered off, washed with water and dried (1.24g).

LC/MS: m/z 307 [MH]⁺, RT 2.61min.

Preparation of 2-(3-chloropropyl)-5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazole



- 5 (i) A solution of 2,4-difluorophenylacetyl chloride (10mmol) in dry DCM (15ml) was added over 10min. to a mixture of t-butyl carbazate (1.32g, 10mmol) and DIPEA (1.77ml, 10.2mmol) in dry DCM (20ml). After stirring for 1.5h the mixture was washed with 1M HCl then with aqueous NaHCO₃. The organic phase was evaporated to afford 1,1-dimethylethyl 2-[(2,4-difluorophenyl)acetyl]hydrazinecarboxylate as a white solid.

10

- (ii) 1,1-dimethylethyl 2-[(2,4-difluorophenyl)acetyl]hydrazinecarboxylate (10mmol) in dioxan (5ml) was stirred with 4M HCl in dioxan (8ml) for 1.5h. The mixture was partitioned between EtOAc and saturated aqueous NaHCO₃ and the organic phase washed with brine, dried (Na₂SO₄) and evaporated. Reaction was incomplete so the residue was stirred again with 4M HCl in dioxan (10ml) for 2.5h. Workup as previously gave 2-(2,4-difluorophenyl)acetohydrazide as a solid (570mg).
- 15

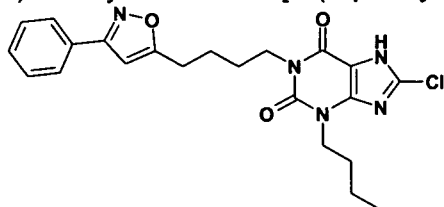
- (iii) A mixture of 2-(2,4-difluorophenyl)acetohydrazide (570mg, 3.06mmol) and DIPEA (0.553ml, 3.2mmol) in dry DCM (30ml) was added to 4-chlorobutyl chloride (0.343ml, 3.06mmol) in dry DCM (5ml) over 15min. An immediate white precipitate formed. After stirring for 1h, 2M HCl (20ml) was added and the solid 2-(3-chloropropyl)-5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazole was filtered off, washed with water and dried (726mg).
- 20

LC/MS: m/z 291 [MH]⁺, RT 2.45min.

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Example 212 : 3-Butyl-8-chloro-1-[4-(3-phenyl-5-isoxazolyl)butyl]-3,7-dihydro-1H-purine-2,6-dione

a) 3-Butyl-8-chloro-1-[4-(3-phenyl-5-isoxazolyl)butyl]-3,7-dihydro-1H-purine-2,6-dione

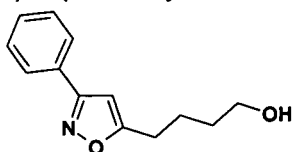


30

- 3-Butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (100mg, 0.354mmol) and 4-(3-phenyl-5-isoxazolyl)-1-butanol (77mg, 0.355mmol) were dissolved in dry THF (4ml) under nitrogen. A solution of dibenzyl azodicarboxylate (94%, 224mg, 0.708mmol) in dry THF (2ml) was added. The mixture was cooled to 0°C and a solution of triphenylphosphine (185mg, 0.708mmol) in dry THF (1ml) was added. The mixture was stirred for 20min at 0°C then at room temperature overnight. The
- 35

mixture was degassed then stirred with morpholine (0.308ml) and tetrakis(triphenylphosphine)palladium(0) (82mg) for 4.5h. A further 60mg of tetrakis(triphenylphosphine)palladium(0) was added and stirring continued overnight. The reaction was worked up by partition between EtOAc and 2M HCl, the organic phase evaporated and purified by aminopropyl SPE (5g) washing with THF-MeOH (1:1), MeOH and eluting with DCM-MeOH (1:1) containing 5% AcOH. Further purification by MDAP afforded the title compound (56mg).
LC/MS: m/z 442 [MH]⁺, RT 3.59min.

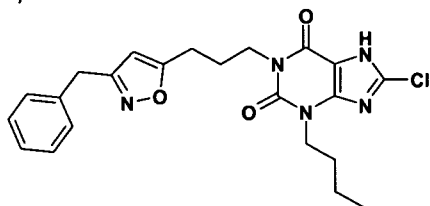
10 b) 4-(3-Phenyl-5-isoxazolyl)-1-butanol



To *N*-hydroxybenzenecarboximidoyl chloride (622mg, 4mmol) in dry DCM (6ml) was added 5-hexyn-1-ol (431mg, 4.4mmol). The mixture was cooled to 0°C under nitrogen as triethylamine (0.612ml, 4.4mmol) was added dropwise over 10min. Stirred for a further 20min at 0°C then at room temperature overnight. The mixture was washed with water and the organic phase evaporated. The product was purified by silica SPE (20g) eluting with EtOAc-cyclohexane (1:2, then 3:1) to give a white waxy solid (443mg).
LC/MS: m/z 218 [MH]⁺, RT 2.74min.

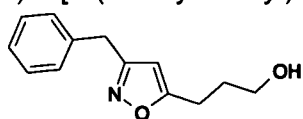
20 **Example 213: 3-Butyl-8-chloro-1-{3-[3-(phenylmethyl)-5-isoxazolyl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione**

a) 3-Butyl-8-chloro-1-{3-[3-(phenylmethyl)-5-isoxazolyl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



Prepared analogously to 3-butyl-8-chloro-1-[4-(3-phenyl-5-isoxazolyl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione (Example 213) using half the molar quantities, starting from 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (50mg, 0.177mmol) and 3-[3-(phenylmethyl)-5-isoxazolyl]-1-propanol (38.4mg, 0.177mmol). Yield 24.2mg, LC/MS: m/z 442 [MH]⁺, RT 3.43min.

b) 3-[3-(Phenylmethyl)-5-isoxazolyl]-1-propanol

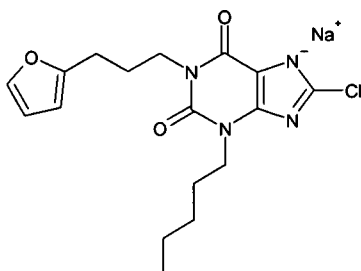


Synthesised as with 4-(3-phenyl-5-isoxazolyl)-1-butanol, using *N*-hydroxy-2-phenylethanimidoyl chloride (253mg, 1.5mmol) and 4-pentyn-1-ol (139mg, 1.65mmol). Yield 61mg of pale yellow oil.

LC/MS: m/z 218 $[MH]^+$, RT 2.62min.

5

Comparative Example B: 8-Chloro-1-[3-(2-furanyl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt



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A GreenHouseTM tube equipped with a stirrer was charged with a 0.25ml aliquot of a 0.54M solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (0.13mmol) in THF. To the mixture was added 3-(2-furanyl)-1-propanol (21mg, 0.16mmol, 1.2eq) in THF (0.25ml), followed by a 0.25ml aliquot of a 0.71M solution of bis(1,1-dimethylethyl) (*E*)-1,2-diazenedicarboxylate (0.18mmol) in THF and then a 0.25ml aliquot of a 0.71M solution of triphenylphosphine (0.18mmol) in THF. The solution was stirred in a GreenHouseTM under nitrogen for 16h. To the mixture was added a further 0.25ml aliquot of a 1.4M solution of bis(1,1-dimethylethyl) (*E*)-1,2-diazenedicarboxylate (0.36mmol) in THF and then a further 0.25ml aliquot of a 1.4M solution of triphenylphosphine (0.36mmol) in THF. The mixture was stirred for 16h under a stream of nitrogen.

15

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Tetrakis(triphenylphosphine)palladium(0) (16mg, 0.014mmol) and morpholine (0.12ml, 1.35mmol) were added to the mixture which was stirred for 16h under a stream of nitrogen. The reaction mixture was concentrated under nitrogen and the crude material dissolved in aqueous NaOH solution (0.5ml, 2M). The resulting solution was purified using aminopropyl SPE (eluting with AcOH in DCM and MeOH). Further purification using C18 SPE (eluting with a water, ammonia and MeCN mixture) afforded the title compound as a clear gum (22mg, 45%).

25

30

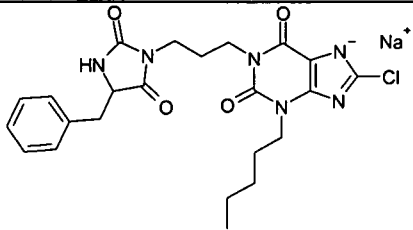
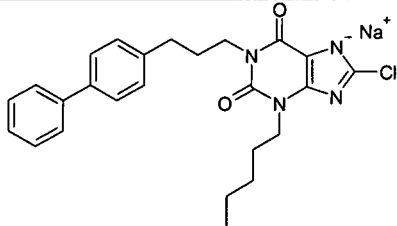
LC/MS: m/z 365 $[MH]^+$, RT 3.48min.

¹H NMR (DMSO-*d*₆) δ : 0.85 (t, 3H, *J* = 7Hz), 1.35-1.19 (m, 4H), 1.62 (m, 2H), 1.79 (m, 2H), 2.59 (t, 2H, *J* = 8Hz), 3.93 – 3.80 (m, 4H), 6.14 (d, 1H, *J* = 3Hz), 6.32 (dd, 1H, *J* = 3 and 2Hz), 7.48 (d, 1H, *J* = 2Hz).

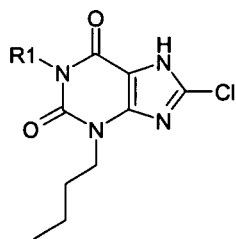
35

The following compounds (Table 16) were prepared by a method analogous to that for Comparative Example B.

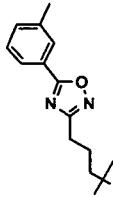
Table 16

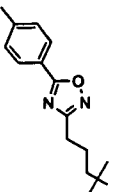
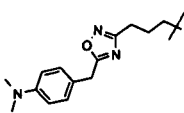
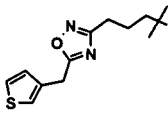
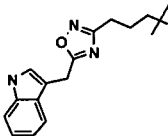
Example	Structure	Yield (mg)	LC/MS
214	 8-chloro-1-{3-[2,5-dioxo-4-(phenylmethyl)-1-imidazolidinyl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	9	m/z 487 [MH] ⁺ RT 3.15min
215	 1-[3-(4-biphenyl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	19	m/z 451 [MH] ⁺ RT 4.06min

5 The following compounds (**Table 17**) were prepared using a method analogous to that for **Example 113**, from the corresponding acids and (1Z)-4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxybutanimidamide.

Table 17

10

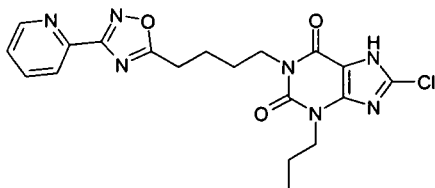
Example	Name	Compound: R1 =	LC/MS
216	3-butyl-8-chloro-1-{3-[5-(3-methylphenyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione		m/z 443 [MH] ⁺ RT 3.47min

Example	Name	Compound: R1 =	LC/MS
217	3-butyl-8-chloro-1-{3-[5-(4-methylphenyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione		m/z 443 [MH] ⁺ RT 3.34min
218	3-butyl-8-chloro-1-{3-[5-([4-(dimethylamino)phenyl]methyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione		m/z 486 [MH] ⁺ RT 3.24min
219	3-butyl-8-chloro-1-{3-[5-(3-thienylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione		m/z 449 [MH] ⁺ RT 3.24min
220	3-butyl-8-chloro-1-{3-[5-(1H-indol-3-ylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione		m/z 482 [MH] ⁺ RT 3.29min

Example 221: 8-Chloro-3-propyl-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione

5

a) 8-Chloro-3-propyl-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione



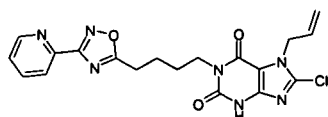
- 10 A solution of 8-chloro-7-(2-propen-1-yl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione (40mg, 0.09mmol) in DMF (3ml) was treated with potassium carbonate (15mg, 0.11mmol) and 1-iodopropane (19mg, 0.11mmol). The mixture was heated at 40°C for 3h then at 70°C for a further 3h. The mixture was cooled and degassed by the successive application of vacuum and nitrogen gas.
- 15 The mixture was then treated with a solution of tetrakis(triphenylphosphine)palladium(0) (10mg, 0.009mmol) and morpholine (0.1ml, 1.2mmol) and then stirred overnight. The mixture was evaporated and partitioned between chloroform (2ml) and water (2ml). The aqueous phase was extracted with further chloroform (2ml) and the combined organics evaporated and the residue dissolved in methanol (2ml). The solution was applied to a
- 20 1g aminopropyl SPE and eluted with methanol and then with 5% acetic acid in

methanol. Product-containing fractions were pooled and evaporated and the product further purified by MDAP to reveal 8-chloro-3-propyl-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione (1.4mg) as a white solid.

LC/MS: m/z 430 $[MH]^+$, RT 2.84min.

5

b) 8-Chloro-7-(2-propen-1-yl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



10

A suspension of *N*-hydroxy-2-pyridinecarboximidamide (1.15g, 8.4mmol) in anhydrous THF (20ml) was treated with sodium methoxide (0.38g, 7.0mmol) and the mixture stirred for 5min. The mixture was treated with ethyl 5-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]pentanoate (2g, 5.6mmol) and the stirred for about 5min until all the material had dissolved. The mixture was then sealed and heated in a microwave at 120°C for 15min then cooled and partitioned between ethyl acetate (100ml) and saturated aqueous sodium bicarbonate (50ml). The aqueous phase was extracted with further ethyl acetate (50ml) and the combined organics dried ($MgSO_4$), filtered and evaporated. The product was purified by flash chromatography using a gradient elution from 1:9 ethyl acetate/cyclohexane to ethyl acetate to reveal 8-chloro-7-(2-propen-1-yl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione (1.49g) as a white solid.

15

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LC/MS: m/z 428 $[MH]^+$, RT 2.70min.

