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.

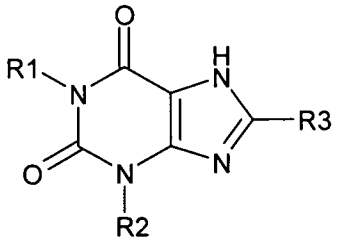
Summary of the Invention

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, hypercholesteraemia, 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

R^1 represents –(alkylene)$_m$-X-(alkylene)$_n$-Y;

Wherein X represents A, A1, A2 or a direct link;

A represents a group selected from
cycloalkylene, cycloalkenylene, aryl, heteroaryl, heterocyclyl, and -CH_2-OC(O)-;

A1 represents a group selected from
-CH_2-O-$(CH_2)_q$aryl-O-, -CH_2-O-$(CH_2)_w$N(R^5)C(O)O-, -CH_2-N(R^5)C(O)O-,
-CH_2-N(R^5)C(O)- , -CH_2-$(O)_p$-$(CH_2)_q$C(O)NR^5-, -CH_2-N(R^5)C(O)N(R^5)-,
-CH_2-C(O)N($(CH_2)_w$OH)-, -CH_2-NR^5-S$(O)_2$-, CH_2-S$(O)_2$NR^5-, -CH_2-C(O)O-, -O-,
-NR^5-, and -S-;

A2 represents -CH(OH)-;

When X is A, A1 or A2, Y represents a group selected from
heteroaryl, heterocyclyl, aryl, cycloalkyl, cycloalkenyl, -NH-aryl, -O$(CH_2)_n$-aryl,
-O-heteroaryl, -OR^5, -C(O)OR^5, -C(O)O-C_6aryl, -OC(O)R^4, -CH(aryl)$_2$,
-CH(heteroaryl)$_2$, and -C_{1-6} haloalkyl;

When X is A1 and Y is selected from
-O$(CH_2)_n$-aryl, -O-heteroaryl, -OR^5, -OC(O)R^4, and -NH-aryl,
n is an integer selected from 2, 3, 4 and 5;

When X is A1 and Y is -C_{1-6} haloalkyl, or when X is A2, n is an integer selected from 1, 2, 3, 4 and 5;

When X is a direct link, (m + n) is an integer selected from 2 to 10;

When X is a direct link and (m + n) is an integer selected from 3 to 10, Y represents a group selected from
-C(O)$(CH_2)_q$OR^4, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocyclyl, heteroaryl, heterocyclyl, Aryl, 3 or 4 ring fused system, -CH(aryl)$_2$, -CH(heteroaryl)$_2$, -OR^5, -N$R^5$$R^6$, -N$R^5$C(O)O$R^7$, -$(O)_p$C(O)N$R^5$$R^7$, and -N$R^5$C(O)$R^7$;

When X is a direct link and (m + n) is 2, Y represents a group selected from
-OR^5, -NH_2, and -NR^5C(O)OR^8;

When Y incorporates a ring, that ring may be optionally substituted by one or more of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -$(CH_2)_q$ N$R^5$$R^7$,
-$(CH_2)_q$-$(O)_p$-$(CH_2)_q$-N(R^5)C(O)OR^8, -$(CH_2)_q$-N(R^5)C(O)R^8,
-$(CH_2)_q$-$(O)_p$-$(CH_2)_q$-C(O)N$R^5$$R^6$, -$(CH_2)_q$-N($R^5$)C(O)N($R^5$)$R^6$,

$-(CH_2)_q-C(O)N((CH_2)_mOH)R^5$, $-(CH_2)_q-N(R^5)-S(O)_2R^8$, $-CH_2-S(O)_2N(R^5)R^6$, $-C_{1-6}$ haloalkyl, $-OCF_3$, $-OCH(F)_2$, $-OCH_2F$, $-C(O)OR^5$, $-OR^5$, $-R^8CN$, -CN, $-SO_2R^9$, $-(CH_2)_n$heteroaryl, $-(CH_2)_n$heterocycyl, $-(CH_2)_n$cycloalkyl, $-(CH_2)_n$cycloalkenyl, and $-(CH_2)_n$aryl;

Provided that when X is A1, A1 is -O- and Y is a ring which is substituted by aryl or heteroaryl, then m is an integer selected from 3, 4 and 5;

R^2 is selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, and heteroaryl, each of which may be optionally substituted by one or more of a group independently selected from: C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_{1-6} haloalkyl, halogen, -CN, $-OR^4$, $-(CH_2)_nCOR^4$, $-C(O)OR^4$, $-OCOR^4$, $-(CH_2)_nNR^5R^6$, $-(NH)_pCONR^5R^6$, $-OCONR^5R^7$, and $-NR^5C(O)OR^7$;

R^3 represents a group selected from halogen and CN;

R^4 is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n$ cycloalkyl, $-(CH_2)_n$ cycloalkenyl, $-(CH_2)_n$ heterocyclyl, $-(CH_2)_n$ aryl, and $-(CH_2)_n$ heteroaryl;

R^5 and R^6 are independently selected from hydrogen and C_{1-4} alkyl;

R^7 represents a group selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_t$ cycloalkyl, $-(CH_2)_n$ cycloalkenyl, $-(CH_2)_t$ heterocyclyl, $-(CH_2)_t$ aryl, and $-(CH_2)_t$ heteroaryl;

R^8 represents a group selected from C_{1-4} alkyl;

R^9 represents a group selected from C_{1-6} alkyl C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n$ cycloalkyl, $-(CH_2)_n$cycloalkenyl, $-(CH_2)_n$heterocyclyl, $-(CH_2)_n$ aryl, $-(CH_2)_n$heteroaryl, and CN;

m represents an integer selected from 1, 2, 3, 4 and 5;

n represents an integer selected from 0, 1, 2, 3, 4 and 5;

p represents an integer selected from 0 and 1;

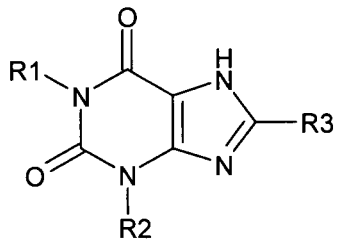
q represents an integer selected from 0, 1 and 2;

t represents an integer selected from 1 and 2; and

w represents an integer selected from 2, 3 and 4.

The compounds are 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 or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, 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.

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



(I)

and pharmaceutically acceptable derivatives thereof, wherein

R^1 represents $-(alkylene)_m-X-(alkylene)_n-Y$

Wherein X represents A, A1, A2 or a direct link;

A represents a group selected from:
cycloalkylene, cycloalkenylene, aryl, heteroaryl, heterocyclyl, and $-CH_2-OC(O)-$;

A1 represents a group selected from:
$-CH_2-O-(CH_2)_q$aryl-O-, $-CH_2-O-(CH_2)_wN(R^5)C(O)O-$, $-CH_2-N(R^5)C(O)O-$, $-CH_2-N(R^5)C(O)-$, $-CH_2-(O)_p-(CH_2)_qC(O)NR^5-$, $-CH_2-N(R^5)C(O)N(R^5)-$, $-CH_2-C(O)N((CH_2)_mOH)-$, $-CH_2-NR^5-S(O)_2-$, $CH_2-S(O)_2NR^5-$, $-CH_2-C(O)O-$, -O-, -NH-, and -S-;

A2 represents:
-CH(OH)-;

When X is A, A1 or A2, Y represents a group selected from:
heteroaryl, heterocyclyl, aryl, cycloalkyl, cycloalkenyl, -NH-aryl, -O$(CH_2)_n$-aryl, -O-heteroaryl, -OR^5, -C(O)OR^5, -C(O)O-C_6 aryl, -OC(O)R^5, -CH(aryl)$_2$, -CH(heteroaryl)$_2$, and -C_{1-6} haloalkyl;

When X is A1 and Y is selected from:
-O$(CH_2)_n$-aryl, -O-heteroaryl, -OR^5, -OC(O)R^5, and -NH-aryl,
n is an integer selected from 2, 3, 4 and 5;

When X is A1 and Y is -CF_3, or when X is A2, n is an integer selected from 1, 2, 3, 4 and 5;

When X is a direct link, (m + n) is an integer selected from 2 to 10;

When X is a direct link and (m + n) is an integer selected from 3 to 10, Y represents a group selected from: -C(O)$(CH_2)_q$$OR^5$, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocyclyl, heteroaryl, heterocyclyl, Aryl, 3 or 4 ring fused system, -CH(aryl)$_2$, -CH(heteroaryl)$_2$, -OR^5, -NR^5R^6, -NC(O)OR^8, -$(O)_p$C(O)NR^5R^6, and -NR^5C(O)R^8;

When X is a direct link and (m + n) is 2, Y represents a group selected from:
-OR^5, -NH_2, and –NC(O)OR^8;

When Y incorporates a ring, that ring may be optionally substituted by one or more of:
C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -NH_2, -$(CH_2)_q$-$(O)_p$-$(CH_2)_q$-$N(R^5)C(O)OR^8$, -$(CH_2)_q$-$N(R^5)C(O)R^8$, -$(CH_2)_q$-$(O)_p$-$(CH_2)_q$-$C(O)NR^5R^6$, -$(CH_2)_q$-$N(R^5)C(O)N(R^5)R^6$, -$(CH_2)_q$-$C(O)N((CH_2)_mOH)R^5$, -$(CH_2)_q$-$N(R^5)$-$S(O)_2R^8$, -CH_2-$S(O)_2N(R^5)R^6$, -C_{1-6} haloalkyl, -OCF_3, -$OCH(F)_2$, -OCH_2F, -C(O)OR^5, -OR^5, -$(R^8)_p$CN, -SO_2R^9, -$(CH_2)_n$heteroaryl, -$(CH_2)_n$heterocycyl, -$(CH_2)_n$cycloalkyl, -$(CH_2)_n$cycloalkenyl, and -$(CH_2)_n$aryl;

Provided that when X is A1, A1 is -O- and Y is a ring which is substituted by aryl or heteroaryl, then m is an integer selected from 3, 4 and 5;

R^2 is selected from: H; or C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, cycloalkyl, cycloalkenyl heterocyclyl, aryl, and heteroaryl, each of which may be optionally substituted by one or more of: C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_{1-6} haloalkyl, halogen, -CN, -OR^4, -$(CH_2)_n$$COR^4$, -C(O)$OR^4$, -$OCOR^4$, -$(CH_2)_n$$NR^5R^6$, -$(NH)_p$$CONR^5R^6$, -$OCONR^5R^7$, and -NHC(O)$OR^7$;

R^3 is selected from: halogen and CN;

R^4 is selected from: H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n$ cycloalkyl, $-(CH_2)_n$ cycloalkenyl, $-(CH_2)_n$ heterocyclyl, $-(CH_2)_n$ aryl, and $-(CH_2)_n$ heteroaryl;

R^5 and R^6 are selected from: hydrogen and C_{1-4} alkyl;

R^7 is selected from: H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_t$ cycloalkyl, $-(CH_2)_n$ cycloalkenyl, $-(CH_2)_t$ heterocyclyl, $-(CH_2)_t$ aryl, and $-(CH_2)_t$ heteroaryl;

R^8 is selected from C_{1-4} alkyl;

R^9 is selected from, C_{1-6} alkyl C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n$ cycloalkyl, $-(CH_2)_n$cycloalkenyl, $-(CH_2)_n$heterocyclyl, $-(CH_2)_n$ aryl, and $-(CH_2)_n$heteroaryl, CN;

m represents an integer selected from: 1, 2, 3, 4 and 5;

n represents an integer selected from: 0, 1, 2, 3, 4 and 5;

p represents an integer selected from: 0 and 1;

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

t represents an integer selected from: 1 and 2;

w represents an integer selected from: 2, 3 and 4.

In one embodiment, X represents A or A1. In a further embodiment, A is selected from heteroaryl, heterocyclyl, and A1 is selected from CH_2-O-$(CH_2)_w$N(R^5)C(O)O-, for example $CH_2O(CH_2)_2NHC(O)O$-, CH_2-N(R^5)C(O)O- for example CH_2-NHC(O)O, CH_2-N(R^5)C(O)- for example, CH_2-NHC(O)-, CH_2-$(O)_p$-$(CH_2)_q$C(O)NR^5- for example $CH_2C(O)NCH_3$- , CH_2-N(R^5)C(O)N(R^5)- for example CH_2-NHC(O)NCH_3-, CH_2-C(O)N($(CH_2)_mOH$)- for example CH_2-C(O)N($(CH_2)_2OH$)-, CH_2-NR^5-$S(O)_2$- for example CH_2-NH-$S(O)_2$-, CH_2-$S(O)_2NR^5$- for example CH_2-$S(O)_2NCH_3$-, and CH_2-C(O)O-. In another embodiment, X represents A and A represents a heteroaryl. In another embodiment A represents a heteroaryl comprising a nitrogen heteroatom, for example, triazolyl, furazanyl, oxadiazolyl, tetrazolyl, imidazolyl or pyrazolyl.

In one embodiment, Y represents an optionally substituted group selected from: aryl, for example phenyl or napthyl, heteroaryl, for example pyridinyl, thiazolyl, thienyl, benzofuranyl or indolyl, and O-aryl, for example O-phenyl.

In a further embodiment, Y is substituted by one or more groups selected from OR^5 for example OH or OCH_3, halogen, for example F or Cl, aryl, for example phenyl,

C_{1-6} haloalkyl for example CF_3 or CH_2CF_3, OCF_3, $(R^8)_pCN$ for example CN, $(CH_2)_q$-$N(R^5)$-$S(O)_2R^8$, 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 -$(CH_2)_q$-$N(R^5)C(O)R^8$.

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

In yet a further embodiment, wherein Y is a ring, it is not further substituted.

In one embodiment of the invention, when X represents A or A1, and A represents cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocyclyl, and A1 represents -CH_2-O-$(CH_2)_w$-$N(R^5)C(O)O$-, -CH_2-$N(R^5)C(O)O$-, -CH_2-$N(R^5)C(O)$- , -CH_2-$(O)_p$-$(CH_2)_q$-$C(O)NR^5$-, -CH_2-$N(R^5)C(O)N(R^5)$-, or -CH_2-$C(O)N((CH_2)_mOH)$-, and Y represents a ring, for example when X represents oxadizolyl, tetrazolyl or pyrazolyl and Y represents phenyl, pyridinyl, or thienyl, m is an integer selected from 3 and 4 and n is an integer selected from 0 and 1, for example m is 4 and n is 0, or m is 3 and n is 1;

In one embodiment R^2 represents C_{1-10} alkyl which may be optionally substituted by one or more of: cycloalkyl, heterocyclyl, aryl, heteroaryl, C_{1-6} haloalkyl, halogen, -CN, $-OR^4$, -$(CH_2)_nCOR^5$, $-C(O)OR^4$, $-OCOR^4$, -$(CH_2)_nNR^5R^6$, and -$(NH)_pCONR^5R^6$. In a further embodiment, R^2 is selected from C_{1-10} alkyl which may be optionally substituted by one or more of: cycloalkyl, aryl, heteroaryl, C_{1-6} haloalkyl, halogen, -CN, $-OR^4$, -$(CH_2)_nCOR^5$, $-C(O)OR^4$ and $-OCOR^4$. In yet a further embodiment R^2 is selected from C_{1-6} alkyl which may be optionally substituted by one or more of: cycloalkyl, C_{1-6} haloalkyl, halogen, -CN or $-OR^4$. In yet another further embodiment, R^2 is selected from C_{3-6} alkyl, for example butyl or pentyl.

In one embodiment, R^3 represents halogen. In a further embodiment, R^3 is selected from: chlorine and bromine. In another embodiment, R^3 represents chlorine.

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 individual enantiomers or diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof.

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, C_3-C_{10}alkyl means a straight or branched hydrocarbon chain containing at least 3 and at most 10 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“ or as used herein means both straight and branched chain, or cyclic saturated hydrocarbon linker groups. Examples of alkylene groups include methylene (-CH_2-), ethylene (-CH_2CH_2-), ethene (-CH=CH-), or cyclopropylene and the like. For example, as used herein, -$(alk)_n$-, where n is 3 represents -$(CH_2)_3$-, -$C(CH_3)_2$-, -CH_2CH=CH-, or -cyclopropylene- and the like. For example as used herein, -$(alk)_m$- where m is 4 represents -$(CH_2)_4$-, -$CH_2C(CH_3)_2$-, -$CH_2CH=CHCH_2$-, or -CH_2cyclopropylene- and the like.

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.

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.

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 or cyclooctyl and the like.

The term "cycloalkylene" as used herein refers to a saturated monocyclic hydrocarbon ring of 3 to 8 carbon linker goups. Examples of such groups include cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cycloheptylene or cyclooctylene and the like.

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 or cyclooctenyl and the like.

The term "cycloalkenylene" as used herein refers to an unsaturated non-aromatic monocyclic hydrocarbon ring of 3 to 8 carbon linker groups containing one or more carbon-carbon double bonds. Examples of such groups include cyclopropenylene, cyclobutenylene, cyclopentenylene, cyclohexenylene, cycloheptenylene or cyclooctenylene and the like.

The term "aryl" as used herein refers to a C_{6-12} 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.

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 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, pyranyl, 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, indolizinyl, indazolyl, purinyl, pyrrolopyridinyl, furopyridinyl, benzofuranyl, isobenzofuranyl, benzothienyl, benzoimidazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

The term "heterocyclyl" 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 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, azetidinyl, 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.

The term "3 or 4 ring fused system" as used herein refers to a fused 12-18 membered tricyclic or tetracyclic ring which contains 1 to 4 heteroatoms of N and wherein at least one ring is aromatic. There may be one or more optional oxo substituents on the ring carbon atoms. Examples of such fused aromatic rings include carbazolyl, acenaphthyl, naphthotriazolyl and the like.

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

The term "C_{1-6} haloalkyl" as used herein refers to a C_{1-6} alkyl group as defined herein wherein at least one hydrogen atom is replaced with halogen. Examples of such groups include fluoroethyl, trifluoromethyl or trifluoroethyl and the like.

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.

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 herein by reference.

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 being acceptable in the sense of being compatible with any other ingredients present in the pharmaceutical formulation and not being deleterious to the recipient thereof.

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 referred to as a hydrate of the solute in question.

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.

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, triethylmine, choline and meglumine; or salts with amino acids such as arginine, lysine and histidine.

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 C_{1-6}alkyl esters, e.g. methyl esters, ethyl esters, and the like.

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.

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.

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-1*H*-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-1*H*-purine-2,6-dione form 2.

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 form 2) having a melting point onset measured by DSC (± 0.5°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 (°).

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, hypercholesteraemia, 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.

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 erythematosis, 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 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.

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.

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

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, $G_{o1}\alpha$.

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 F-12 HAM media 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 [^{35}S]-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 1,000*g* for 10 min in a microcentrifuge to pellet the nuclei and unbroken cells and P2 particulate fractions were recovered by microcentrifugation at 16,000*g* for 30min. P2 particulate fractions were resuspended in buffer A and stored at –80°C until required.

[^{35}S]-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 $MgCl_2$, 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. [^{35}S]-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 μl. For this 10 μl 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 μg membrane and 100 μg Leadseeker WGA beads. For the low volume protocol, membrane, beads and [^{35}S]-GTPγS were mixed together and then 10 μl of this mix were dispensed to each well. Incubation and plate read were identical for the 10μl and 50 μl assays.

All exemplified compounds were tested in one or both of the [^{35}S]-GTPγS binding assays described above (i.e. the 10μl and 50μl 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 pEC_{50} and as % efficacy compared to the maximal response of nicotinic acid binding.

In-vivo testing

HM74A agonists 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 (10,000*g* 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 HM74A compounds 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 experimention. 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^{O}C until assayed for NEFA concentrations.

Compounds according to Formula (I) have been synthesised (see synthetic examples below) and tested in the [^{35}S]-GTPγS binding assays discussed above.

Some compounds according to formula (I) including:

3-butyl-8-chloro-1-[3-(dimethylamino)propyl]-3,7-dihydro-1H-purine-2,6-dione;
8-chloro-3-(3,3-dimethylbutyl)-1-[2-(ethyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione;
3-butyl-8-chloro-1-[3-(5-phenyl-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione;
1-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-1H-naphtho[2,3-d][1,2,3]triazole-4,9-dione;
2-({4-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]phenyl}oxy)ethyl acetate.

have utility as intermediates in the production of other compounds according to formula (I).

The exemplified compounds (Examples 1 - 894) have a pEC$_{50}$ of 4.3 (+/- 0.3 log unit) or greater and an efficacy of 30% or greater (in relation to nicotinic acid) in the [^{35}S]-GTPγS binding assays described above, in which they were tested.

The following compounds were tested and found to have activity lower than a pEC$_{50}$ of 4.3 (+/- 0.3 log unit) and an efficacy of less than 30% (in relation to nicotinic acid) in the [^{35}S]-GTPγS binding assays described above, in which they were tested.

8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(1-piperidinyl)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione;

8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(hexahydro-1*H*-azepin-1-yl)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione;
8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(1-pyrrolidinyl)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione;
8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(dimethylamino)-2-methylpropyl]-3,7-dihydro-1*H*-purine-2,6-dione;
8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[3-(dimethylamino)propyl]-3,7-dihydro-1*H*-purine-2,6-dione;
8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[3-(4-methyl-1-piperazinyl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione;
8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(dimethylamino)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione.

General purification and analytical methods:

LC/MS: Method
Analytical HPLC was conducted on a Supelcosil™ ABZ+PLUS column (Supelco) (3µm, 3.3cm x 4.6mm ID) eluting with 0.1% HCO_2H and 0.01 M ammonium acetate in water (solvent A), and 95% MeCN and 5% water (containing 0.5% HCO_2H) (solvent B), using the following elution gradient 0-0.7min 0%B, 0.7-4.2min 0→100%B, 4.2-4.6minutes 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 $M(NH_4)^+$ molecular ions] or electrospray negative ionisation [(ES-ve to give $(M-H)^-$ molecular ion] modes. Only the parent ion of major isotopes quoted.