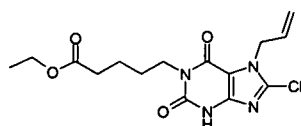
25

Similarly prepared was 8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione using ethyl 4-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]butanoate.

LC/MS: m/z 463 $[MH]^+$, RT 3.09min.

30

c) Ethyl 5-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]pentanoate



35

A solution of 8-chloro-7-(2-propen-1-yl)-3-({[2-(trimethylsilyl)ethyl]oxy}methyl)-3,7-dihydro-1*H*-purine-2,6-dione (10g, 28mmol) in DMF (10ml) was treated with potassium carbonate (4.8g, 35mmol) and ethyl 5-bromopentanoate (6.5g, 31mmol) and then heated to 70°C for 3h, cooled and evaporated. The residue was partitioned between

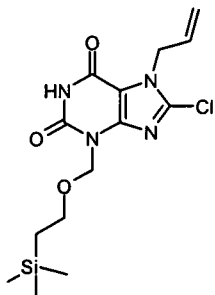
ethyl acetate (100ml) and water (50ml). The organic phase was dried (MgSO_4), filtered and evaporated and the crude intermediate dissolved in dichloromethane (90ml), treated with trifluoroacetic acid (17ml) and the mixture stirred at ambient temperature overnight. Toluene (50ml) was added and the mixture evaporated to dryness. The product was purified by flash chromatography using a gradient elution from cyclohexane to ethyl acetate to reveal 8.65g of ethyl 5-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1H-purin-1-yl]pentanoate as a white solid.

LC/MS: m/z 355 $[\text{MH}]^+$, RT 2.75min.

Similarly prepared was ethyl 4-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1H-purin-1-yl]butanoate.

LC/MS: m/z 341 $[\text{MH}]^+$, RT 2.61min.

d) 8-Chloro-7-(2-propen-1-yl)-3-([2-(trimethylsilyl)ethyl]oxy)methyl)-3,7-dihydro-1H-purine-2,6-dione

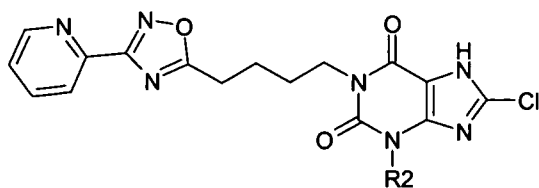


To a solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (5g, 22.1mmol) in DMF (80ml) was added 2,2-(trimethylsilyl)ethoxymethyl chloride (4.3ml, 24.2mmol) and sodium carbonate (2.6g, 24.2mmol). After stirring at room temperature overnight further 2,2-(trimethylsilyl)ethoxymethyl chloride (4.3ml, 24.2mmol) and sodium carbonate (1.3g, 12.1mmol) were added and stirring continued for 2h. The reaction mixture was then partitioned between 5% LiCl aq and ethyl acetate. The organic extract was separated, washed with brine, dried (MgSO_4) and concentrated. Purification by BiotageTM chromatography using a silica cartridge eluting 1:4-1:2 ethyl acetate/cyclohexane afforded the title compound (3.14g, 40%).

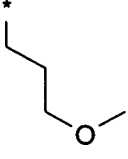
m/z 374 $[\text{MNH}_4]^+$

The following compounds (**Table 18**) were prepared by a method analogous to that for **Example 221**, from 8-chloro-7-(2-propen-1-yl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione and the appropriate alkylating agent.

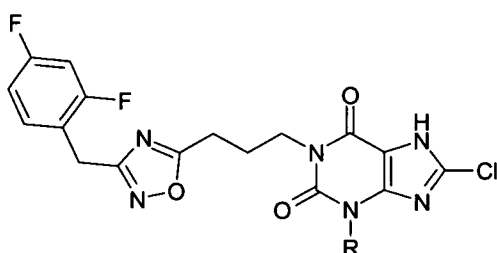
Table 18

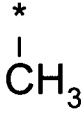
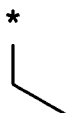
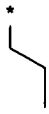


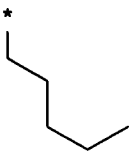
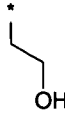
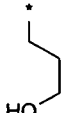
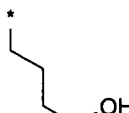
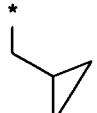
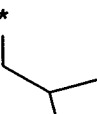
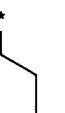
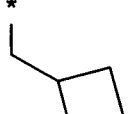
Example	R ² =	Name	Yield (mg)	m/z	RT (min)
222		8-chloro-3-methyl-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	1.7	402	2.53
223		8-chloro-3-ethyl-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	1.4	416	2.66
224		8-chloro-3-(2-methylpropyl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	2.0	444	2.99
225		8-chloro-3-(3-methylbutyl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	1.6	458	3.21
226		8-chloro-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	2.1	498	3.07
227		8-chloro-3-[2-(phenyloxy)ethyl]-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	1.7	508	3.11

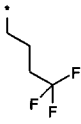
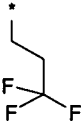
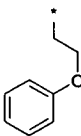
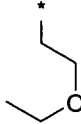
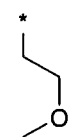
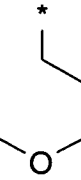
Example	R ² =	Name	Yield (mg)	m/z	RT (min)
228		8-chloro-3-[3-(methoxy)propyl]-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	1.0	460	2.65

The following compounds (**Table 19**) were prepared by a method analogous to that for **Example 221**, from 8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione and the appropriate alkylating agent.

Table 19

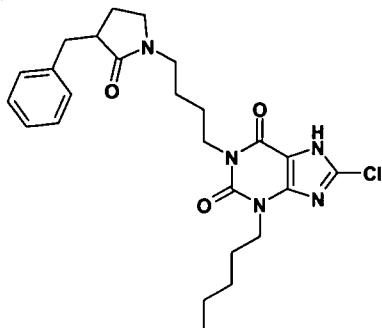
Example	R =	Name	Yield (mg)	m/z	RT (min)
229		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-methyl-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	1.7	437	2.92
230		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-ethyl-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	1.4	451	3.06
231		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-propyl-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	2.2	465	3.22

Example	R =	Name	Yield (mg)	m/z	RT (min)
232		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	2.6	493	3.54
233		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(2-hydroxyethyl)-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	2.7	467	2.72
234		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(3-hydroxypropyl)-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	2.0	481	2.77
235		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(4-hydroxybutyl)-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	1.4	495	2.80
236		8-chloro-3-(cyclopropylmethyl)-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	1.8	477	3.30
237		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(2-methylpropyl)-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	3.5	479	3.36
238		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(3-methylbutyl)-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	3.1	493	3.53
239		8-chloro-3-(cyclobutylmethyl)-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-	2.2	491	3.45

Example	R =	Name	Yield (mg)	m/z	RT (min)
		dihydro-1 <i>H</i> -purine-2,6-dione			
240		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	3.0	533	3.39
241		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	2.7	519	3.34
242		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(phenyloxy)ethyl]-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	1.6	543	3.44
243		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(ethyloxy)ethyl]-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	2.8	495	3.11
244		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(methyloxy)ethyl]-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	2.6	481	2.98
245		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[3-(methyloxy)propyl]-3,7-dihydro-1 <i>H</i> -purine-2,6-dione	2.1	495	3.04

Example 246: 8-Chloro-1-{4-[2-oxo-3-(phenylmethyl)-1-pyrrolidinyl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione

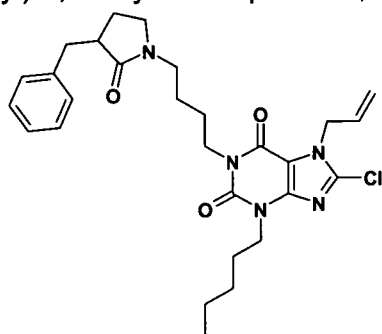
a) 8-Chloro-1-{4-[2-oxo-3-(phenylmethyl)-1-pyrrolidinyl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione



A solution of 8-chloro-1-{4-[2-oxo-3-(phenylmethyl)-1-pyrrolidinyl]butyl}-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (0.35g, 0.67mmol), Pd(PPh₃)₄ (0.082g, 0.07mmol) and morpholine (0.6ml, 6.7mmol) in THF (10ml) was degassed (sequential evacuation followed by addition of nitrogen x 3) then stirred for 4h. The solution was then loaded onto an aminopropyl SPE (5g) and eluted first with MeOH then 5%AcOH/MeOH to provide the title compound containing a small impurity. Further purification over silica (10g SPE, gradient elution ether/ethyl acetate 1:0 to 0:1) provided the title compound as a clear oil (0.10g, 31%).

LC/MS: m/z 486 [MH]⁺

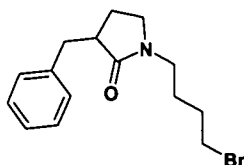
b) 8-Chloro-1-{4-[2-oxo-3-(phenylmethyl)-1-pyrrolidinyl]butyl}-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione



Prepared as with 8-chloro-1-(2-hydroxy-6-phenylhexyl)-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione using 1-(4-bromobutyl)-3-(phenylmethyl)-2-pyrrolidinone as the alkylating agent, potassium carbonate as base and heating at 50°C for 18h. Yield 86%.

LC/MS: m/z 526 [MH]⁺

c) 1-(4-bromobutyl)-3-(phenylmethyl)-2-pyrrolidinone

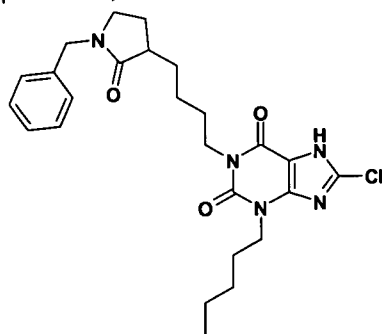


To a solution of 3-(phenylmethyl)-2-pyrrolidinone (0.23g, 1.3mmol) and 1,4-dibromobutane (0.57g, 4.2mmol) in DMF (5ml) was added sodium t-butoxide (0.151g, 1.6mmol) and the solution stirred for 18h. The solution was concentrated and the residues chromatographed over silica (20g SPE, eluting first with cyclohexane then with DCM) to provide the title compound as a colourless oil containing a trace of DMF (0.25g, 61%).

LC/MS: m/z 311 [MH]⁺

Example 247: 8-Chloro-1-{4-[2-oxo-1-(phenylmethyl)-3-pyrrolidinyl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione

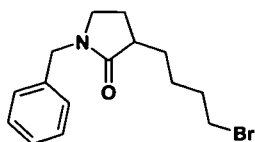
a) 8-Chloro-1-{4-[2-oxo-1-(phenylmethyl)-3-pyrrolidinyl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione



To a solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (0.086g, 0.29mmol) and 3-(4-bromobutyl)-1-(phenylmethyl)-2-pyrrolidinone (0.17g, 0.55mmol, 1:1 mixture with 2-(phenylmethyl)-2-azaspiro[4.4]nonan-1-one) in THF (5ml) was added potassium carbonate (0.08g, 0.58mmol) and the mixture heated and stirred at 50°C for 18h. The solution was allowed to cool then degassed (sequential evacuation followed by addition of nitrogen x 3) and Pd(PPh₃)₄ (0.09g, 0.077mmol) followed by morpholine (0.2ml, 2.2mmol) added and the solution stirred at ambient temperature for 18h. The solution was separated between ethyl acetate and dil HCl and the organics washed with brine, dried and concentrated. Purification of the residues using an aminopropyl SPE (5g) eluting first with MeOH then 5%AcOH/MeOH yielded the title compound as a yellow oil which crystallised on standing under ether (0.031g, 22%).

LC/MS: m/z 486 [MH]⁺

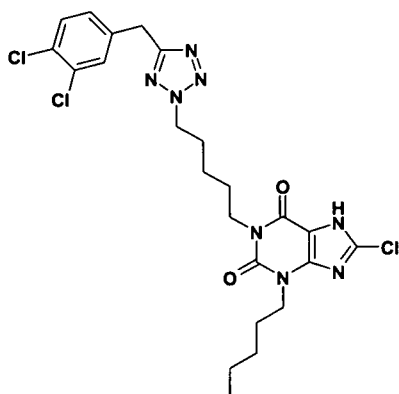
b) 3-(4-Bromobutyl)-1-(phenylmethyl)-2-pyrrolidinone



To a solution of 1-(phenylmethyl)-2-pyrrolidinone (0.47g, 2.7mmol) in THF (10ml) at -78°C was added lithium hexamethyldisilylazine (2.8ml, 2.7mmol, 1M solution) over 5min. After 15min 1,4-dibromobutane (0.32ml, 2.7mmol) was added and the solution
5 allowed to attain ambient temperature over 2h then stirred for a further 18h. The solution was separated between ethyl acetate and water and the organics isolated, dried and concentrated. Chromatography over silica (20g SPE) eluting with cyclohexane then DCM and finally ether provided a clear oil which was a 1:1 mixture of the title compound and 2-(phenylmethyl)-2-azaspiro[4.4]nonan-1-one (0.17g). This was
10 used in the next step without further purification.

LC/MS: m/z 310, 312 [MH]⁺

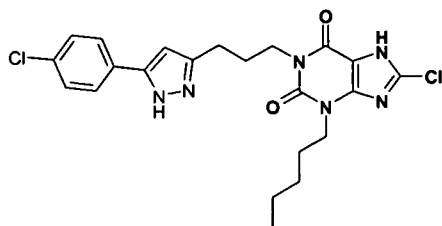
Comparative Example C: 8-Chloro-1-(5-{5-[(3,4-dichlorophenyl)methyl]-2H-tetrazol-2-yl}pentyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione



To a solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (0.18g, 0.61mmol) in THF (5ml) was added 5-{5-[(3,4-dichlorophenyl)methyl]-2H-tetrazol-2-yl}-1-pentanol (0.191g, 0.61mmol; prepared in similar fashion to **Example 35**), triphenylphosphine (0.36g, 1.3mmol) and finally dibenzylazodicarboxylate (0.40g, 1.3mmol). The solution was stirred for 18h after which Pd(PPh₃)₄ (0.16g, 0.137mmol) followed by morpholine (0.75ml, 8.3mmol) was added and the solution stirred at ambient temperature for 6h. The solution was loaded onto an aminopropyl SPE (5g) and eluted with MeOH then 5%AcOH/MeOH to yield the title compound containing
20 minor impurities. Further chromatography (silica SPE, 20g) eluting with ether yielded the title compound as a white solid (0.061g, 18%).

LC/MS: m/z 553 [MH]⁺

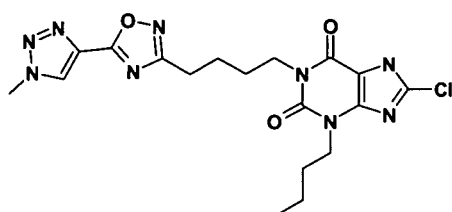
Example 248: 8-Chloro-1-{3-[5-(4-chlorophenyl)-1H-pyrazol-3-yl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione



Prepared as with 8-chloro-1-(5-{5-[(3,4-dichlorophenyl)methyl]-2H-tetrazol-2-yl}pentyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione (Comparative Example C) using 3-[5-(4-chlorophenyl)-1H-pyrazol-3-yl]-1-propanol. The final product material was washed with ether to yield the title compound as a cream solid (30%).

LC/MS: m/z 475 [MH]⁺

Example 249: 3-Butyl-8-chloro-1-{4-[5-(1-methyl-1H-1,2,3-triazol-4-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione



A solution of the 1-methyl-1H-1,2,3-triazole-4-carboxylic acid (18mg, 0.14mmol) in DMF (0.5ml) was treated with CDI (23mg, 0.14mmol) at rt for 1h. A solution of (1Z)-5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (50mg, 0.14mmol) in DMSO (0.4ml) was added to the mixture then heated to 100°C for 18h. The reaction mixture was purified by MDAP to give the title compound as a white solid (18mg).

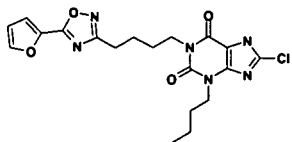
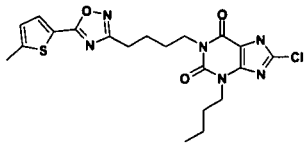
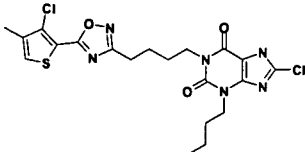
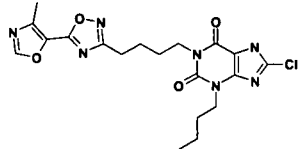
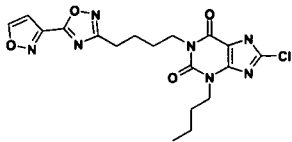
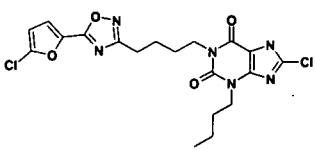
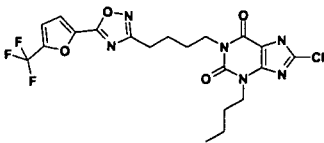
LC/MS: m/z 448 [MH]⁺, RT 2.86min.

The following compounds (**Table 20**) were prepared using a method analogous to that for **Example 249**, using the appropriate carboxylic acid.

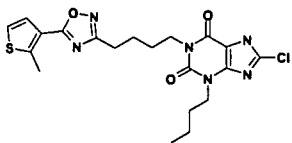
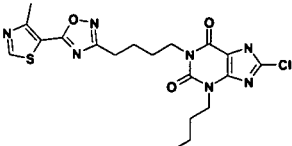
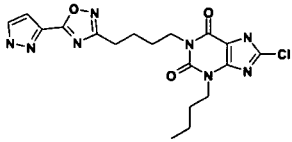
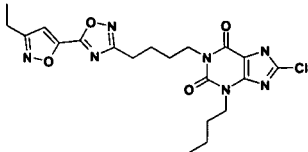
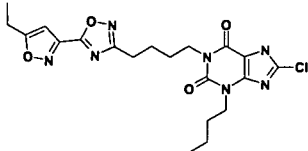
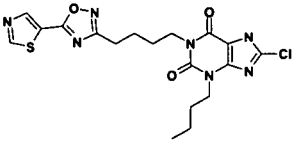
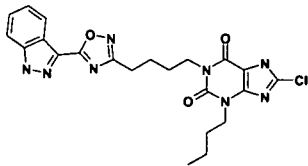
Table 20

Example	Structure	Name	Yield (mg)	LC/MS
250		3-butyl-8-chloro-1-{4-[5-(1H-imidazol-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	16	m/z 433 [MH] ⁺ RT 2.79min

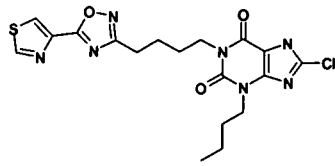
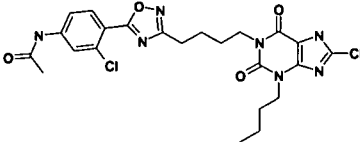
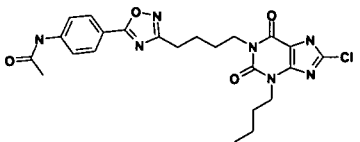
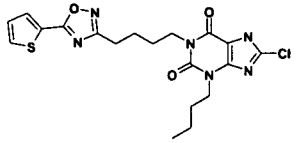
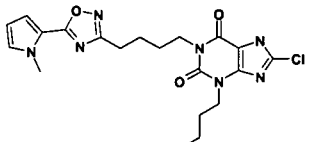
251		3-butyl-8-chloro-1-(4-{5-[4-(trifluoromethyl)-1H-pyrazol-5-yl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	19	m/z 501 [MH] ⁺ RT 3.28min
252		3-butyl-8-chloro-1-(4-{5-[2-chloro-3-thienyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	26	m/z 483 [MH] ⁺ RT 3.59min
253		3-butyl-8-chloro-1-(4-{5-[3-methyl-5-isoxazolyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	25	m/z 448 [MH] ⁺ RT 3.21min
254		3-butyl-8-chloro-1-(4-{5-[1-methyl-1H-imidazol-4-yl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	16	m/z 447 [MH] ⁺ RT 2.74min
255		3-butyl-8-chloro-1-(4-{5-[1-methyl-1H-imidazol-2-yl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	9	m/z 447 [MH] ⁺ RT 2.91min
256		3-butyl-8-chloro-1-(4-{5-[1H-1,2,4-triazol-3-yl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	10	m/z 434 [MH] ⁺ RT 2.73min
257		3-butyl-8-chloro-1-(4-{5-[5-isothiazolyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	17	m/z 450 [MH] ⁺ RT 3.34min

258		3-butyl-8-chloro-1-{4-[5-(2-furanyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	26	m/z 433 [MH] ⁺ RT 3.27min
259		3-butyl-8-chloro-1-{4-[5-(5-methyl-2-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	29	m/z 463 [MH] ⁺ RT 3.61min
260		3-butyl-8-chloro-1-{4-[5-(3-chloro-4-methyl-2-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	30	m/z 497 [MH] ⁺ RT 3.76min
261		3-butyl-8-chloro-1-{4-[5-(4-methyl-1,3-oxazol-5-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	25	m/z 448 [MH] ⁺ RT 3.13min
262		3-butyl-8-chloro-1-{4-[5-(3-isoxazolyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	23	m/z 434 [MH] ⁺ RT 3.20min
263		3-butyl-8-chloro-1-{4-[5-(5-chloro-2-furanyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	27	m/z 467 [MH] ⁺ RT 3.51min
264		3-butyl-8-chloro-1-{4-[5-(5-(trifluoromethyl)-2-furanyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	27	m/z 501 [MH] ⁺ RT 3.61min

265		3-butyl-8-chloro-1-{4-[5-(3-methyl-2-furanyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	27	m/z 447 [MH] ⁺ RT 3.43min
266		3-butyl-8-chloro-1-{4-[5-(1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	25	m/z 447 [MH] ⁺ RT 3.02min
267		3-butyl-8-chloro-1-{4-[5-(1-methyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	8	m/z 447 [MH] ⁺ RT 2.99min
268		3-butyl-8-chloro-1-{4-[5-(3-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	19	m/z 449 [MH] ⁺ RT 3.43min
269		3-butyl-8-chloro-1-{4-[5-(5-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	26	m/z 447 [MH] ⁺ RT 3.03min
270		3-butyl-8-chloro-1-{4-[5-(3-methyl-2-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	27	m/z 463 [MH] ⁺ RT 3.62min
271		3-butyl-8-chloro-1-{4-[5-(1H-pyrrol-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	13	m/z 432 [MH] ⁺ RT 3.26min

272		3-butyl-8-chloro-1-{4-[5-(2-methyl-3-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	18	m/z 463 [MH] ⁺ RT 3.64min
273		3-butyl-8-chloro-1-{4-[5-(4-methyl-1,3-thiazol-5-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	24	m/z 464 [MH] ⁺ RT 3.26min
274		3-butyl-8-chloro-1-{4-[5-(1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	20	m/z 433 [MH] ⁺ RT 3.00min
275		3-butyl-8-chloro-1-{4-[5-(3-ethyl-5-isoxazolyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	20	m/z 462 [MH] ⁺ RT 3.43min
276		3-butyl-8-chloro-1-{4-[5-(5-ethyl-3-isoxazolyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	23	m/z 462 [MH] ⁺ RT 3.46min
277		3-butyl-8-chloro-1-{4-[5-(1,3-thiazol-5-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	20	m/z 450 [MH] ⁺ RT 3.13min
278		3-butyl-8-chloro-1-{4-[5-(1H-indazol-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	24	m/z 483 [MH] ⁺ RT 3.50min

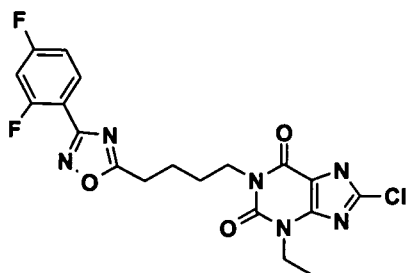
279		1-{4-[5-(1-benzofuran-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione	6	m/z 483 [MH] ⁺ RT 3.72min
280		3-butyl-8-chloro-1-{4-[5-(5-methyl-3-isoxazolyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	13	m/z 448 [MH] ⁺ RT 3.30min
2810		3-butyl-8-chloro-1-{4-[5-(2-methyl-1,3-thiazol-4-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	20	m/z 464 [MH] ⁺ RT 3.14min
282		3-butyl-8-chloro-1-{4-[5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	14	m/z 465 [MH] ⁺ RT 3.40min
283		3-butyl-8-chloro-1-{4-[5-(1,2,5-thiadiazol-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	24	m/z 451 [MH] ⁺ RT 3.27min
284		3-butyl-8-chloro-1-{4-[5-(3-furanyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	21	m/z 433 [MH] ⁺ RT 3.29min
285		3-butyl-8-chloro-1-{4-[5-(1-methyl-1H-pyrazol-5-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	23	m/z 447 [MH] ⁺ RT 3.22min

286		3-butyl-8-chloro-1-{4-[5-(1,3-thiazol-4-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	20	m/z 450 [MH] ⁺ RT 3.06min
287		N-(4-{3-[4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butyl]-1,2,4-oxadiazol-5-yl}-3-chlorophenyl)acetamide	23	m/z 534 [MH] ⁺ RT 3.44min
288		N-(4-{3-[4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butyl]-1,2,4-oxadiazol-5-yl}phenyl)acetamide	16	m/z 500 [MH] ⁺ RT 3.23min
289		3-butyl-8-chloro-1-{4-[5-(2-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	27	m/z 449 [MH] ⁺ RT 3.45min
290		3-butyl-8-chloro-1-{4-[5-(1-methyl-1H-pyrrol-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	15	m/z 446 [MH] ⁺ RT 3.45min

Example 291 : 8-Chloro-1-{4-[3-(2,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-ethyl-3,7-dihydro-1H-purine-2,6-dione

5

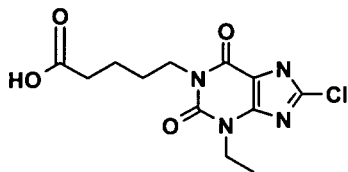
a) 8-Chloro-1-{4-[3-(2,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-ethyl-3,7-dihydro-1H-purine-2,6-dione



A solution of 5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (0.05g, 0.16mmol) in DMSO (1ml) was treated with CDI (0.029g, 0.18mmol) and the mixture stirred at room temperature for 1h. Subsequently, the mixture was treated with 2,4-difluorobenzamidoxy (0.03g, 0.18mmol) and then heated to 120°C for 30 min. The product was purified from the crude mixture using MDAP. Product-containing fractions were evaporated using a stream of nitrogen and the resulting colourless gum triturated in ether and dried to reveal the title compound as a white solid (50mg, 70%).

LC/MS: m/z 451 $[MH]^+$, RT 2.23min.

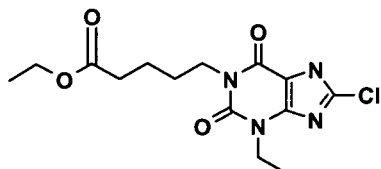
b) 5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid



A solution of ethyl 5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (2.3g, 6.7mmol) in methanol (75ml) was treated with water (3ml) and lithium hydroxide (0.481g, 20.1mmol) and the mixture stirred at 40°C for 17h. The mixture was evaporated to dryness and the residue treated with 50ml of ethyl acetate and 50ml of water. The 2 phases were separated and the aqueous phase adjusted to pH5 using 2M aqueous hydrochloric acid. The precipitated product was filtered off and dried to yield 5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid as a white solid (1.99g, 95%).