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

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

Companion™ system refers to the Teledyne Isco Combiflash Companion™ purification system. This is a gradient controlled purification system with integral, variable 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% HCO_2H in water and solvent B: 95% MeCN, 5%

water (containing 0.5% HCO_2H). 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% HCO_2H in water and MeCN (with 0.5% HCO_2H). 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 funtionalised silica sorbent (sold by 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% HCO_2H in water and MeCN (0.5% HCO_2H).
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

dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, 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, 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 including dyslipidaemia and hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, 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 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 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 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, hypercholesteraemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity, coronary artery disease, thrombosis, angina, chronic renal failure, stroke and 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 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 erythematosis, 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, hypercholesteraemia, 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 0.1μg to 1mg, per minute. Infusion fluids suitable for this purpose may contain, for example, from 0.01μg to 0.1mg, per millilitre. Unit doses may contain, for example, from 0.01μg to 1g of a compound of the invention. Thus ampoules for injection may contain, for example, from 0.01μg 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 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 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. 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 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 and freeze-drying.

Formulations suitable for rectal administration may be presented as unit-dose suppositories. These may be prepared by admixing a a compound of formula (I) or a 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 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 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 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.

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.

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.

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- tetrafluorethane, carbon dioxide or other suitable gas.

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.

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).

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 a medicament for the combination therapy of disorders of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, 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.

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, 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 they may be provided in any convenient formulation, conveniently in such a manner as are known for such compounds in the art.

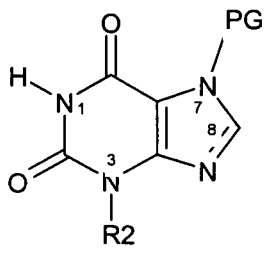
When in combination with a second therapeutic agent active against the same disease, the dose of each component may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

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.

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.

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.

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):



(II)

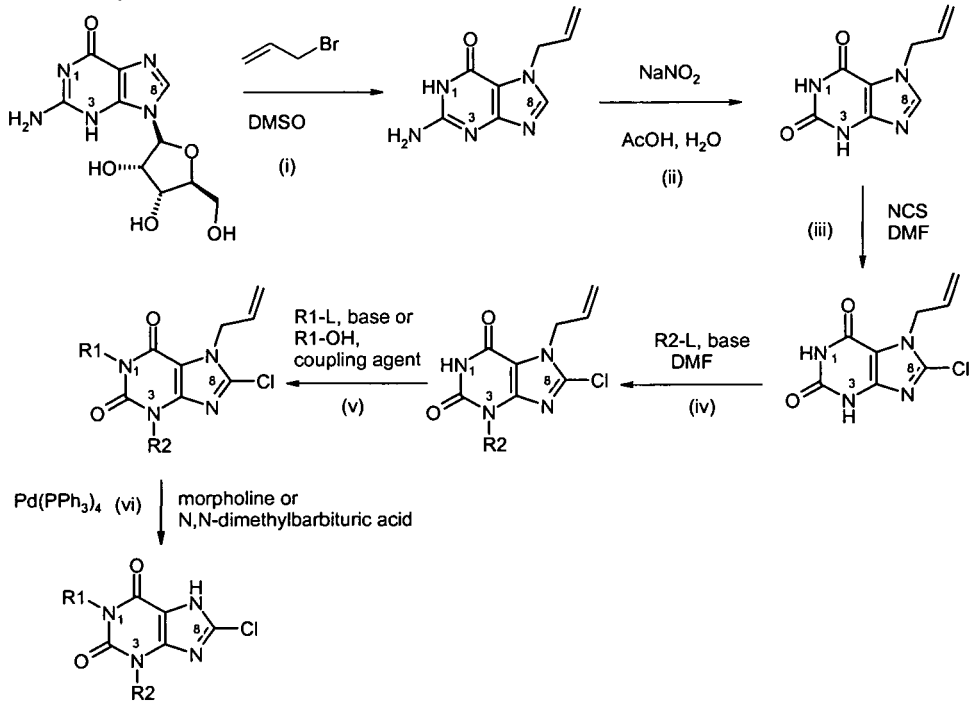
wherein PG = protecting group, the method comprising:

(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 cycloalkyl, heterocyclyl, cycloalkenyl, heteroaryl or aryl.

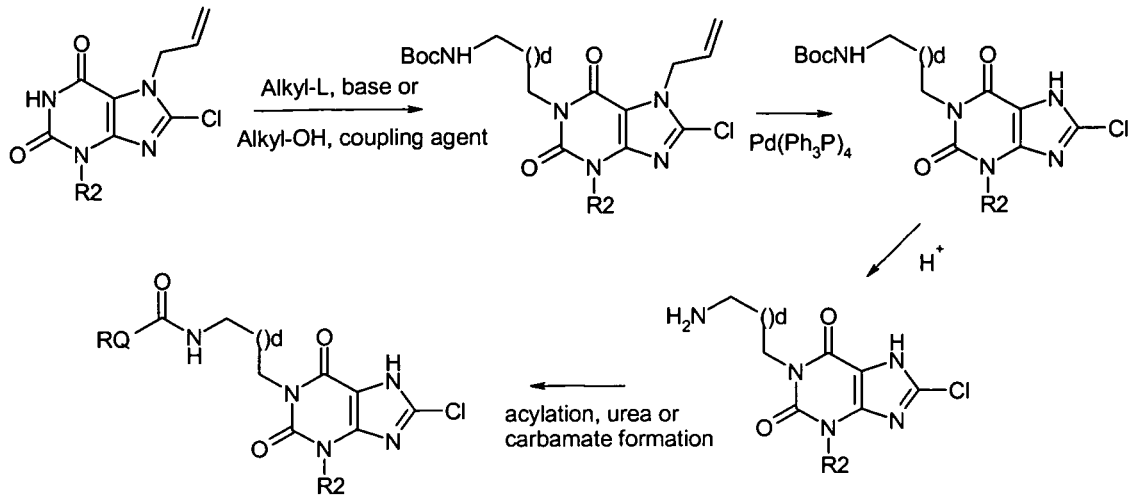


i) Alkylation of guanine with allyl bromide
ii) Diazotisation with sodium nitrite followed by hydrolysis to form the xanthine
iii) Chlorination
iv) Alkylation at N3
v) Alkylation at N1
vi) Palladium catalysed removal of the allyl group

wherein L represents a leaving group, for example halogen.

Process 2:

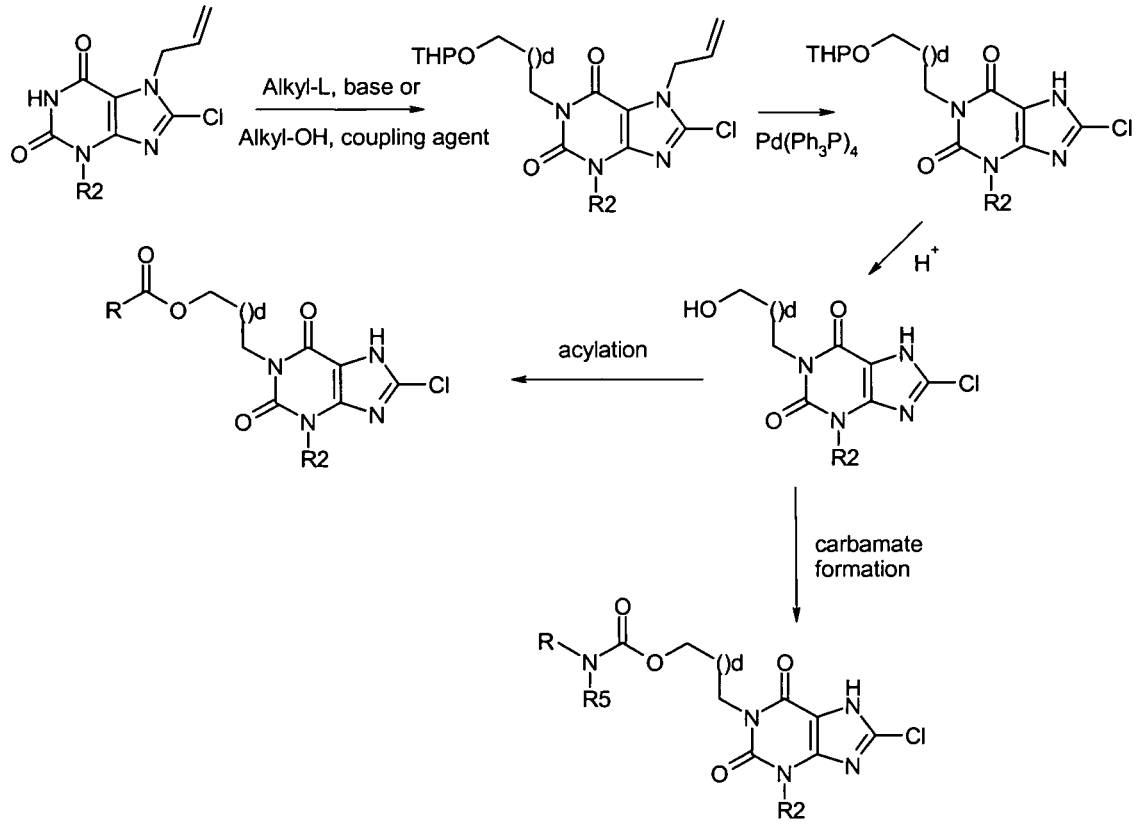
A process according to the invention for preparing compound(s) of formula (I) in which R1 incorporates an amide, carbamate or urea



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.

Process 3:

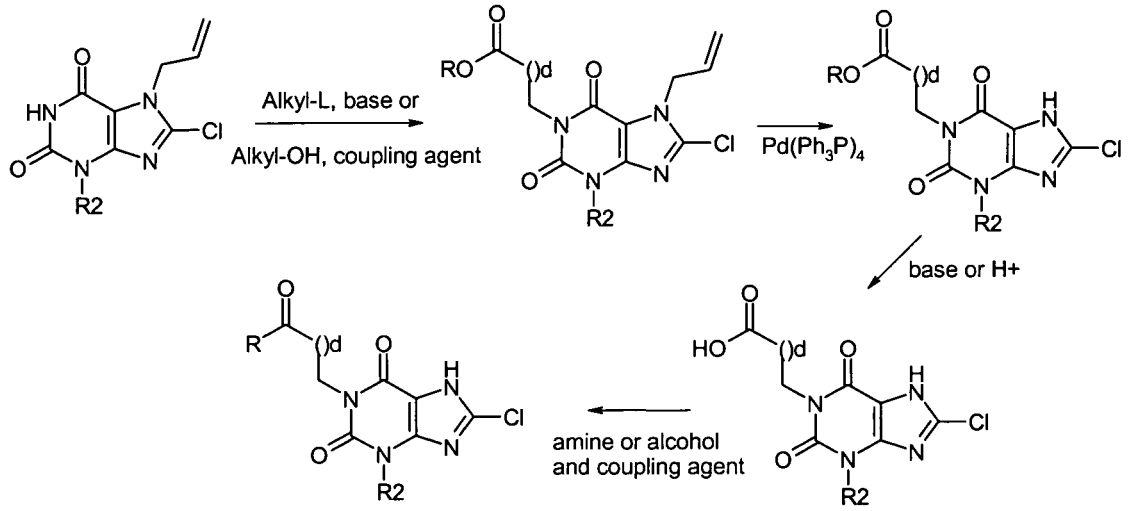
A process according to the invention for preparing compound(s) of formula (I) in which R1 incorporates a 'reverse' carbamate or ester



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

Process 4:

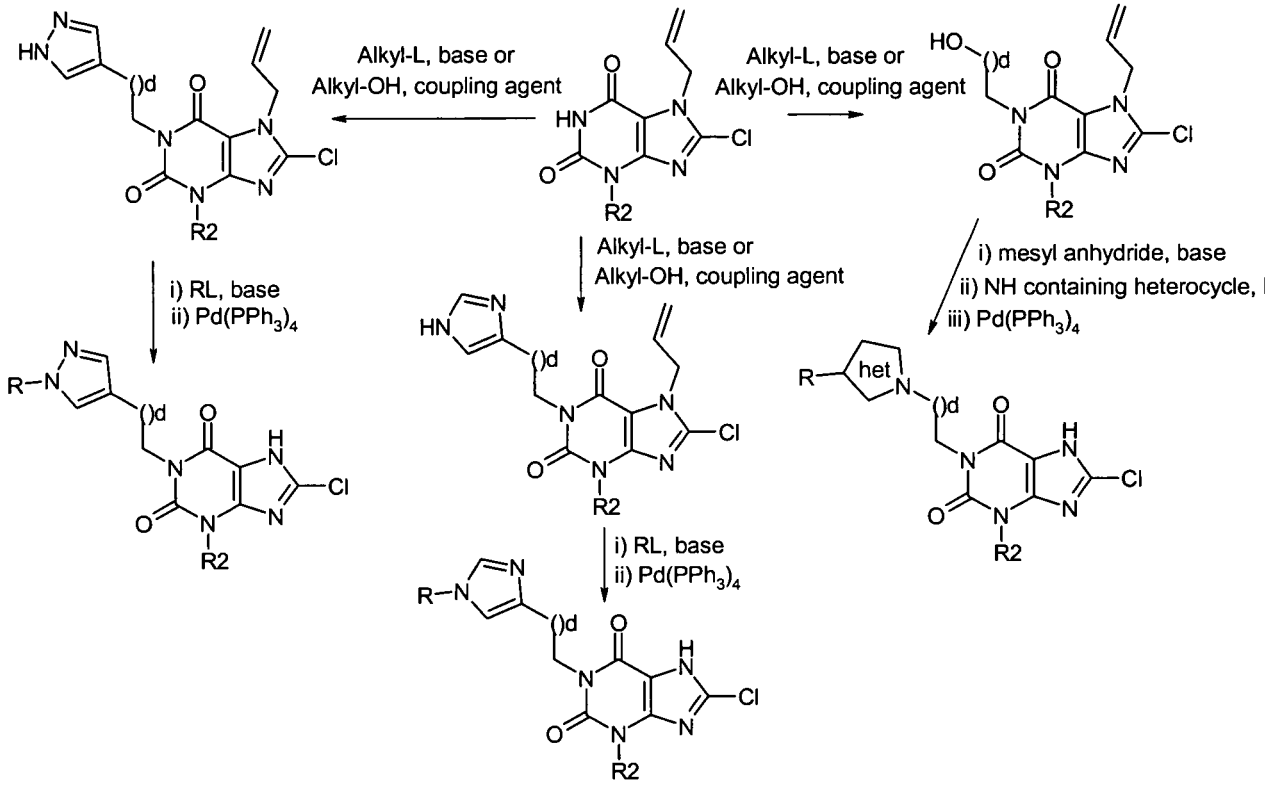
A process according to the invention for preparing compound(s) of formula (I) in which R1 incorporates an ester or amide



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

Process 5:

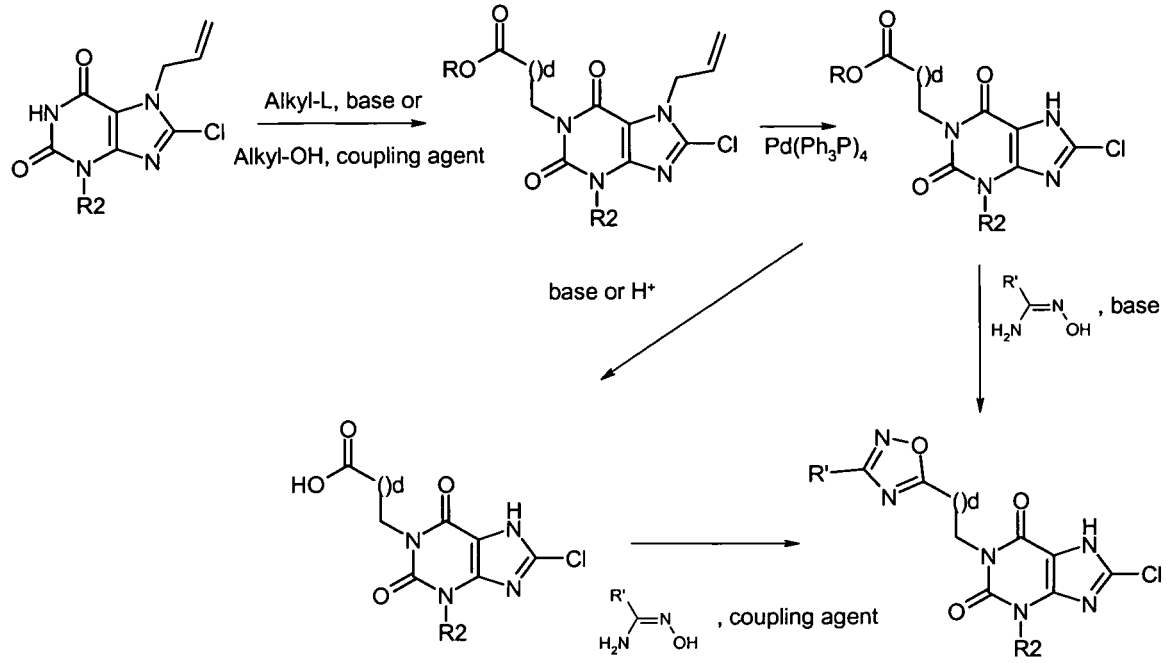
A process according to the invention for preparing compound(s) of formula (I) in which R1 incorporates a pyrazole, imidazole or tetrazole.



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

Process 6:

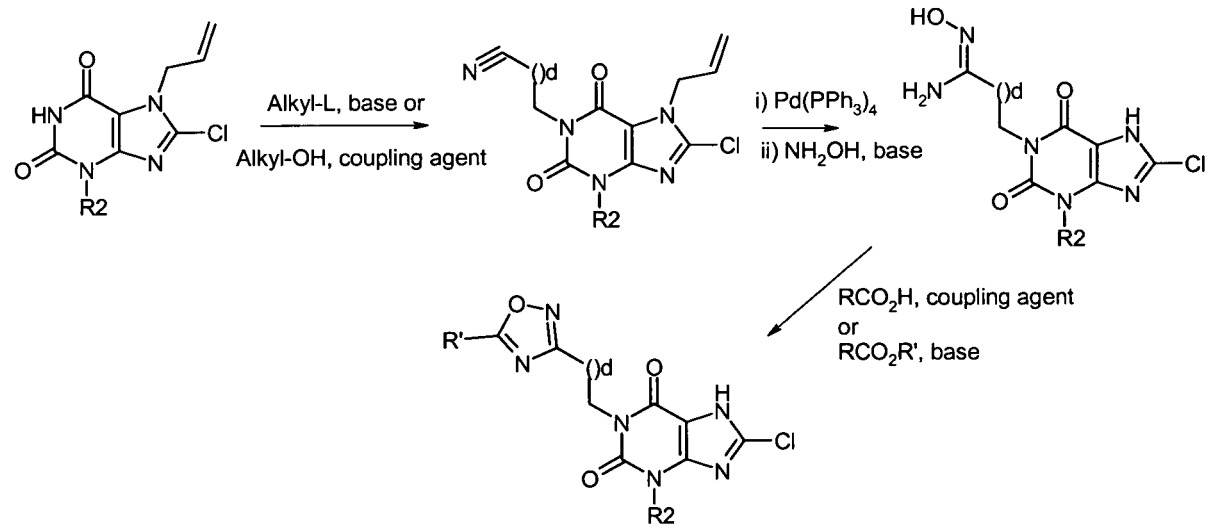
A process according to the invention for preparing compound(s) of formula (I) in which R1 incorporates an oxadiazole.



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

Process 7:

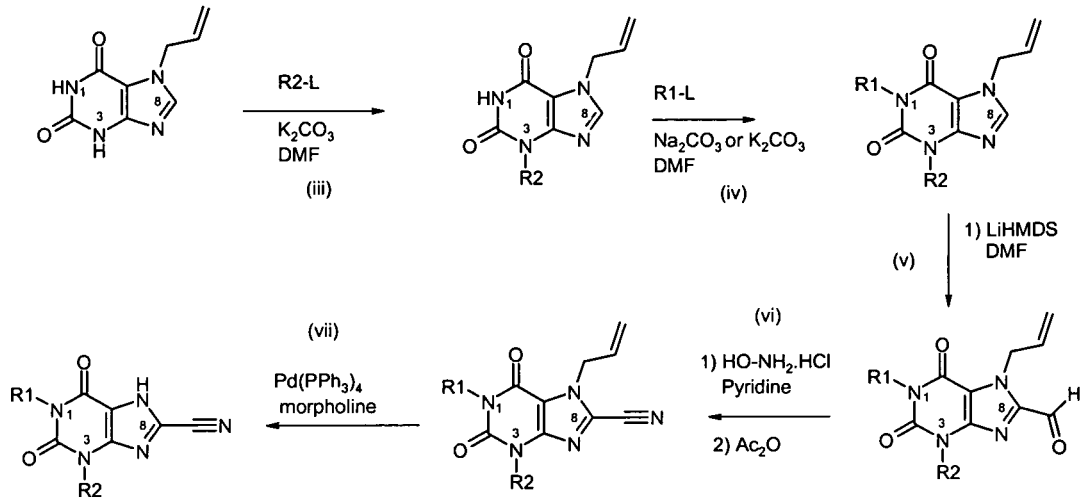
A process according to the invention for preparing compound(s) of formula (I) in which R1 incorporates an oxadiazole



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

Process 8:

A process according to the invention for preparing compound(s) of formula (I) in which R^3 is CN 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

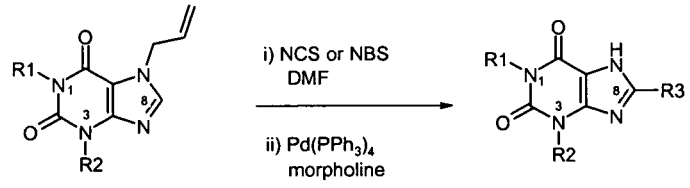
vi) Conversion of the aldehyde to the nitrile

vii) Palladium catalysed removal of the allyl group

wherein L represents a leaving group.