LC/MS: m/z 315 $[MH]^+$, RT 2.34min.

c) Ethyl 5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate

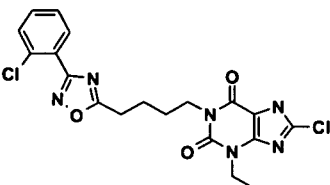
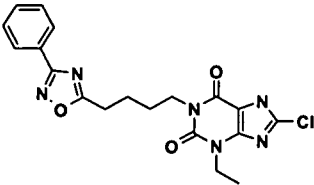


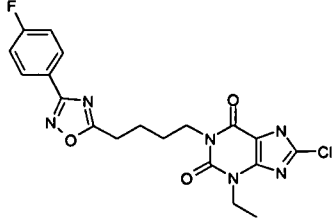
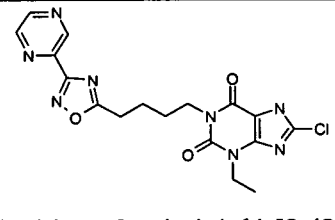
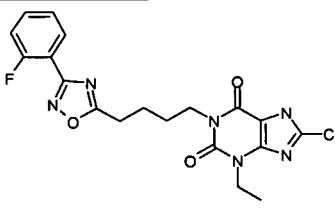
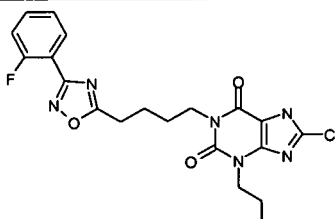
A solution of 8-chloro-7-(2-propen-1-yl)-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione (3g, 11.8mmol) in DMF (40ml) was treated with potassium carbonate (1.9g, 14.1mmol) and ethyl 5-bromopentanoate (2.24ml, 14.1mmol) and the mixture heated in a nitrogen atmosphere at 70°C for 5h and then cooled. The mixture was degassed by the repeated application of vacuum followed by backfilling with nitrogen gas and then treated with tetrakis(triphenylphosphine)palladium(0) (1.36g, 1.1mmol) and morpholine (10.3ml, 118mmol). The mixture was stirred in a nitrogen atmosphere for 4h and then evaporated to dryness. The residue was partitioned between 100ml of ethyl acetate and 100ml of water. The aqueous phase was re-extracted with 100ml of ethyl acetate and the combined organics dried over magnesium sulfate, filtered and evaporated. The residue was triturated in diethyl ether, filtered and dried to reveal ethyl 5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate compound as a white solid (2.3g, 57%).

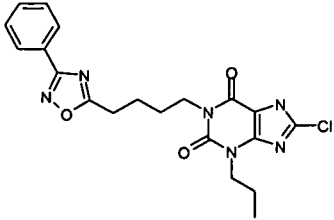
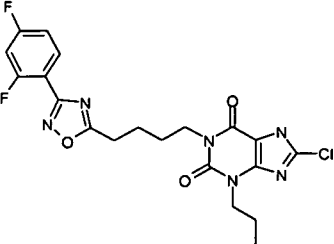
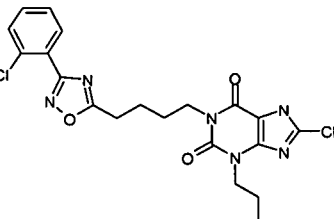
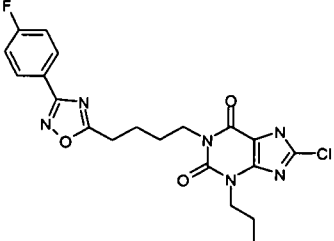
LC/MS: m/z 343 $[MH]^+$, RT 2.73min.

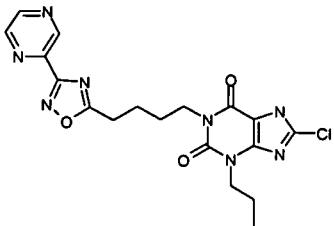
The following compounds (**Table 21**) were prepared by a method analogous to that for **Example 291**.

Table 21

Example	Structure	Precursor	Yield (mg)	LC/MS
292	 8-chloro-1-{4-[3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-ethyl-3,7-dihydro-1<i>H</i>-purine-2,6-dione	5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1 <i>H</i> -purin-1-yl)pentanoic acid	33	m/z 449 $[MH]^+$ RT 3.27min
293	 8-chloro-1-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-3-ethyl-3,7-dihydro-1<i>H</i>-purine-2,6-dione	5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1 <i>H</i> -purin-1-yl)pentanoic acid	32	m/z 415 $[MH]^+$ RT 3.22min

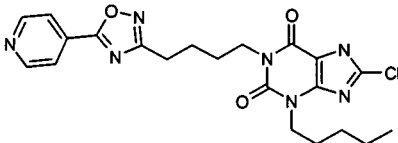
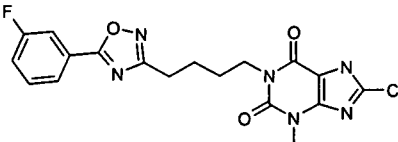
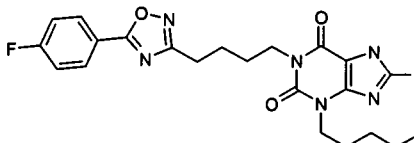
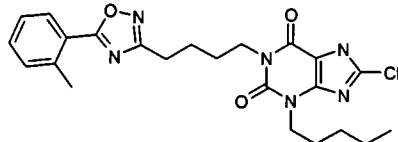
294	 8-chloro-3-ethyl-1-{4-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoic acid	31	m/z 433 [MH] ⁺ RT 3.26min
295	 8-chloro-3-ethyl-1-{4-[3-(2-pyrazinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoic acid	2	m/z 417 [MH] ⁺ RT 2.54min
296	 8-chloro-3-ethyl-1-{4-[3-(2-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoic acid	38	m/z 433 [MH] ⁺ RT 3.12min
297	 8-chloro-1-{4-[3-(2-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-propyl-3,7-dihydro-1H-purine-2,6-dione	5-(8-chloro-3-propyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoic acid	29	m/z 447 [MH] ⁺ RT 3.28min

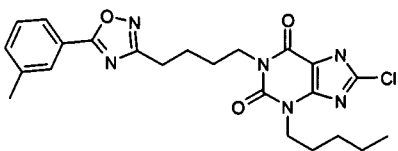
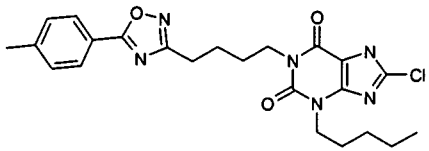
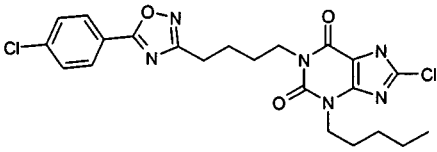
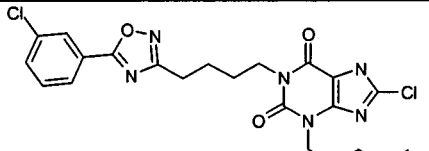
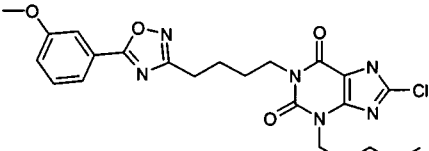
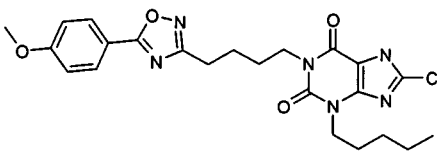
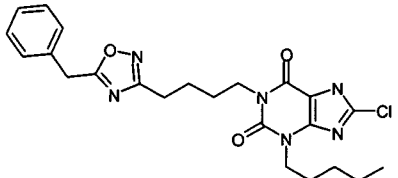
298	 8-chloro-1-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	5-(8-chloro-3-propyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoic acid	11	m/z 429 [MH] ⁺ RT 3.35min
299	 8-chloro-1-[4-[3-(2,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]butyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	5-(8-chloro-3-propyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoic acid	32	m/z 465 [MH] ⁺ RT 3.40min
300	 8-chloro-1-[4-[3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl]butyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	5-(8-chloro-3-propyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoic acid	25	m/z 463 [MH] ⁺ RT 3.40min
301	 8-chloro-1-[4-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	5-(8-chloro-3-propyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoic acid	26	m/z 447 [MH] ⁺ RT 3.44min

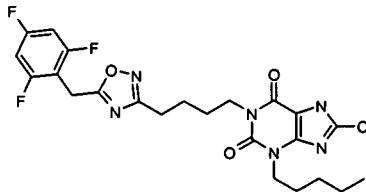
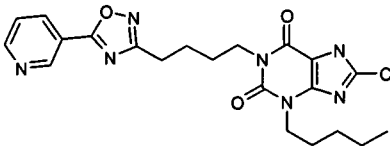
	purine-2,6-dione			
302	 8-chloro-3-propyl-1-{4-[3-(2-pyrazinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	5-(8-chloro-3-propyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoic acid	25	m/z 431 [MH] ⁺ RT 3.09min

The following compounds (**Table 22**) were prepared using a method analogous to that for **Example 127**, using the appropriate acid.

5 **Table 22**

Example	Structure	Name	Yield (mg)	LC/MS
303		8-chloro-3-pentyl-1-{4-[5-(4-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	8.0	m/z 458 [MH] ⁺ RT 3.25min
304		8-chloro-1-{4-[5-(3-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	9.1	m/z 475 [MH] ⁺ RT 3.73min
305		8-chloro-1-{4-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	16.1	m/z 475 [MH] ⁺ RT 3.69min
306		8-chloro-1-{4-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	22.9	m/z 471 [MH] ⁺ RT 3.82min

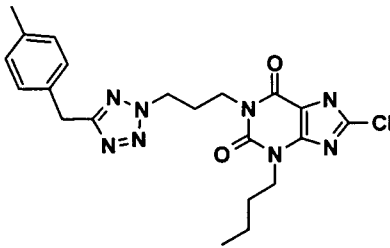
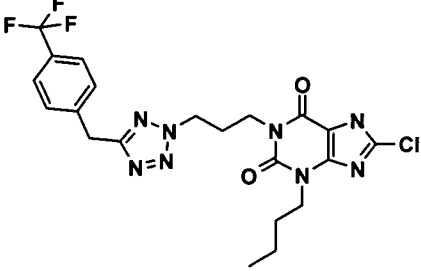
307		8-chloro-1-(4-{5-[(3-methylphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	18.0	m/z 471 [MH] ⁺ RT 3.81min
308		8-chloro-1-(4-{5-[(4-methylphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	25.0	m/z 471 [MH] ⁺ RT 3.80min
309		8-chloro-1-(4-{5-[(4-chlorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	16.6	m/z 491 [MH] ⁺ RT 3.89min
310		8-chloro-1-(4-{5-[(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	12.8	m/z 491 [MH] ⁺ RT 3.91min
311		8-chloro-1-(4-{5-[(3-methoxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	23.0	m/z 487 [MH] ⁺ RT 3.71min
312		8-chloro-1-(4-{5-[(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	15.8	m/z 487 [MH] ⁺ RT 3.67min
313		8-chloro-3-pentyl-1-(4-{5-[(phenylmethyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	21.0	m/z 471 [MH] ⁺ RT 3.55min

314		8-chloro-3-pentyl-1-(4-{5-[(2,4,6-trifluorophenyl)methyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	29.3	m/z 525 [MH] ⁺ RT 3.62min
315		8-chloro-3-pentyl-1-(4-[5-(3-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl)-3,7-dihydro-1H-purine-2,6-dione	8.2	m/z 458 [MH] ⁺ RT 3.23min

The following compounds (**Table 23**) were prepared using a method analogous to that for **Example 19**, using the appropriate tetrazole and 3-[3-alkyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1H-purin-1-yl]propyl methanesulfonate. MDAP was employed to further purify those compounds insufficiently pure following normal phase chromatography.

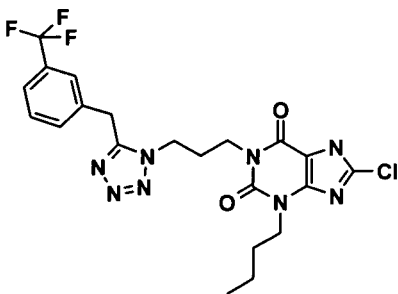
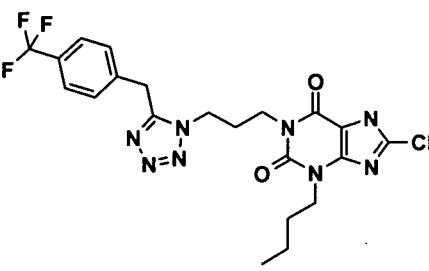
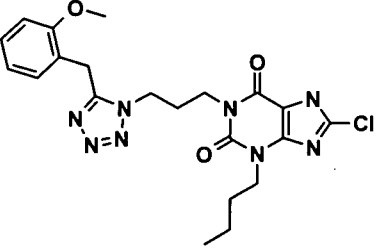
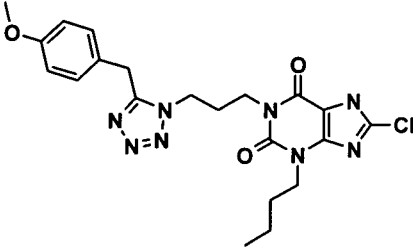
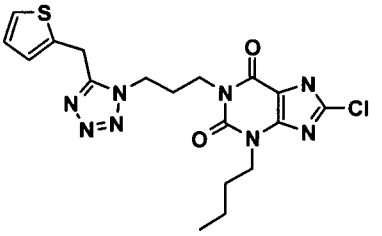
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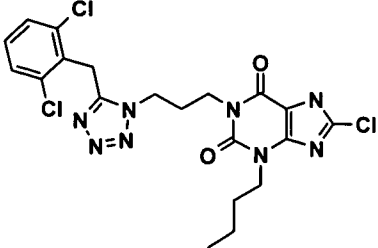
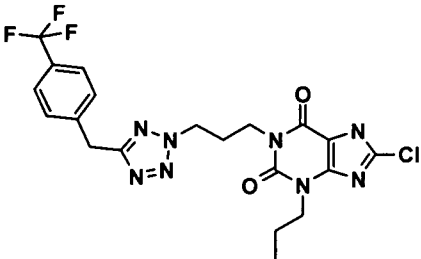
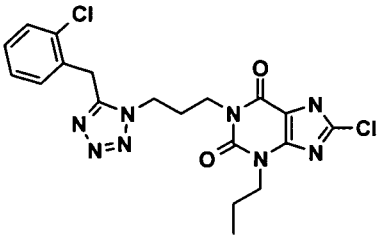
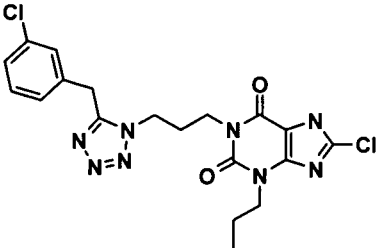
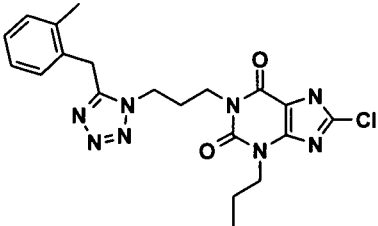
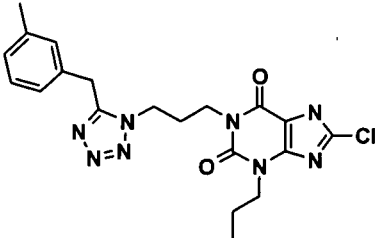
Table 23