Process 9:

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:

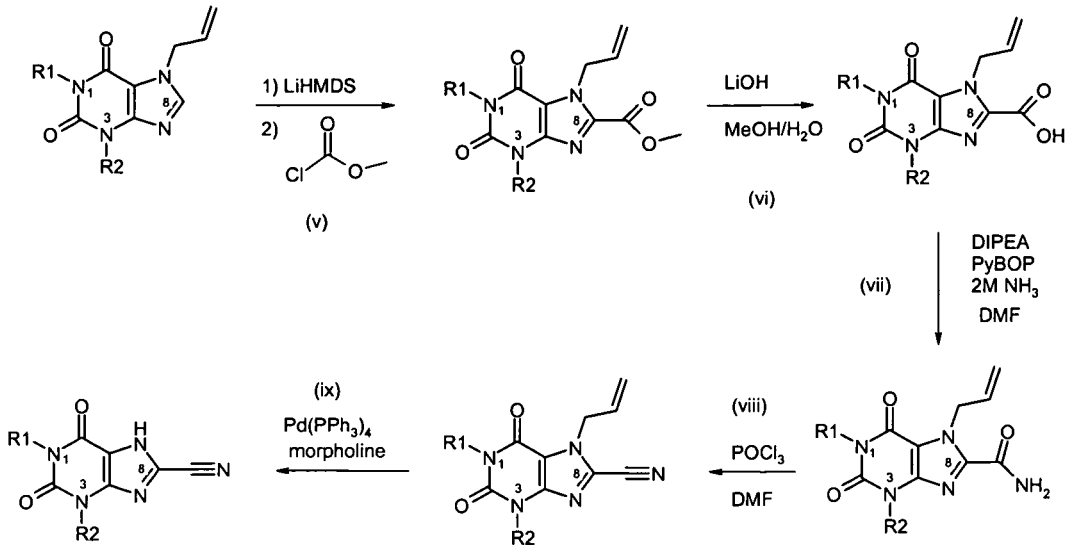


i) Halogenation at C8 using NCS or NBS

ii) Palladium catalysed removal of the allyl group

Process 10:

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



v) Formation of ester

vi) Hydrolysis of the methyl ester

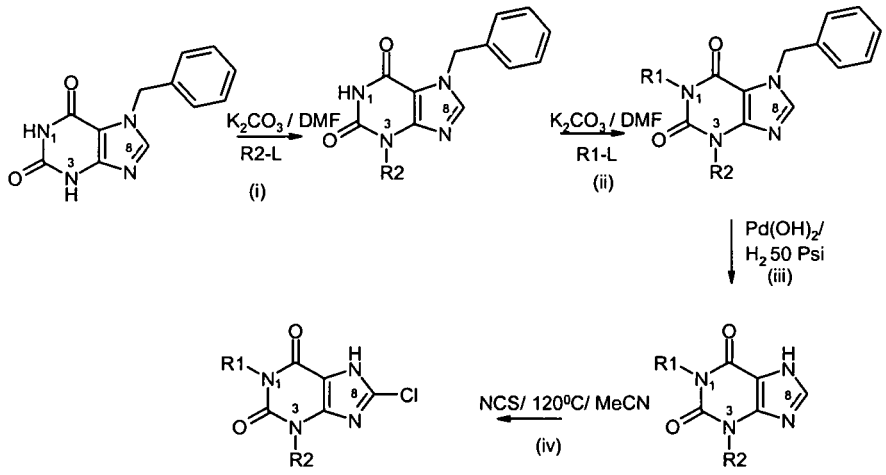
vii) Conversion of the acid to the amide.

viii) Conversion of the amide to the nitrile

ix) Palladium catalysed removal of the allyl group

Process 11:

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



i) Alkylation at N3

ii) Alkylation at N1

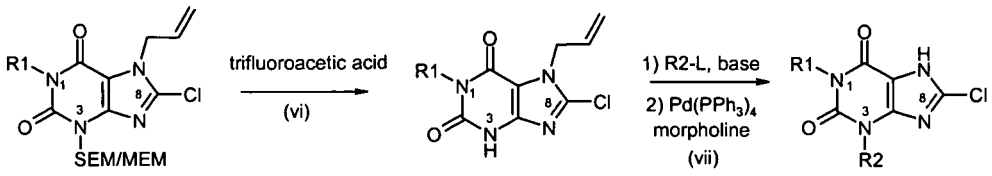
iii) Debenzylation

iii) Chlorination at C8

wherein L represents a leaving group

Process 12:

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:



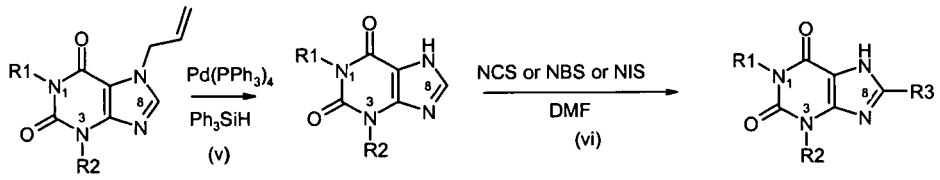
vi) Cleavage of MEM or SEM protecting group group

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

wherein L represents a leaving group

Process 13:

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:

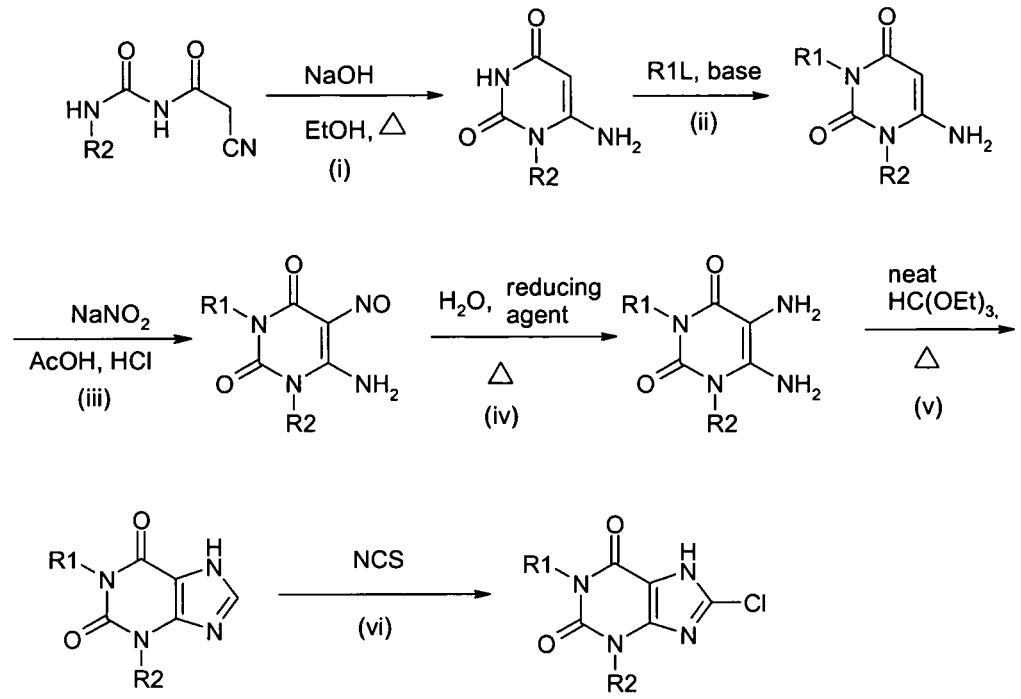


v) Palladium catalysed removal of allyl group

vi) Halogenation at C8 using NCS, NBS or NIS

Process 14:

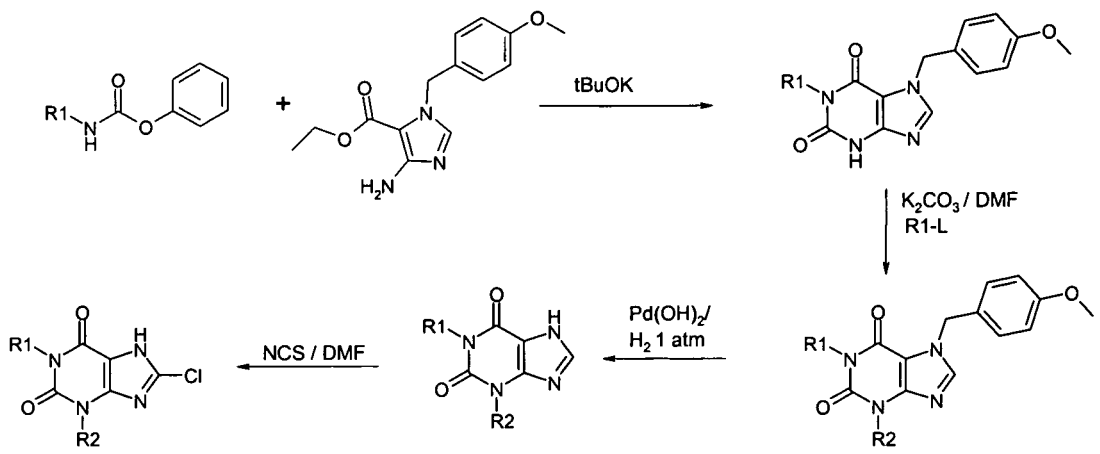
A process according to the invention for preparing compound(s) of formula (I) comprises:



i) Pyrimidinedione formation
ii) Alkylation at N1
iii) Nitrosation
iv) Reduction using $Na_2S_2O_4$ or a similar reducing agent
v) Xanthine formation
vi) Halogenation at C8 using NCS

wherein L represents a leaving group

Process 15:
A process according to the invention for preparing compound(s) of formula (I):



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 Redisep 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 salt form or vice versa or converting one salt form into another pharmaceutically acceptable salt form.

ABBREVIATIONS

AcOH	Acetic acid
atm	Atmosphere
br	Broad (NMR)
CDI	Carbonyldiimidazole
d	Doublet (NMR)
DBAD	Di-*t*-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	t-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.

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.

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.

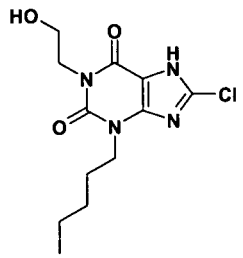
The following non-limiting examples illustrate the present invention:

Synthetic Examples

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. Journal of Organic Chemistry (1975), 40(20), 2979-80)

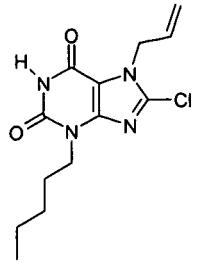
Example 1: 8-Chloro-1-(2-hydroxyethyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-1-(2-hydroxyethyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



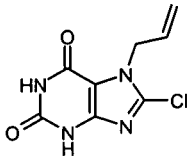
8-Chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.5g, 5.1mmol), Cs_2CO_3 (1.8g, 5.6mmol) and 2-chloroethanol (509µL, 7.7mmol) were reacted together in DMF (20ml) at 60°C for 18h. The reaction was allowed to cool to rt and the mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (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, and then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was taken up into MeOH and then passed down an aminopropyl column with the product eluting with 3% AcOH/MeOH. The product fractions were combined and concentrated then purified by recrystallisation from EtOAc. The resulting solid was collected by filtration and washed with EtOAc to give the title compound as a white solid (713mg, 47%).
LC/MS: m/z 301 $[MH]^+$, RT 2.7min.
^1H NMR (DMSO-d_6) δ: 0.86 (t, 3H, J = 7Hz), 1.22-1.36 (m, 4H), 1.63 (m, 2H), 3.50 (br t, 2H, J = 6Hz), 3.90 (t, 2H, J = 7.5Hz), 3.95 (t, 2H, J = 6.5Hz), 4.75 (br s, 1H), 14.5 (br s, 1H).