Example	Structure	Name	Yield (mg)	LC/MS
316		3-butyl-8-chloro-1-(3-{5-[(4-methylphenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	35.1	m/z 457 [MH] ⁺ RT 3.40min
317		3-butyl-8-chloro-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	43.6	m/z 511 [MH] ⁺ RT 3.52min

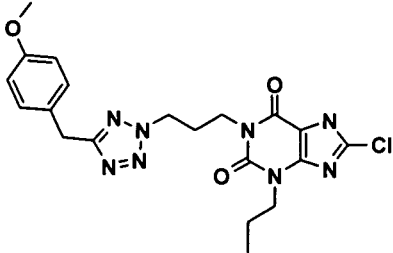
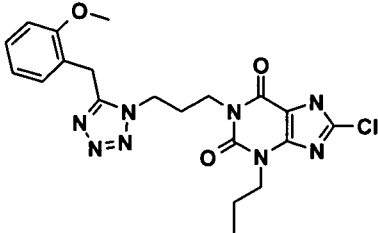
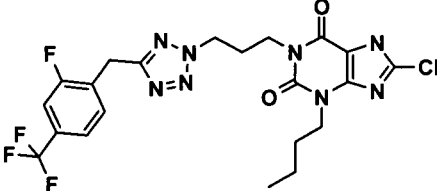
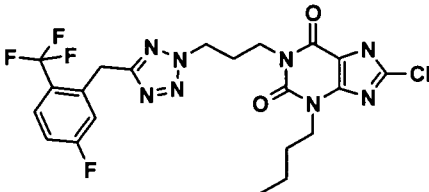
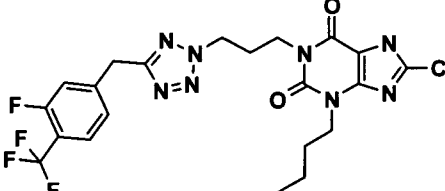
		2,6-dione		
318		3-butyl-8-chloro-1- [3-(5-{[4- (methoxy)phenyl] methyl}-2H-tetrazol- 2-yl)propyl]-3,7- dihydro-1H-purine- 2,6-dione	38.2	m/z 473 [MH] ⁺ RT 3.24m in
319		3-butyl-8-chloro-1- (3-{5-[(2- fluorophenyl)methyl]-1H-tetrazol-1- yl}propyl)-3,7- dihydro-1H-purine- 2,6-dione	13.7	m/z 461 [MH] ⁺ RT 3.07m in
320		3-butyl-8-chloro-1- (3-{5-[(3- fluorophenyl)methyl]-1H-tetrazol-1- yl}propyl)-3,7- dihydro-1H-purine- 2,6-dione	15.0	m/z 461 [MH] ⁺ RT 3.10m in
321		3-butyl-8-chloro-1- (3-{5-[(4- fluorophenyl)methyl]-1H-tetrazol-1- yl}propyl)-3,7- dihydro-1H-purine- 2,6-dione	17.7	m/z 461 [MH] ⁺ RT 3.10m in
322		3-butyl-8-chloro-1- (3-{5-[(2- chlorophenyl)methy l]-1H-tetrazol-1- yl}propyl)-3,7- dihydro-1H-purine- 2,6-dione	8.4	m/z 477 [MH] ⁺ RT 3.17m in

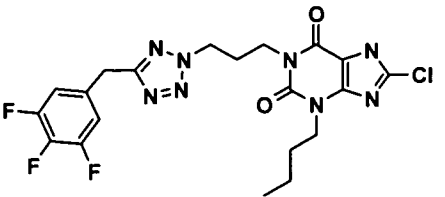
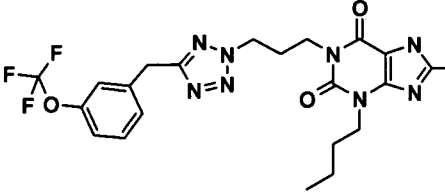
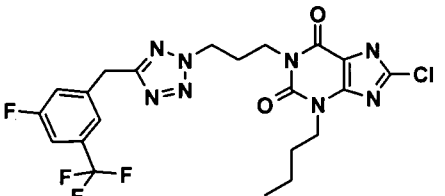
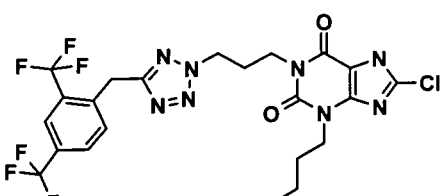
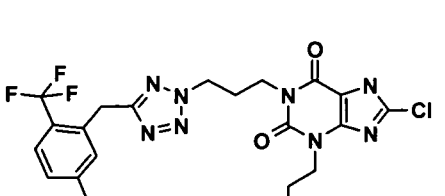
323		3-butyl-8-chloro-1-(3-{5-[(3-chlorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	16.4	m/z 477 [MH] ⁺ RT 3.23m in
324		3-butyl-8-chloro-1-(3-{5-[(4-chlorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	17.0	m/z 477 [MH] ⁺ RT 3.24m in
325		3-butyl-8-chloro-1-(3-{5-[(2-methylphenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	15.1	m/z 457 [MH] ⁺ RT 3.15m in
326		3-butyl-8-chloro-1-(3-{5-[(3-methylphenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	18.6	m/z 457 [MH] ⁺ RT 3.18m in
327		3-butyl-8-chloro-1-(3-{5-[(4-methylphenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	16.3	m/z 457 [MH] ⁺ RT 3.19m in

328		3-butyl-8-chloro-1-[3-(5-((3-(trifluoromethyl)phenyl)methyl)-1H-tetrazol-1-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	17.7	m/z 511 [MH] ⁺ RT 3.31min
329		3-butyl-8-chloro-1-[3-(5-((4-(trifluoromethyl)phenyl)methyl)-1H-tetrazol-1-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	21.6	m/z 511 [MH] ⁺ RT 3.33min
330		3-butyl-8-chloro-1-[3-(5-((2-(methoxy)phenyl)methyl)-1H-tetrazol-1-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	16.3	m/z 473 [MH] ⁺ RT 3.10min
331		3-butyl-8-chloro-1-[3-(5-((4-(methoxy)phenyl)methyl)-1H-tetrazol-1-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	20.8	m/z 473 [MH] ⁺ RT 3.05min
332		3-butyl-8-chloro-1-[3-(5-((2-thienyl)methyl)-1H-tetrazol-1-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	11.8	m/z 448 [MH] ⁺ RT 3.02min

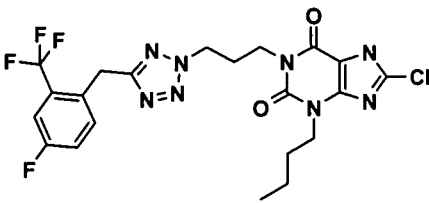
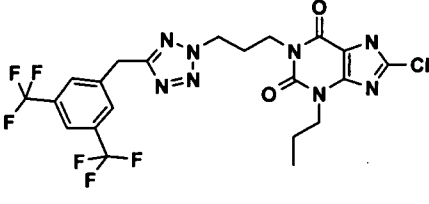
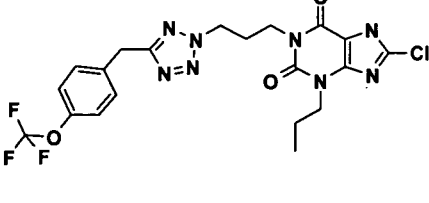
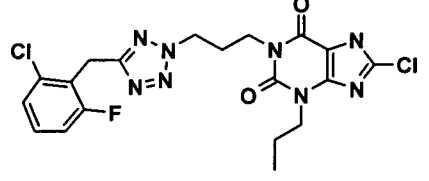
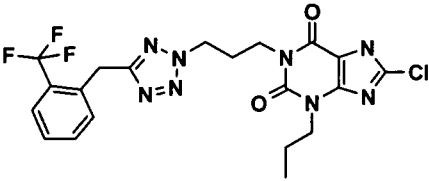
333		3-butyl-8-chloro-1-(3-{5-[(2,6-dichlorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	12.4	m/z 512 [MH] ⁺ RT 3.27m in
334		8-chloro-3-propyl-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	15.5	m/z 497 [MH] ⁺ RT 3.38m in
335		8-chloro-1-(3-{5-[(2-chlorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	1.6	m/z 463 [MH] ⁺ RT 3.00m in
336		8-chloro-1-(3-{5-[(3-chlorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	7.1	m/z 463 [MH] ⁺ RT 3.06m in
337		8-chloro-1-(3-{5-[(2-methylphenyl)methyl]-1H-tetrazol-1-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	7.2	m/z 443 [MH] ⁺ RT 2.97m in
338		8-chloro-1-(3-{5-[(3-methylphenyl)methyl]-1H-tetrazol-1-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	5.7	m/z 443 [MH] ⁺ RT 3.01m in

339		8-chloro-1-(3-{5-[(4-methylphenyl)methyl]-1H-tetrazol-1-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	5.5	m/z 443 [MH] ⁺ RT 3.01m in
340		8-chloro-3-propyl-1-[3-(5-{3-(trifluoromethyl)phenyl}methyl)-1H-tetrazol-1-yl]propyl-3,7-dihydro-1H-purine-2,6-dione	3.3	m/z 497 [MH] ⁺ RT 3.16m in
341		8-chloro-1-(3-{5-[(2-methylphenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	24.1	m/z 443 [MH] ⁺ RT 3.20m in
342		8-chloro-1-(3-{5-[(2-fluorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	1.3	m/z 447 [MH] ⁺ RT 2.89m in
343		8-chloro-3-propyl-1-[3-(5-(2-thienylmethyl)-1H-tetrazol-1-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	5.2	m/z 435 [MH] ⁺ RT 2.83m in
344		8-chloro-1-[3-(5-{4-(methoxy)phenyl}methyl)-1H-tetrazol-1-yl]propyl-3-propyl-3,7-dihydro-1H-purine-2,6-dione	1.2	m/z 459 [MH] ⁺ RT 2.87m in

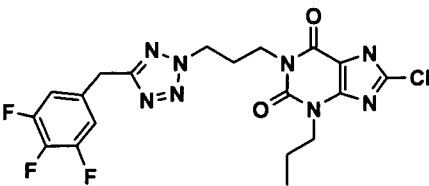
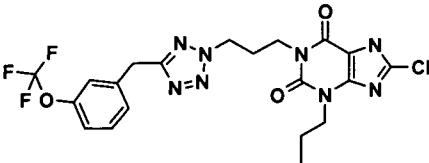
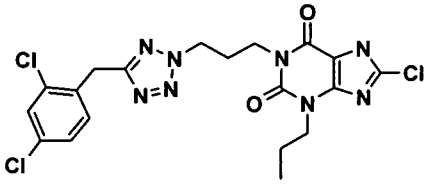
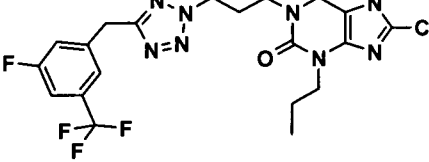
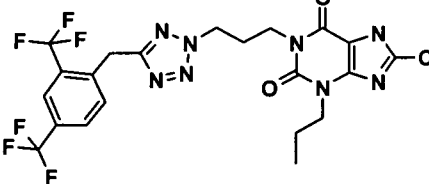
345		8-chloro-1-[3-(5-{[4-(methoxy)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	19.7	m/z 459 [MH] ⁺ RT 3.07m in
346		8-chloro-1-[3-(5-{[2-(methoxy)phenyl]methyl}-1H-tetrazol-1-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	1.9	m/z 459 [MH] ⁺ RT 2.92m in
347		3-butyl-8-chloro-1-[3-(5-{[2-fluoro-4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	24.5	m/z 529 [MH] ⁺ RT 3.22m in
348		3-butyl-8-chloro-1-[3-(5-{[5-fluoro-2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	25.3	m/z 529 [MH] ⁺ RT 3.51m in
349		3-butyl-8-chloro-1-[3-(5-{[3-fluoro-4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	11.5	m/z 529 [MH] ⁺ RT 3.56m in

350		3-butyl-8-chloro-1- (3-{5-[(3,4,5- trifluorophenyl)meth yl]-2H-tetrazol-2- yl}propyl)-3,7- dihydro-1H-purine- 2,6-dione	19.4	m/z 497 [MH] ⁺ RT 3.45m in
351		3-butyl-8-chloro-1- {3-[5-({3- [(trifluoromethyl)oxy]phenyl)methyl)-2H- tetrazol-2- yl}propyl)-3,7- dihydro-1H-purine- 2,6-dione	27.2	m/z 527 [MH] ⁺ RT 3.55m in
352		3-butyl-8-chloro-1- [3-(5-{[3-fluoro-5- (trifluoromethyl)phe nyl)methyl]-2H- tetrazol-2- yl}propyl)-3,7- dihydro-1H-purine- 2,6-dione	19.8	m/z 529 [MH] ⁺ RT 3.56m in
353		1-[3-(5-{[2,4- bis(trifluoromethyl)p henyl)methyl]-2H- tetrazol-2- yl}propyl)-3-butyl-8- chloro-3,7-dihydro- 1H-purine-2,6- dione	36.6	m/z 579 [MH] ⁺ RT 3.72m in
354		1-[3-(5-{[2,5- bis(trifluoromethyl)p henyl)methyl]-2H- tetrazol-2- yl}propyl)-3-butyl-8- chloro-3,7-dihydro- 1H-purine-2,6- dione	50.3	m/z 579 [MH] ⁺ RT 3.65m in

355		8-chloro-1-[3-(5-([4-fluoro-2-(trifluoromethyl)phenyl]methyl)-2H-tetrazol-2-yl)propyl]-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione	25.0	m/z 583 [MH] ⁺ RT 3.50m in
356		8-chloro-1-[3-(5-([4-fluoro-2-(trifluoromethyl)phenyl]methyl)-2H-tetrazol-2-yl)propyl]-3-[2-(methyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	23.0	m/z 531 [MH] ⁺ RT 3.16m in
357		8-chloro-3-[2-(ethyloxy)ethyl]-1-[3-(5-([4-fluoro-2-(trifluoromethyl)phenyl]methyl)-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	13.1	m/z 545 [MH] ⁺ RT 3.30m in
358		8-chloro-1-[3-(5-([4-fluoro-2-(trifluoromethyl)phenyl]methyl)-2H-tetrazol-2-yl)propyl]-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	36.3	m/z 569 [MH] ⁺ RT 3.46m in
359		8-chloro-1-[3-(5-([4-fluoro-2-(trifluoromethyl)phenyl]methyl)-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	32.0	m/z 515 [MH] ⁺ RT 3.37m in

		3,7-dihydro-1H-purine-2,6-dione		
360		3-butyl-8-chloro-1-[3-(5-([4-fluoro-2-(trifluoromethyl)phenyl)methyl]-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	30.3	m/z 529 [MH] ⁺ RT 3.53m in
361		1-[3-(5-([3,5-bis(trifluoromethyl)phenyl)methyl]-2H-tetrazol-2-yl)propyl]-8-chloro-3-propyl-3,7-dihydro-1H-purine-2,6-dione	22.9	m/z 565 [MH] ⁺ RT 3.54m in
362		8-chloro-3-propyl-1-[3-(5-([4-((trifluoromethyl)oxy)phenyl)methyl]-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	21.6	m/z 513 [MH] ⁺ RT 3.42m in
363		8-chloro-1-(3-(5-[(2-chloro-6-fluorophenyl)methyl]-2H-tetrazol-2-yl)propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	12.4	m/z 481 [MH] ⁺ RT 3.20m in
364		8-chloro-3-propyl-1-[3-(5-([2-(trifluoromethyl)phenyl)methyl]-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	17.7	m/z 497 [MH] ⁺ RT 3.26m in

365		8-chloro-1-(3-((3,5-difluorophenyl)methyl)-2H-tetrazol-2-yl)propyl-3-propyl-3,7-dihydro-1H-purine-2,6-dione	21.6	m/z 465 [MH] ⁺ RT 3.16m in
366		8-chloro-3-propyl-1-(3-((2-((trifluoromethyl)oxy)phenyl)methyl)-2H-tetrazol-2-yl)propyl)-3,7-dihydro-1H-purine-2,6-dione	22.3	m/z 513 [MH] ⁺ RT 3.27m in
367		8-chloro-1-(3-((5-(2-(trifluoromethyl)phenyl)methyl)-2H-tetrazol-2-yl)propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	9.7	m/z 515 [MH] ⁺ RT 3.40m in
368		8-chloro-1-(3-((5-(2-(trifluoromethyl)phenyl)methyl)-2H-tetrazol-2-yl)propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	26.8	m/z 515 [MH] ⁺ RT 3.26m in
369		8-chloro-1-(3-((3-fluoro-4-(trifluoromethyl)phenyl)methyl)-2H-tetrazol-2-yl)propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	20.7	m/z 515 [MH] ⁺ RT 3.31m in

370		8-chloro-3-propyl-1-(3-{5-[(3,4,5-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	10.2	m/z 483 [MH] ⁺ RT 3.23m in
371		8-chloro-3-propyl-1-{3-[5-({3-[(trifluoromethyl)oxy]phenyl)methyl]-2H-tetrazol-2-yl}propyl}-3,7-dihydro-1H-purine-2,6-dione	9.8	m/z 513 [MH] ⁺ RT 3.35m in
372		8-chloro-1-(3-{5-[(2,4-dichlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	27.6	m/z 497 [MH] ⁺ RT 3.40m in
373		8-chloro-1-[3-(5-{[3-fluoro-5-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	17.6	m/z 515 [MH] ⁺ RT 3.23m in
374		1-[3-(5-{[2,4-bis(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-8-chloro-3-propyl-3,7-dihydro-1H-purine-2,6-dione	21.0	m/z 565 [MH] ⁺ RT 3.40m in

375		1-[3-(5-{[2,5-bis(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-8-chloro-3-propyl-3,7-dihydro-1H-purine-2,6-dione	9.7	m/z 565 [MH] ⁺ RT 3.50m in
376		1-[3-(5-{[3,5-bis(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione	28.1	m/z 579 [MH] ⁺ RT 3.68m in
377		3-butyl-8-chloro-1-{3-[5-({4-[(trifluoromethyl)oxy]phenyl}methyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	32.1	m/z 527 [MH] ⁺ RT 3.57m in
378		8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(methyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	15.0	m/z 463 [MH] ⁺ RT 2.89m in
379		8-chloro-3-[2-(ethyloxy)ethyl]-1-(3-{5-[(4-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	12.6	m/z 477 [MH] ⁺ RT 3.03m in

380		8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	17.8	m/z 501 [MH] ⁺ RT 3.21m in
381		8-chloro-3-[2-(methyloxy)ethyl]-1-[3-(5-{[2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	14.2	m/z 513 [MH] ⁺ RT 3.10m in
382		8-chloro-3-[2-(ethyloxy)ethyl]-1-[3-(5-{[2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	20.8	m/z 527 [MH] ⁺ RT 3.18m in
383		8-chloro-1-[3-(5-{[2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	35.8	m/z 551 [MH] ⁺ RT 3.35m in
384		8-chloro-3-[2-(methyloxy)ethyl]-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	15.3	m/z 513 [MH] ⁺ RT 3.14m in

385		8-chloro-1-([3-(5-((3,3,3-trifluoropropyl)-3,7-dihydro-1H-purin-2(1H)-yl)methyl)-2H-tetrazol-2-yl]propyl)-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purin-2,6-dione	29.4	m/z 551 [MH] ⁺ RT 3.42min
386		8-chloro-1-([3-(5-((2,4-difluorophenyl)methyl)-2H-tetrazol-2-yl]propyl)-3-(2-(methyloxy)ethyl)-3,7-dihydro-1H-purin-2,6-dione	17.8	m/z 481 [MH] ⁺ RT 2.96min
387		8-chloro-1-([3-(5-((2,4-difluorophenyl)methyl)-2H-tetrazol-2-yl]propyl)-3-(2-(ethyloxy)ethyl)-3,7-dihydro-1H-purin-2,6-dione	14.4	m/z 495 [MH] ⁺ RT 2.86min
388		8-chloro-1-([3-(5-((2,4-difluorophenyl)methyl)-2H-tetrazol-2-yl]propyl)-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purin-2,6-dione	29.9	m/z 519 [MH] ⁺ RT 3.19min
389		8-chloro-3-([2-(methyloxy)ethyl]-1-([3-(5-((2,4,6-trifluorophenyl)methyl)-2H-tetrazol-2-yl]propyl)-3,7-dihydro-1H-purin-2,6-dione	21.3	m/z 499 [MH] ⁺ RT 2.93min

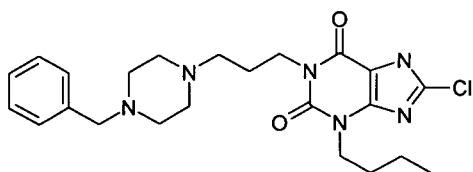
390		8-chloro-3-[2-(ethyloxy)ethyl]-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	15.5	m/z 513 [MH] ⁺ RT 2.93m in
391		8-chloro-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	32.3	m/z 537 [MH] ⁺ RT 3.29m in
392		8-chloro-1-(3-{5-[(3,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(methyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	14.5	m/z 481 [MH] ⁺ RT 2.97m in
393		8-chloro-1-(3-{5-[(3,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(ethyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	7.2	m/z 495 [MH] ⁺ RT 3.06m in
394		8-chloro-1-(3-{5-[(3,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	27.8	m/z 519 [MH] ⁺ RT 3.27m in

395		8-chloro-1-(3-{5-[(2,5-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(methoxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	17.1	m/z 481 [MH] ⁺ RT 2.89m in
396		8-chloro-1-(3-{5-[(2,5-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(ethoxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	13.5	m/z 495 [MH] ⁺ RT 3.05m in
397		8-chloro-3-[2-(ethoxy)ethyl]-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	14.6	m/z 527 [MH] ⁺ RT 3.26m in
398		8-chloro-3-(4,4,4-trifluorobutyl)-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	12.1	m/z 565 [MH] ⁺ RT 3.51m in
399		8-chloro-3-[2-(methoxy)ethyl]-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-	17.3	m/z 513 [MH] ⁺ RT 3.17m in

		2,6-dione		
400		8-chloro-3-[2-(ethyloxy)ethyl]-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	15.2	m/z 527 [MH] ⁺ RT 3.30m in
401		8-chloro-3-(4,4,4-trifluorobutyl)-1-[3-(5-{[2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	5.8	m/z 565 [MH] ⁺ RT 3.46m in
402		8-chloro-1-(3-{5-[(2,5-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione	14.7	m/z 533 [MH] ⁺ RT 3.34m in
403		8-chloro-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	26.1	m/z 551 [MH] ⁺ RT 3.46m in
404		8-chloro-1-(3-{5-[(2,5-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	18.0	m/z 519 [MH] ⁺ RT 3.29m in

		2,6-dione		
405		8-chloro-1-(3-{5-[(2-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(methyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	3.4	m/z 463 [MH] ⁺ RT 2.84m in
406		8-chloro-3-[2-(ethyloxy)ethyl]-1-(3-{5-[(2-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	8.2	m/z 477 [MH] ⁺ RT 2.85m in
407		8-chloro-1-(3-{5-[(2-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	32.7	m/z 501 [MH] ⁺ RT 3.25m in

Example 408 : 3-Butyl-8-chloro-1-{3-[4-(phenylmethyl)-1-piperazinyl]propyl}-3,7-dihydro-1H-purine-2,6-dione



5

A solution of 3-[3-butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1H-purin-1-yl]propyl methanesulfonate (0.08g, 0.19mmol) in DMF (5ml) was treated with potassium carbonate (0.08g, 0.6mmol) and 1-benzylpiperazine (0.04g, 0.23mmol) and then heated at 70°C for 2h. The mixture was cooled, evaporated to dryness and partitioned between 10ml of DCM and 10ml of water. The organic phase was evaporated to dryness and the residue dissolved in anhydrous THF (5ml). The solution was cautiously degassed by the repeated application of vacuum to the reaction mixture and subsequent backfilling with nitrogen gas and then treated with tetrakis(triphenylphosphine)palladium(0) (0.010g, 0.009mmol) and morpholine (0.200ml, 2.3mmol) and the mixture stirred for 2h in a nitrogen atmosphere. The

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mixture was evaporated and the residue taken up in 5ml of methanol and added to a 2g aminopropyl SPE cartridge which was then washed with methanol and the product eluted using a 3% solution of acetic acid in methanol. Product-containing fractions were pooled and evaporated to dryness. The product was then purified by flash chromatography using a gradient elution from DCM /2% Acetic acid to DCM /20% MeOH /2% Acetic acid and the final product freeze-dried from 1,4-dioxan to give the title compound as a white solid (0.021g, 24%).

LC/MS: m/z 459 [MH]⁺, RT 2.37min.

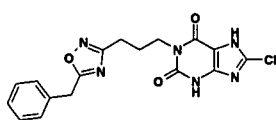
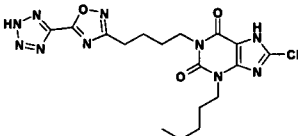
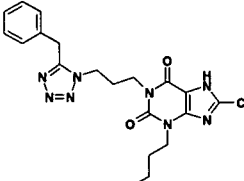
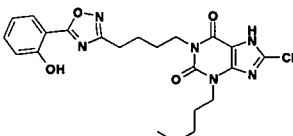
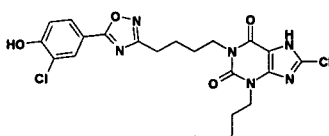
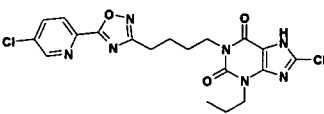
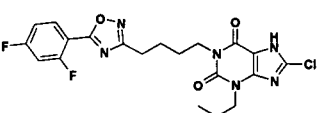
- 10 The following compounds (**Table 24**) were prepared by the appropriate general methodology described above.