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



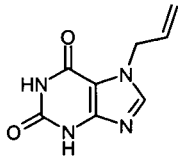
To a solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.44mmol) in anhydrous DMF (3ml) was added sodium carbonate (0.051g, 0.484mmol). After 10min stirring at rt pentyl iodide (0.063ml, 0.484mmol) was added and stirring continued under nitrogen at rt for 18h. The reaction mixture was diluted with water (25ml) and extracted with EtOAc (2x25ml). The combined organic extracts were dried ($MgSO_4$) filtered and evaporated. Purification by SPE (Si, 5g) eluting with 4:1 EtOAc/cyclohexane afforded the title compound as a white solid (96mg, 74%).
LC/MS: m/z 297 $[MH]^+$.

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



To a solution of 7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione) (10.52g, 54.7mmol) in anhydrous DMF (60ml) was added NCS (8.04g, 60.2mmol). The reaction mixture was left to stir under nitrogen at 20°C for 6h. The reaction mixture was concentrated *in vacuo* to give an amber oil. MeOH was added and left to stand for 18h. The resulting residue was filtered and dried under vacuum to give the title compound (7.69g, 62%).
LC/MS: m/z 227 $[MH]^+$.

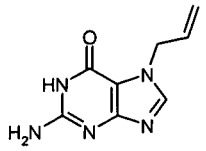
d) 7-(2-Propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



A mixture of 2-amino-7-(2-propen-1-yl)-1,7-dihydro-6*H*-purin-6-one (40g, 0.209mol) in AcOH (900ml) and water (100ml) was heated at 55°C. Sodium nitrite (57.74g, 0.837mol) in water (100ml) was added dropwise. Care; toxic fumes. After the addition was complete (ca. 25min) the reaction mixture was allowed to cool to ambient temperature and then concentrated to ca. 1/3 of its original volume. Water (500ml) was added and the resulting precipitate collected by filtration. The residue was washed with water then dried at 50°C over P_2O_5 and under vacuum for 2h to give the title compound (17.20g). The aqueous fraction was concentrated and water added (100ml). Again the resulting solid was filtered and dried. This gave more of the title compound (2.31g). Combined product (19.52g, 49%).

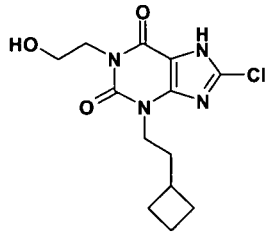
LC/MS: m/z 193 $[MH]^+$.

e) 2-Amino-7-(2-propen-1-yl)-1,7-dihydro-6*H*-purin-6-one



A mixture of guanosine (20g, 0.071mol), allyl bromide (14.7ml, 0.169mol) and anhydrous DMSO (100ml) was stirred at rt, under nitrogen, for 18h. Conc. HCl (50ml of 37%) was added in one portion and the mixture stirred for 45min then poured into MeOH (600ml). The methanolic solution was neutralised with 2M NaOH (aq) solution and the resulting white precipitate collected by filtration. The white solid was dried under vacuum at 50°C for 18h to afford the title compound (16g) which was used without further purification.
LC/MS: m/z 192 $[MH]^+$.

Example 2: 8-Chloro-3-(2-cyclobutylethyl)-1-(2-hydroxyethyl)-3,7-dihydro-1*H*-purine-2,6-dione



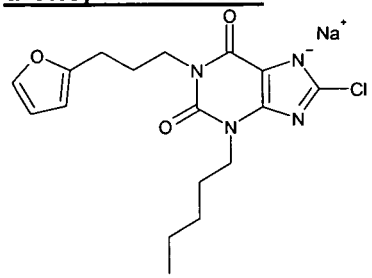
7-(2-Propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (575mg, 2.54mmol) was stirred in dry THF (20ml) with 2-cyclobutylethanol (c.73 mol%, remainder 1-butanol) (254mg). Dibenzyl azodicarboxylate (94%, 1.57g, 4.95mmol) was added, the mixture cooled to 0°C and a solution of triphenylphosphine (1.302g, 4.97mmol) in dry THF (10ml) was added dropwise. The mixture was stirred for 30min. at 0°C then at rt for 18h under nitrogen. The solvent was evaporated and the residue purified on a Biotage system (100g) eluting with EtOAc-cyclohexane (2:3). The material thus obtained (0.53g) was a mixture of the required compound, the corresponding n-butyl analogue and dibenzyl hydrazinedicarboxylate, and was alkylated without further purification.
This mixture (256mg) and Cs_2CO_3 (326mg, 1mmol) were stirred in dry DMF (5ml). 2-Chloroethanol (80.5mg, 1mmol) was added and the mixture was stirred and heated at 55 ° C for 65h. After cooling, it was thoroughly degassed, tetrakis(triphenylphosphine)palladium(0) (200mg) and morpholine (0.7ml) were added, and the mixture was stirred for 6h. EtOAc and 2M HCl were added and the mixture filtered, the organic phase washed with brine, dried (Na_2SO_4) and evaporated and the residue separated from non-acidic material by aminopropyl SPE (5g, MeOH-THF and MeOH wash, elution with DCM-MeOH with 5% added AcOH). The material obtained

from the acid wash (105mg) was further purified by MDAP to provide the title compound (42.7mg).

LC/MS: m/z 313 $[MH]^+$, RT 2.58min.

^{1}H NMR (DMSO-d_6) δ: 1.53-1.64 (m, 2H), 1.71-1.84 (m, 4H), 1.94-2.02 (m, 2H), 2.21-2.30 (m, 1H), 3.47-3.53 (m, 2H), 3.84 (t, 2H, J = 7Hz), 3.95 (t, 2H, J = 7Hz), 4.76 (br s, 1H), 14.45 (br s, 1H)

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



A GreenHouse™ 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-1*H*-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 GreenHouse™ 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.

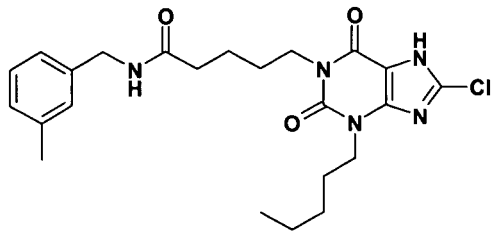
Tetrakis(triphenylphosphine)palladium(0) (16mg, 0.014mmol) and morpholine (0.12ml, 1.35mmol) were added to the mixture which was stirred for 16h under a stream of nitrogen. The reaction mixture was concentrated under nitrogen and the crude material dissolved in aqueous NaOH solution (0.5ml, 2M). The 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%).

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

^{1}H 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).

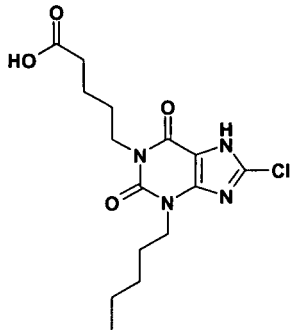
Example 4: 5-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-[(3-methylphenyl)methyl]pentanamide

a) 5-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-[(3-methylphenyl)methyl]pentanamide



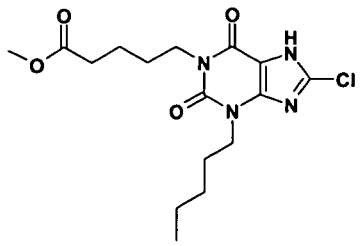
A mixture of 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (50mg, 0.14mmol) in DCM (3ml) was treated with CDI (27mg, 0.17mmol) and left to stir at rt for 1h. [(3-Methylphenyl)methyl]amine (25µl, 0.20mmol) was added and left to stir for a further 1h. The mixture was concentrated then purified by aminopropyl SPE. The title compound was eluted with 2-3% AcOH/MeOH then concentrated to give the title compound as a white solid (56mg, 87%).
LC/MS: m/z 460 $[MH]^+$, RT 3.3min.

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



A mixture of methyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (8.40g, 0.023mol), LiOH (1.63g, 0.068mol), MeOH (150ml) and water (10ml) was left to stir at ambient temperature for 64h. The mixture was partitioned between water and EtOAc and the aqueous acidified. The organic layer was separated and the aqueous extracted again with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated, giving the title compound as an off-white solid (9.09g).
LC/MS: m/z 357 $[MH]^+$, RT 3.0min.

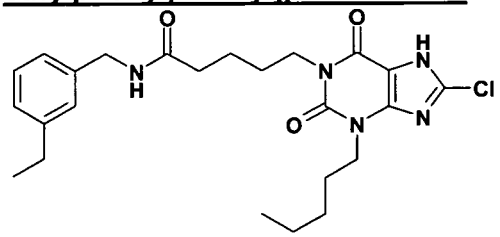
c) Methyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate



A solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2.0g, 6.7mmol) in anhydrous DMF (40ml) was treated with Cs_2CO_3 (2.42g, 7.4mmol) and methyl 5-bromovalerate (1.16ml, 8.1mmol). The mixture was heated at 50°C for 18h then allowed to cool to rt and degassed under a gentle vacuum, then nitrogen introduced. This was repeated twice. $Pd(PPh_3)_4$ (779mg, 0.67mmol) was added and the mixture degassed once more. Morpholine (5.9ml, 67mmol) was added and left to stir for 3h at rt. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated, giving a yellow residue/oil (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 then 10% AcOH/MeOH and finally 15% AcOH/MeOH. The product fractions were combined and concentrated giving the title compound as an off-white solid (2.28g, 91%).

LC/MS: m/z 371 $[MH]^+$, RT 3.1min.

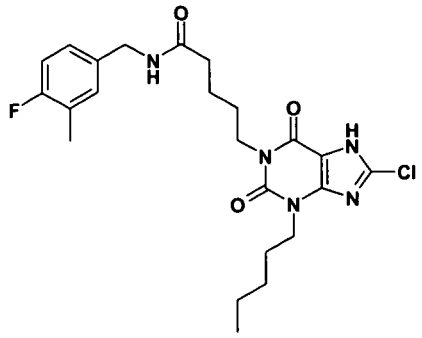
Example 5 : 5-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-[(3-ethylphenyl)methyl]pentanamide



A mixture of 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (50mg, 0.14mmol) in DCM (3ml) was treated with CDI (27mg, 0.17mmol) and left to stir at rt for 1h. [(3-ethylphenyl)methyl]amine (25µl 0.20mmol) was added and left to stir for a further 1h. The mixture was concentrated then purified on an aminopropyl SPE. The title compound was eluted with 2-3% AcOH/MeOH to give a white solid (61mg, 92%).

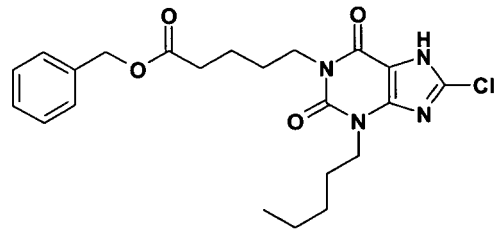
LC/MS: m/z 474 $[MH]^+$, RT 3.5min.