Table 24

Example	Structure	Name	LC/MS
409		8-chloro-3-pentyl-1-{3-[1-(phenylmethyl)-1H-imidazol-4-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 455 [MH] ⁺ RT 2.61min
410		3-butyl-8-chloro-1-{3-[5-(phenylmethyl)-1H-1,2,4-triazol-1-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 442 [MH] ⁺ RT 2.94min
411		8-chloro-1-{3-[5-(phenylmethyl)-2H-tetrazol-2-yl]propyl}-3-propyl-3,7-dihydro-1H-purine-2,6-dione	m/z 429 [MH] ⁺ RT 3.14min
412		8-chloro-3-methyl-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 401 [MH] ⁺ RT 2.88min
413		8-chloro-3-methyl-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 401 [MH] ⁺ RT 2.89min

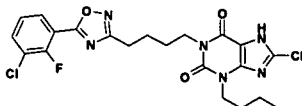
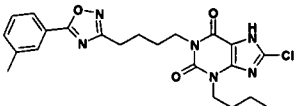
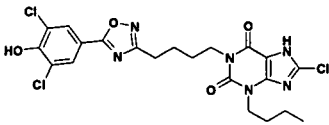
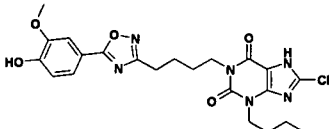
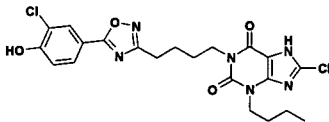
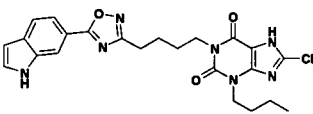
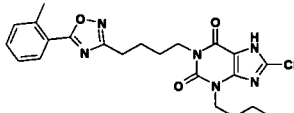
414		8-chloro-3-ethyl-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 415 [MH] ⁺ RT 2.97min
415		8-chloro-3-pentyl-1-[3-(3-[(trifluoromethyl)-1H-pyrazol-1-yl]methyl)-1,2,4-oxadiazol-5-yl]propyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 515 [MH] ⁺ RT 3.43min
416		8-chloro-1-{4-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 475 [MH] ⁺ RT 3.71min
417		8-chloro-3-pentyl-1-(4-{3-[4-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-5-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 525 [MH] ⁺ RT 3.92min
418		8-chloro-1-(4-{3-[4-(dimethylamino)phenyl]-1,2,4-oxadiazol-5-yl}butyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 500 [MH] ⁺ RT 3.73min
419		8-chloro-1-{4-[3-(5-chloro-2-thienyl)-1,2,4-oxadiazol-5-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 497 [MH] ⁺ RT 3.88min
420		8-chloro-3-pentyl-1-[3-(3-phenyl-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 443 [MH] ⁺ RT 3.51min

421		8-chloro-1-{4-[3-(3,4-dichlorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 525 [MH] ⁺ RT 4.12min
422		8-chloro-3-pentyl-1-{4-[3-(pyridin-3-ylmethyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 472 [MH] ⁺ RT 2.90min
423		8-chloro-3-pentyl-1-[3-(3-[(4-(trifluoromethyl)phenyl)methyl]-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 525 [MH] ⁺ RT 3.69min
424		8-chloro-1-(3-{3-[(pentafluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 547 [MH] ⁺ RT 3.66min
425		1-{3-[3-(1-benzothien-2-yl)-1,2,4-oxadiazol-5-yl]propyl}-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 499 [MH] ⁺ RT 3.77min
426		8-chloro-1-{3-[3-(2-methylphenyl)-1,2,4-oxadiazol-5-yl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 457 [MH] ⁺ RT 3.62min
427		8-chloro-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 387 [MH] ⁺ RT 2.63min

428		8-chloro-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 387 [MH] ⁺ RT 2.65min
429		8-chloro-3-pentyl-1-{4-[5-(1H-tetrazol-5-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 449 [MH] ⁺ RT 4.03min
430		3-butyl-8-chloro-1-{3-[5-(phenylmethyl)-1H-tetrazol-1-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 443 [MH] ⁺ RT 3.11min
431		8-chloro-1-{4-[5-(2-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 473 [MH] ⁺ RT 3.84min
432		8-chloro-1-{4-[5-(3-chloro-4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 507 [MH] ⁺ RT 3.74min
433		8-chloro-1-{4-[5-(5-chloropyridin-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3-propyl-3,7-dihydro-1H-purine-2,6-dione	m/z 464 [MH] ⁺ RT 3.30min
434		8-chloro-1-{4-[5-(2,4-difluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-propyl-3,7-dihydro-1H-purine-2,6-dione	m/z 465 [MH] ⁺ RT 3.48min

435		3-butyl-8-chloro-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 443 [MH] ⁺ RT 3.49min
436		3-butyl-8-chloro-1-(4-{5-[2-fluoro-4-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 529 [MH] ⁺ RT 3.71min
437		3-butyl-8-chloro-1-{4-[5-(4-chloro-2-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 495 [MH] ⁺ RT 3.64min
438		3-butyl-8-chloro-1-{4-[5-(2,4-difluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 479 [MH] ⁺ RT 3.49min
439		3-butyl-8-chloro-1-{4-[5-(2,3-difluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 479 [MH] ⁺ RT 3.53min
440		3-butyl-8-chloro-1-{4-[5-(2-fluoro-4-methylphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 475 [MH] ⁺ RT 3.51min
441		3-butyl-8-chloro-1-{4-[5-(2,5-difluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 479 [MH] ⁺ RT 3.50min

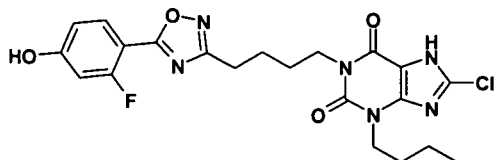
442		3-butyl-8-chloro-1-(4-[5-(3,5-dichlorophenyl)-2H-tetrazol-2-yl]butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 511 [MH] ⁺ RT 3.92min
443		3-butyl-8-chloro-1-(4-[5-(6-methylpyridin-2-yl)-1,2,4-oxadiazol-3-yl]butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 458 [MH] ⁺ RT 3.12min
444		3-butyl-8-chloro-1-(4-[5-(2-fluoro-5-(methoxy)phenyl)-1,2,4-oxadiazol-3-yl]butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 491 [MH] ⁺ RT 3.51min
445		3-butyl-8-chloro-1-(4-[2,4-dioxo-5-(phenylmethyl)-1,3-thiazolidin-3-yl]butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 504 [MH] ⁺ RT 3.36min
446		3-butyl-8-chloro-1-(4-(3,5-dioxo-1-phenyl-1,2,4-triazolidin-4-yl)butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 474 [MH] ⁺ RT 2.91min
447		3-butyl-8-chloro-1-(4-[5-(6-oxo-1,6-dihydropyridin-2-yl)-1,2,4-oxadiazol-3-yl]butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 460 [MH] ⁺ RT 2.86min
448		3-butyl-8-chloro-1-(4-[5-(6-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 462 [MH] ⁺ RT 3.23min

449		3-butyl-8-chloro-1-(4-[5-(3-chloro-2-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 495 [MH] ⁺ RT 3.69min
450		3-butyl-8-chloro-1-(4-[5-(3-methylphenyl)-1,2,4-oxadiazol-3-yl]butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 457 [MH] ⁺ RT 3.67min
451		3-butyl-8-chloro-1-(4-[5-(3,5-dichloro-4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 527 [MH] ⁺ RT 3.92min
452		3-butyl-8-chloro-1-(4-[5-(4-hydroxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl]butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 489 [MH] ⁺ RT 3.27min
453		3-butyl-8-chloro-1-(4-[5-(3-chloro-4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 493 [MH] ⁺ RT 3.61min
454		3-butyl-8-chloro-1-(4-[5-(1H-indol-6-yl)-1,2,4-oxadiazol-3-yl]butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 482 [MH] ⁺ RT 3.55min
455		3-butyl-8-chloro-1-(4-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 457 [MH] ⁺ RT 3.67min

456		3-butyl-8-chloro-1-(4-{5-[4-(methoxy)phenyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 473 [MH] ⁺ RT 3.51min
457		3-butyl-8-chloro-1-{4-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 461 [MH] ⁺ RT 3.54min
458		3-butyl-8-chloro-1-[4-(5-pyrazin-2-yl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 445 [MH] ⁺ RT 2.96min
459		3-butyl-8-chloro-1-{4-[5-(6-oxo-1,6-dihydropyridin-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 460 [MH] ⁺ RT 2.78min
460		1-{4-[5-(1H-benzimidazol-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione	m/z 483 [MH] ⁺ RT 3.22min
461		3-butyl-8-chloro-1-{4-[5-(3-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 461 [MH] ⁺ RT 3.58min
462		3-butyl-8-chloro-1-[4-(5-pyrimidin-2-yl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 445 [MH] ⁺ RT 2.84min

Example 463: 3-Butyl-8-chloro-1-{4-[5-(2-fluoro-4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione

a) 3-Butyl-8-chloro-1-{4-[5-(2-fluoro-4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione

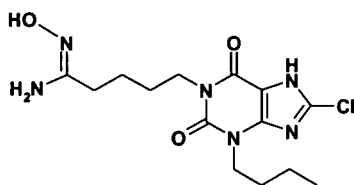


CDI (45mg, 0.28mmol) in anhydrous DMSO (0.5ml) was added to 2-fluoro-4-hydroxybenzoic acid (40mg, 0.25mmol) and stirred at rt for 2h. 5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide (100mg, 0.28mmol) in DMSO (0.4ml) was added and the resulting mixture heated at 90°C for 18h. Purification by MDAP afforded the title compound as a solid (38mg, 28%).

LC/MS: m/z 477 $[MH]^+$, RT 3.39min.

1H NMR (DMSO- d_6) δ : 0.87 (t, 3H, J = 7Hz), 1.27 (m, 2H), 1.56-1.78 (m, 6H), 2.77 (t, 2H, J = 7Hz), 3.90 (m, 4H), 6.80 (m, 2H), 7.91 (t, 1H, J = 9Hz), 11.01 (s, 1H), 14.45 (br s, 1H).

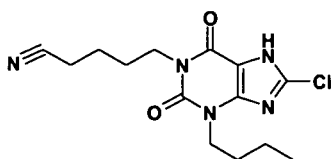
b) 5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide



5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanenitrile (8.5g, 26mmol) was dissolved in EtOH (100ml). Hydroxylamine (50% in water; 2.6ml, 39mmol) was added and the mixture heated at 80°C for 48h under nitrogen. The reaction mixture was concentrated *in vacuo*, the resultant solid washed with methanol and dried to give the title compound as a solid (5.9g, 47%).

LC/MS: m/z 357 $[MH]^+$, RT 2.17min.

c) 5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanenitrile

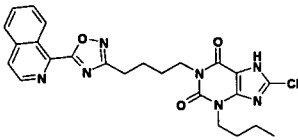
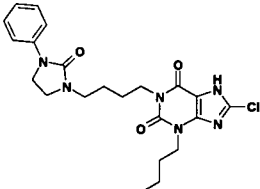
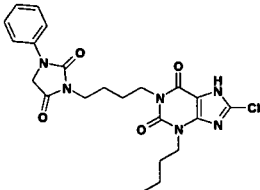
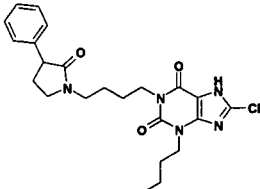


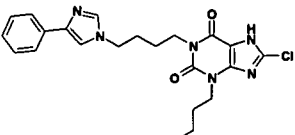
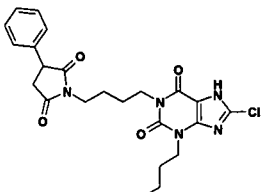
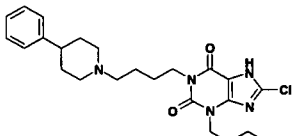
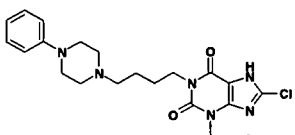
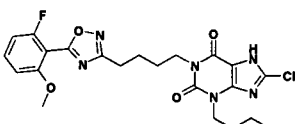
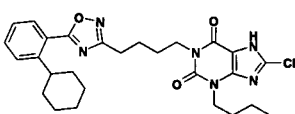
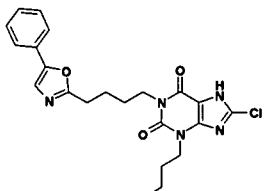
5-Bromopentanenitrile (4.54ml, 39mmol) and cesium carbonate (12.7g) were added to a solution of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (10g, 35mmol) in DMF (100ml) and the mixture stirred under nitrogen at 40°C overnight and allowed to cool.

The mixture was then degassed by the repeated successive application of a vacuum and then nitrogen pressure. The mixture was then treated with tetrakis(triphenylphosphine)palladium(0) (2.86g, 2.5mmol) and morpholine (30.8ml, 350mmol). The mixture was stirred in a nitrogen atmosphere for 3h and then partitioned between EtOAc and 2M aqueous hydrochloric acid. The aqueous layer was separated and extracted with EtOAc (x2). The combined organic phases were concentrated *in vacuo* to give a solid that was washed with ether, filtered and dried. The filtrate was concentrated and purified on an aminopropyl column eluting with MeOH followed by 3% AcOH/MeOH. The product-containing fractions were combined and concentrated to give a solid, which was combined with the filtered product. The title compound was obtained as a solid (10.5g, 93%).
LC/MS: m/z 324 [MH]⁺, RT 2.75min.

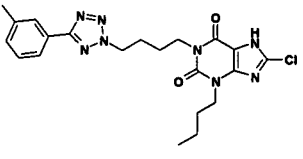
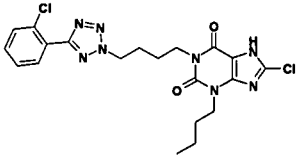
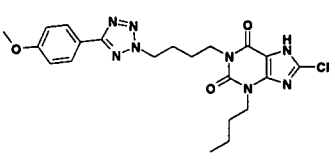
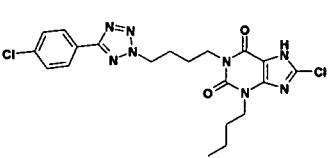
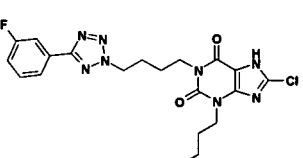
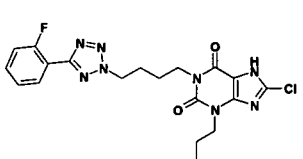
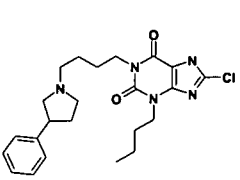
The following compounds (**Table 25**) were prepared using a method analogous to that for **Example 463**, using the appropriate carboxylic acid.