Example 6 : 5-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-[(4-fluoro-3-methylphenyl)methyl]pentanamide



A mixture of 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (50mg, 0.14mmol) and DCM (3ml) was treated with CDI (27mg, 0.17mmol) and stirred at rt for 1h. 1-(4-Fluoro-3-methylphenyl)methanamine (27mg, 0.20mmol) and DIPEA (24µl 0.14mmol) were added. After 1h the mixture was concentrated and then the residue taken up into MeOH and passed down an aminopropyl SPE. The product was eluted with 2% AcOH/MeOH and further purified by MDAP to give the title compound as a solid (15mg, 22%).
LC/MS: m/z 478 $[MH]^+$, RT 3.4min.

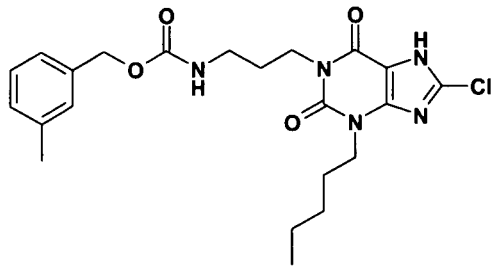
Example 7: Phenylmethyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate



A mixture of 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (50mg, 0.14mmol) in DCM (3ml) was treated with CDI (27mg, 0.17mmol) and left to stir at rt for 1h. Benzyl alcohol (21µl, 0.20mmol) was added and left to stir for a further 1h. The reaction mixture was concentrated and DMF (3ml) was added then heated at 50°C for 2h. The mixture was concentrated then purified by MDAP giving the title compound as a white solid (33mg, 53%).
LC/MS: m/z 447 $[MH]^+$, RT 3.7min.

Example 8: (3-Methylphenyl)methyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate

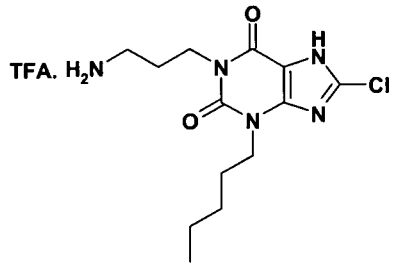
a) (3-Methylphenyl)methyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate



A solution of 3-methylbenzyl alcohol (16µl, 0.13mmol) in DCM (3ml) was treated with CDI (24mg, 0.15mmol) and allowed to stir at rt for 1h. 1-(3-aminopropyl)-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione trifluoroacetate (50mg, 0.16mmol) was added followed by DIPEA (28µl, 0.16mmol) then heated at 50°C for 56h. The reaction mixture was concentrated, the residue taken up into MeOH and purified by aminopropyl SPE. The title compound eluted with 2% AcOH/MeOH and a white solid collected (40mg, 58%).

LC/MS: m/z 462 $[MH]^+$, RT 3.6min.

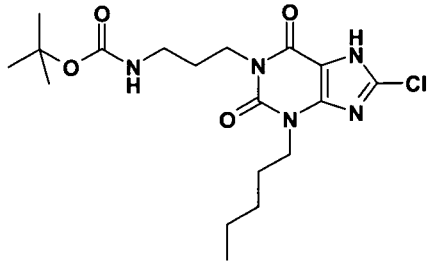
b) 1-(3-Aminopropyl)-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione trifluoroacetate



A solution of 1,1-dimethylethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate (1.59g, 4.38mmol) in DCM (16ml) was treated with TFA (16ml) and stirred at rt for 2h then concentrated *in vacuo*. Residual TFA was removed by azeotroping with DCM then the residue was triturated with Et_2O to give the title compound as a solid (1.48g, quant.).

LC/MS: m/z 314 $[MH]^+$, RT 2.1min.

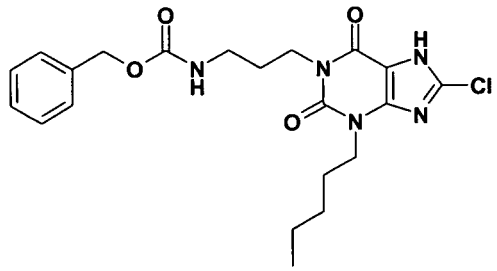
c) 1,1-Dimethylethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate



A solution of 1,1-dimethylethyl (3-hydroxypropyl)carbamate (1.0ml, 6.1mmol) in THF (40ml) was treated with 8-chloro-3-pentyl-1-[3-(tetrahydro-2*H*-pyran-2-yloxy)propyl]-

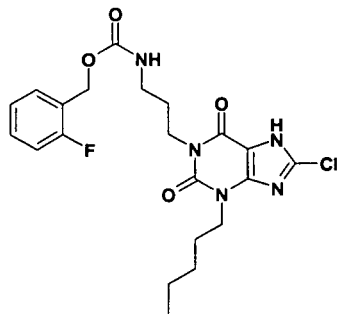
3,7-dihydro-1*H*-purine-2,6-dione (1.5g, 5.1mmol) and PPh_3 (1.73g, 6.6mmol) at rt under nitrogen. DBAD (1.52g, 6.6mmol) was added in one portion and stirred for 18h. The mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (586mg, 0.51mmol) was added and the mixture degassed once more. Morpholine (4.4ml, 50.7mmol) was added and the mixture was stirred under nitrogen for 3h, then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated, giving a yellow oil. 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 the title compound as a clear gummy solid (1.59g, 75%).
LC/MS: m/z 414 $[MH]^+$, RT 3.4min.

Example 9 : Phenylmethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate



1-(3-Aminopropyl)-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione trifluoroacetate (50mg, 0.12mmol) in DCM (3ml) was treated with DIPEA (51µl, 0.29mmol) and benzyl chloroformate (20µl, 0.14mmol). After 1h the reaction mixture was concentrated and purified on an aminopropyl SPE. The title compound eluted with 2% AcOH/MeOH and a white solid collected (35mg, 67%).
LC/MS: m/z 448 $[MH]^+$, RT 3.4min.

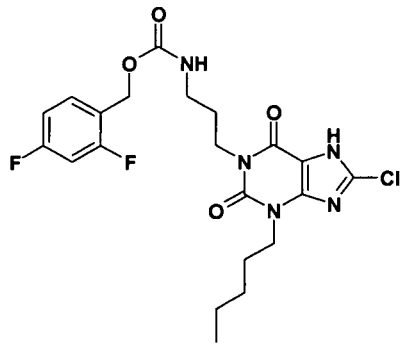
Example 10 : (2-Fluorophenyl)methyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate



(2-Fluorophenyl)methanol (11µl, 0.10mmol) in DCM (3ml) was reacted with CDI (17mg, 0.11mmol) under nitrogen for 1h. 1-(3-Aminopropyl)-8-chloro-3-pentyl-3,7-dihydro-1*H*-

purine-2,6-dione trifluoroacetate (50mg, 0.16mmol) was added followed by DIPEA (20μl, 0.12mmol) then heated at reflux for 18h. THF (3ml) was added and heated at 75°C for 5h. After cooling, the mixture was concentrated *in vacuo* and purified by MDAP to give the title compound as a solid (21mg, 39%).
LC/MS: m/z 466 $[MH]^+$, RT 3.4min.

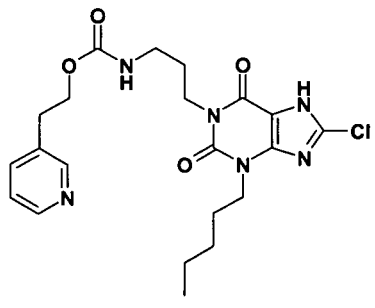
Example 11 : (2,4-Difluorophenyl)methyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate



(2,4-Difluorophenyl)methanol (11μL, 0.10mmol) in DCM (3ml) was reacted with CDI (17mg, 0.11mmol) under nitrogen for 1h. 1-(3-Aminopropyl)-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione trifluoroacetate (50mg, 0.16mmol) was added followed by DIPEA (20μl, 0.12mmol) then heated at reflux for 18h. THF (3ml) was added and heated at 75°C for 5h. After cooling, the mixture was concentrated *in vacuo* and purified by MDAP to give the title compound as a solid (29mg, 21%).
LC/MS: m/z 484 $[MH]^+$, RT 3.4min.

Example 12 : 2-(3-Pyridinyl)ethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate

a) 2-(3-Pyridinyl)ethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate

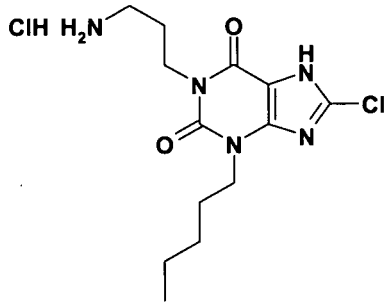


A solution of CDI (21mg, 0.13mmol) in THF (2ml) was treated with 2-(3-pyridinyl)ethanol (16mg, 0.13mmol) and heated at reflux for 1h before the addition of 1-

(3-aminopropyl)-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione hydrochloride (50mg, 0.14mmol) and DIPEA (25µl, 0.14mmol). The reaction was left at reflux for 18h then concentrated and purified by MDAP to provide the title compound as a solid (30mg, 24%).

LC/MS: m/z 463 $[MH]^+$, RT 2.6min.

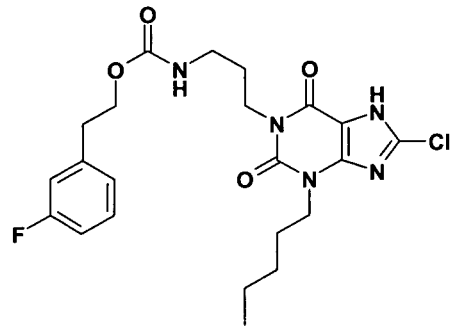
b) 1-(3-Aminopropyl)-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione hydrochloride



A mixture of 1,1-dimethylethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate (5.19g, 12.5mmol) and 4M HCl in 1,4-dioxane (80ml) was stirred at rt for 3h. The mixture was concentrated *in vacuo* and dried under vacuum to provide the title product as a white solid (4.49g, quant.).

LC/MS: m/z 314 $[MH]^+$, RT 2.2min.

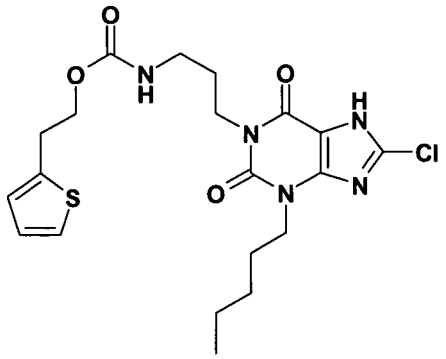
Example 13 : 2-(3-Fluorophenyl)ethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate



A solution of CDI (21mg, 0.13mmol) in THF (2ml) was treated with 2-(3-fluorophenyl)ethanol (16µl, 0.13mmol) and heated at reflux for 1h before the addition of 1-(3-aminopropyl)-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione hydrochloride (50mg, 0.14mmol) and DIPEA (25µL, 0.14mmol). The reaction was left at reflux for 18h then concentrated and purified by MDAP to provide the title compound as a solid (27mg, 39%).

LC/MS: m/z 480 $[MH]^+$, RT 3.5min.