Table 25

464		3-butyl-8-chloro-1-[4-(5-isoquinolin-1-yl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 494 [MH] ⁺ RT 3.49min
465		3-butyl-8-chloro-1-[4-(2-oxo-3-phenylimidazolidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 459 [MH] ⁺ RT 3.23min
466		3-butyl-8-chloro-1-[4-(2,5-dioxo-3-phenylimidazolidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 473 [MH] ⁺ RT 3.19min
467		3-butyl-8-chloro-1-[4-(2-oxo-3-phenylpyrrolidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 458 [MH] ⁺ RT 3.12min

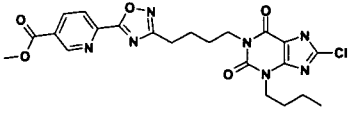
468		3-butyl-8-chloro-1-[4-(4-phenyl-1H-imidazol-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 441 [MH] ⁺ RT 2.60min
469		3-butyl-8-chloro-1-[4-(2,5-dioxo-3-phenylpyrrolidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 472 [MH] ⁺ RT 3.20min
470		3-butyl-8-chloro-1-[4-(4-phenylpiperidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 458 [MH] ⁺ RT 2.56min
471		3-butyl-8-chloro-1-[4-(4-phenylpiperazin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 459 [MH] ⁺ RT 2.49min
472		3-butyl-8-chloro-1-[4-{5-[2-fluoro-6-(methoxy)phenyl]-1,2,4-oxadiazol-3-yl}butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 491 [MH] ⁺ RT 3.33min
473		3-butyl-8-chloro-1-[4-[5-(2-cyclohexylphenyl)-1,2,4-oxadiazol-3-yl]butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 525 [MH] ⁺ RT 4.18min
474		3-butyl-8-chloro-1-[4-(5-phenyl-1,3-oxazol-2-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 442 [MH] ⁺ RT 3.46min

475		3-butyl-8-chloro-1-[4-(4-phenyl-1,3-oxazol-2-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 442 [MH] ⁺ RT 3.48min
476		3-butyl-8-chloro-1-[4-[3-(2-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 461 [MH] ⁺ RT 3.45min
477		3-butyl-8-chloro-1-[4-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 461 [MH] ⁺ RT 3.47min
478		3-butyl-8-chloro-1-[4-[5-(2,6-difluorophenyl)-2H-tetrazol-2-yl]butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 479 [MH] ⁺ RT 3.32min
479		3-butyl-8-chloro-1-[4-(5-pyridin-2-yl-1H-tetrazol-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 444 [MH] ⁺ RT 2.94min
480		3-butyl-8-chloro-1-[4-(5-pyridin-2-yl-2H-tetrazol-2-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 444 [MH] ⁺ RT 3.07min
481		3-butyl-8-chloro-1-[4-[5-(2-methylphenyl)-2H-tetrazol-2-yl]butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 457 [MH] ⁺ RT 3.54min

482		3-butyl-8-chloro-1-{4-[5-(3-methylphenyl)-2H-tetrazol-2-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 457 [MH] ⁺ RT 3.56min
483		3-butyl-8-chloro-1-{4-[5-(2-chlorophenyl)-2H-tetrazol-2-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 477 [MH] ⁺ RT 3.68min
484		3-butyl-8-chloro-1-{4-[5-[4-(methoxy)phenyl]-2H-tetrazol-2-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 473 [MH] ⁺ RT 3.40min
485		3-butyl-8-chloro-1-{4-[5-(4-chlorophenyl)-2H-tetrazol-2-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 477 [MH] ⁺ RT 3.68min
486		3-butyl-8-chloro-1-{4-[5-(3-fluorophenyl)-2H-tetrazol-2-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 461 [MH] ⁺ RT 3.51min
487		3-butyl-8-chloro-1-{4-[5-(2-fluorophenyl)-2H-tetrazol-2-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 461 [MH] ⁺ RT 3.34min
488		3-butyl-8-chloro-1-[4-(3-phenyl-1-pyrrolidiny)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 444 [MH] ⁺ RT 2.51min

489		3-butyl-8-chloro-1-{4-[5-(2-methylphenyl)-1H-tetrazol-1-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 457 [MH] ⁺ RT 3.16min
490		3-butyl-8-chloro-1-[4-(5-phenyl-1H-tetrazol-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 443 [MH] ⁺ RT 3.08min
491		3-butyl-8-chloro-1-(4-{5-[4-(methoxy)phenyl]-1H-tetrazol-1-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 473 [MH] ⁺ RT 3.10min
492		3-butyl-8-chloro-1-(4-{5-[3-(methoxy)phenyl]-2H-tetrazol-2-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 473 [MH] ⁺ RT 3.40min
493		8-chloro-3-ethyl-1-(3-((5Z)-5-[(4-fluorophenyl)methylidene]-2,4-dioxo-1,3-thiazolidin-3-yl)propyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 478 [MH] ⁺ RT 3.31min
494		3-butyl-8-chloro-1-(3-((5Z)-5-[(4-fluorophenyl)methylidene]-2,4-dioxo-1,3-thiazolidin-3-yl)propyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 506 [MH] ⁺ RT 3.63min
495		8-chloro-3-(cyclopropylmethyl)-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 441 [MH] ⁺ RT 3.38min

496		8-chloro-3-(cyclobutylmethyl)-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 455 [MH] ⁺ RT 3.53min
497		8-chloro-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 497 [MH] ⁺ RT 3.46min
498		8-chloro-3-(4-fluorobutyl)-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 461 [MH] ⁺ RT 3.26min
499		8-chloro-3-[2-(ethyloxy)ethyl]-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 459 [MH] ⁺ RT 3.16min
500		8-chloro-3-(2-methylpropyl)-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 443 [MH] ⁺ RT 3.44min
501		8-chloro-3-(3-cyclopropylpropyl)-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 469 [MH] ⁺ RT 3.63min
502		8-chloro-3-methyl-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 401 [MH] ⁺ RT 2.98min

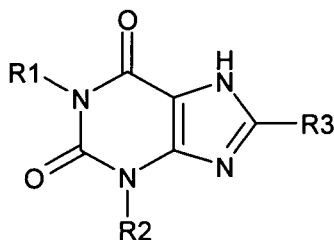
503		methyl 6-{3-[4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1 <i>H</i> -purin-1-yl)butyl]-1,2,4-oxadiazol-5-yl}-3-pyridinecarboxylate	m/z 502 [MH] ⁺ RT 3.22min
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The above starting materials may be purchased commercially and/or made according to processes which are available in the literature.

- 5 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Claims

1. At least one chemical entity selected from compounds of formula (I)
 5 compounds of formula (I)



(I)

10 and pharmaceutically acceptable derivatives thereof, wherein

R¹ represents $-(\text{alkylene})_m-X-(\text{alkylene})_n-Y$;

Wherein m and n represent the number of carbon atoms in the alkylene chain;

15 Wherein X represents a group selected from heteroaryl and heterocyclyl;

Wherein Y represents a group selected from aryl, heteroaryl and O-aryl;
 which may be optionally substituted by one or more groups independently selected
 20 from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, $-(\text{CH}_2)_q\text{NR}^5\text{R}^7$,
 $-(\text{CH}_2)_q-(\text{O})_p-(\text{CH}_2)_q-\text{N}(\text{R}^5)\text{C}(\text{O})\text{OR}^8$, $-(\text{CH}_2)_q-\text{N}(\text{R}^5)\text{C}(\text{O})\text{R}^8$,
 $-(\text{CH}_2)_q-(\text{O})_p-(\text{CH}_2)_q-\text{C}(\text{O})\text{NR}^5\text{R}^6$, $-(\text{CH}_2)_q-\text{N}(\text{R}^5)\text{C}(\text{O})\text{NR}^5\text{R}^6$,
 $-(\text{CH}_2)_q-\text{C}(\text{O})\text{N}((\text{CH}_2)_m\text{OH})\text{R}^5$, $-(\text{CH}_2)_q-\text{N}(\text{R}^5)-\text{S}(\text{O})_2\text{R}^8$, $-\text{CH}_2-\text{S}(\text{O})_2\text{NR}^5\text{R}^6$,
 $-\text{C}_{1-6}$ haloalkyl, $-\text{OCF}_3$, $-\text{OCH}(\text{F})_2$, $-\text{OCH}_2\text{F}$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{OR}^5$, $-\text{R}^8\text{CN}$, CN , $-\text{SO}_2\text{R}^9$,
 25 $-(\text{CH}_2)_n$ heteroaryl, $-(\text{CH}_2)_n$ heterocyclyl, $-(\text{CH}_2)_n$ cycloalkyl, $-(\text{CH}_2)_n$ cycloalkenyl, and
 $-(\text{CH}_2)_n$ aryl;

R² represents C₁₋₆ alkyl which may be optionally substituted by one or more groups
 independently selected from cycloalkyl, C₁₋₆ haloalkyl, halogen, $-\text{CN}$ and $-\text{OR}^4$;

30 R³ represents halogen;

R⁴ represents a group selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
 $-(\text{CH}_2)_n$ cycloalkyl, $-(\text{CH}_2)_n$ cycloalkenyl, $-(\text{CH}_2)_n$ heterocyclyl, $-(\text{CH}_2)_n$ aryl, and
 35 $-(\text{CH}_2)_n$ heteroaryl;

R⁵ and R⁶ are independently selected from hydrogen and C₁₋₄ alkyl;

R⁷ represents a group selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_i cycloalkyl, -(CH₂)_n cycloalkenyl, -(CH₂)_i heterocyclyl, -(CH₂)_i aryl, and -(CH₂)_i heteroaryl;

R⁸ represents C₁₋₄ alkyl;

R⁹ represents a group selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -(CH₂)_n cycloalkyl, -(CH₂)_n cycloalkenyl, -(CH₂)_n heterocyclyl, -(CH₂)_n aryl, -(CH₂)_n heteroaryl, and CN;

m represents an integer selected from 3 and 4;

n represents an integer selected from 0 and 1;

p represents an integer selected from 0 and 1;

q represents an integer selected from 0, 1 and 2; and

t represents an integer selected from 1 and 2.

2. At least one chemical entity according to claim 1 wherein X represents a group selected from heteroaryl.

3. At least one chemical entity according to claim 1 or 2 wherein R² is selected from C₃₋₆ alkyl.

4. At least one chemical entity according to claim 2 or 3 wherein X represents a group selected from heteroaryl comprising a nitrogen heteroatom.

5. At least one chemical entity according to claim 4 wherein X represents oxadiazolyl or tetrazole.

6. At least one chemical entity according to any preceding claim wherein Y represents a group selected from aryl and heteroaryl.

7. At least one chemical entity according to any preceding claim wherein Y is optionally substituted by one or more of halogen and C₁₋₆ haloalkyl.

8. At least one chemical entity according to any preceding claim wherein R³ represents chlorine.

9. At least one chemical entity according to any preceding claim wherein Y represents phenyl and m is 3 and n is 1.
10. At least one chemical entity according to claim 9 wherein X represents tetrazolyl, R² represents butyl and R³ represents chlorine.
11. At least one chemical entity according to claim 8 wherein X represents oxadiazolyl, Y represents piridinyl, R² represents butyl, R³ represents chlorine and m is 4 and n is 0.
12. At least one chemical entity according to any preceding claim for use in human or veterinary medicine.
13. At least one chemical entity according to any one of claims 1 to 11, for use in the treatment of disorders of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia and/or of inflammatory diseases or conditions.
14. At least one chemical entity according to any one of claims 1 to 11 for use in the treatment of diabetic dyslipidaemia, mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity, coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease or stroke.
15. At least one chemical entity according to any one of claims 1 to 11 for use in the manufacture of a medicament for treating diabetic dyslipidaemia, mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity, coronary artery disease, thrombosis, angina, chronic renal failure or stroke.
16. A method for the treatment of a human or animal subject having a condition where under-activation of the HM74A receptor contributes to the condition or where activation of the receptor will be beneficial, which method comprises administering to said human or animal subject an effective amount of at least one chemical entity according to any one of claims 1 to 7.
17. A method according to claim 16 wherein the human or animal subject has a disorder of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia or an inflammatory disease or condition.

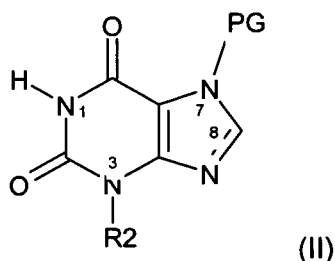
18. A pharmaceutical formulation comprising at least one chemical entity according to any one of claims 1 to 11 and at least one pharmaceutically acceptable diluent, excipient or carrier.

5 19. A combination for administration together or separately, sequentially or simultaneously in separate or combined pharmaceutical formulations, said combination comprising at least one chemical entity according to any one of claims 1 to 11 together with at least one therapeutically active agent.

10 20. A pharmaceutical formulation comprising:

- (i) at least one chemical entity according to any one of claims 1 to 11;
- (ii) one or more therapeutically active agent selected from statins, fibrates, bile-acid binding resins and nicotinic acid; and
- (iii) one or more pharmaceutically acceptable diluent, excipient or carrier.

15 21. A method for the preparation of at least one chemical entity according to any one of claims 1 to 11 from an appropriate starting material, for example compound(s) of formula (II):



wherein PG = protecting group, the method comprising:

- (i) alkylation at N1 of an N7 protected xanthine;
- (ii) alkylation at N3 of an N7 protected xanthine;
- (iii) halogenation at C8; and
- (iv) de-protection of N7;

in any order providing de-protection is carried out after alkylation.