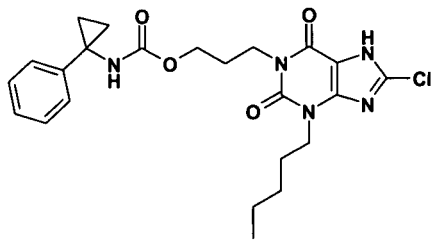
Example 14 : 2-(2-Thienyl)ethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]carbamate



A solution of CDI (21mg, 0.13mmol) in THF (2ml) was treated with 2-(2-thienyl)ethanol (15μl, 0.13mmol) and heated at reflux for 1h before the addition of 1-(3-aminopropyl)-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione hydrochloride (50mg, 0.14mmol) and DIPEA (25μL, 0.14mmol). The reaction was left at reflux for 18h then concentrated and purified by MDAP to provide the title compound as a solid (34mg, 51%).
LC/MS: m/z 468 $[MH]^+$, RT 3.4min.

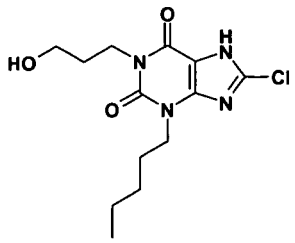
Example 15 : 3-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl (1-phenylcyclopropyl)carbamate

a) 3-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl (1-phenylcyclopropyl)carbamate



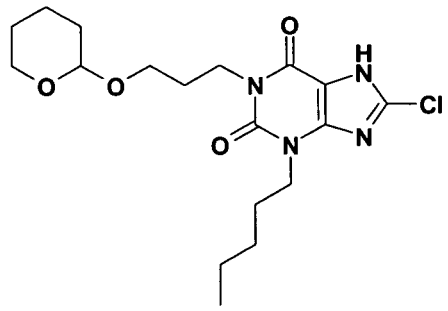
A solution of 8-chloro-1-(3-hydroxypropyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (50mg, 0.16mmol) was treated with CDI (28mg, 0.18mmol) and allowed to stir at rt for 1h. 1-Phenylcyclopropanamine (30mg, 0.20mmol) was added and the mixture heated at reflux under nitrogen for 18h. Another aliquot of 1-phenylcyclopropanamine (30mg, 0.20mmol) was added followed by THF (3ml). The reaction was heated at 75°C for 18h then concentrated and purified by MDAP. This gave the title compound as a white solid (13mg, 18%).
LC/MS: m/z 474 $[MH]^+$, RT 3.5min.

b) 8-Chloro-1-(3-hydroxypropyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



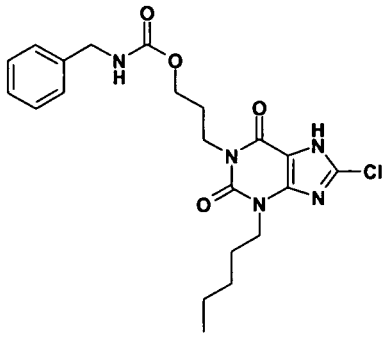
A solution of 8-chloro-3-pentyl-1-[3-(tetrahydro-2*H*-pyran-2-yloxy)propyl]-3,7-dihydro-1*H*-purine-2,6-dione (5.87g, 14.8mmol) in EtOH (100ml) was treated with pTsOH (2.8g, 14.8mmol) and stirred at rt for 18.5h. The mixture was partitioned between 1M HCl (aq) and EtOAc. The organic layer was separated and the aqueous layer extracted once more. The combined extracts were washed with water (x5), brine, then dried ($MgSO_4$) and concentrated, giving a pale yellow solid. The solid was washed with Et_2O and collected by filtration giving a white solid (2.42g, 52%).
LC/MS: m/z 315 $[MH]^+$, RT 2.7min.

c) 8-Chloro-3-pentyl-1-[3-(tetrahydro-2*H*-pyran-2-yloxy)propyl]-3,7-dihydro-1*H*-purine-2,6-dione



8-Chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (5.0g, 16.8mmol), Cs_2CO_3 (6.0g, 18.5mmol) and 2-(3-bromopropoxy)tetrahydro-2H-pyran (3.4ml, 20mmol) were reacted together in DMF (100ml) at 50°C under nitrogen for 24h. The reaction was allowed to cool to rt and the mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (1.4g, 1.2mmol) was added and the mixture degassed once more. Morpholine (14.7ml, 170mmol) was added and the mixture was stirred under nitrogen for 3h, 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 (5.16g). MeOH was added and then passed down an aminopropyl SPE with the product eluting with 5% AcOH/MeOH. The product fractions were combined and concentrated, giving the title compound as a pale yellow solid (5.97g, 89%).
LC/MS: m/z 399 $[MH]^+$, RT 3.3min.

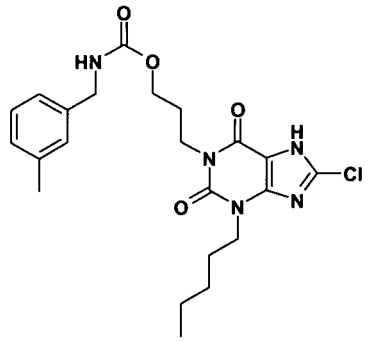
Example 16 : 3-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl (phenylmethyl)carbamate



A solution of 8-chloro-1-(3-hydroxypropyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (50mg, 0.16mmol) in THF (3ml) was treated with triphosgene (47mg, 0.16mmol) and pyridine (13µl, 0.16mmol). After 30min benzylamine (217µl, 2.0mmol) was added and left to stir for a further 30min. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was taken up into MeOH and purified by passing down an aminopropyl SPE, the product eluted with 2-5% AcOH/MeOH. The title compound was obtained as an off-white solid (67mg, 94%).

LC/MS: m/z 448 $[MH]^+$, RT 3.2min.

Example 17 : 3-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl [(3-methylphenyl)methyl]carbamate

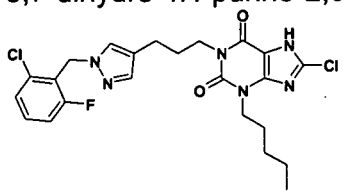


A solution of 8-chloro-1-(3-hydroxypropyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (50mg, 0.16mmol) in DCM (3ml) was treated with CDI (31mg, 0.19mmol) and stirred at rt for 1h. 3-Methylbenzylamine (26µl, 0.21mmol) was added and heated at reflux for 18h. Another aliquot of methylbenzylamine (4µl, 0.03mmol) was added and the mixture left for 4h at reflux. The mixture was concentrated then taken up into MeOH and passed down an aminopropyl SPE. The product was eluted with 2% AcOH/MeOH and then purified further by MDAP. This gave the title compound as a white solid (42mg, 57%).

LC/MS: m/z 462 $[MH]^+$, RT 3.5min.

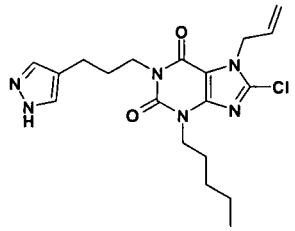
Example 18 : 8-Chloro-1-(3-{1-[(2-chloro-6-fluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

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



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 (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 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.

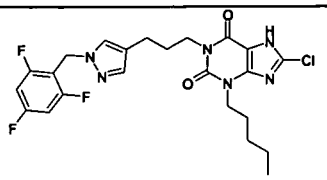
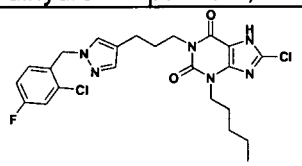
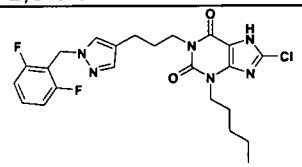
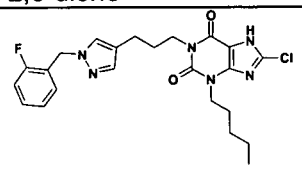
b) 8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione



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 Et_2O (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.

The following compounds (Table 1) were prepared using a method analogous to that for Example 18, from the corresponding benzyl halides.

Table 1

Example	structure	Yield (mg)	LC/MS:
19	 8-chloro-3-pentyl-1-(3-{1-[(2,4,6-trifluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	68	m/z 509 $[MH]^+$ RT 3.58 min
20	 8-chloro-1-(3-{1-[(2-chloro-4-fluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	56	m/z 507 $[MH]^+$ RT 3.73 min
21	 8-chloro-1-(3-{1-[(2,6-difluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	29	m/z 491 $[MH]^+$ RT 3.53 min
22	 8-chloro-1-(3-{1-[(2-fluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	32*	m/z 473 $[MH]^+$ RT 3.55 min

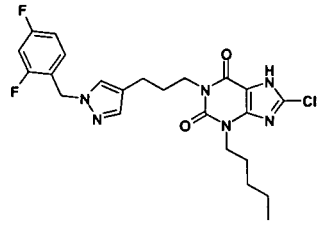
* after additional purification by MDAP.

NMR details for selected examples from Table 1

Example 19: 8-chloro-3-pentyl-1-(3-{1-[(2,4,6-trifluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione

^{1}H NMR (DMSO-d_6) 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 23: 8-Chloro-1-(3-{1-[(2,4-difluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



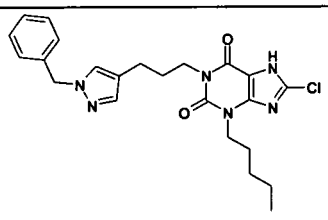
8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione (81mg, 0.2mmol) and sodium carbonate (85mg, 0.8mmol) were stirred in dry DMF (2ml) with 2,4-difluorobenzyl bromide (166mg, 0.8mmol) at 45°C for 18h. The mixture was degassed and stirred with tetrakis(triphenylphosphine)palladium(0) (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.

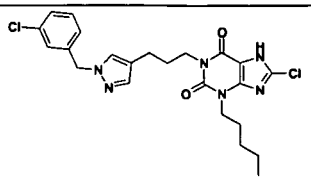
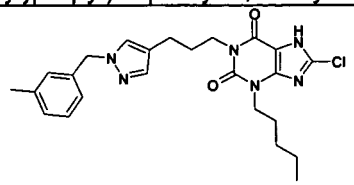
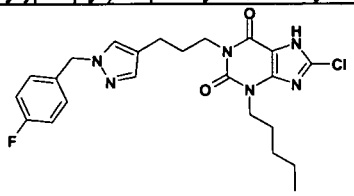
LC/MS: m/z 491 $[MH]^+$, RT 3.42min.

^{1}H NMR (d^6 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).

The following compounds (Table 1) were prepared using a method analogous to that for Example 23, from the corresponding benzyl halides.

Table 2

Example	Structure	Yield (mg)	LC/MS:
24	 8-chloro-3-pentyl-1-{3-[1-(phenylmethyl)-1*H*-pyrazol-4-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	17*	m/z 455 $[MH]^+$ RT 3.52 min

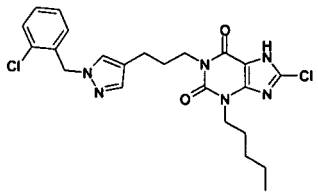
25	 8-chloro-1-(3-{1-[(3-chlorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	11.6*	m/z 489 $[MH]^+$ RT 3.52 min
26	 8-chloro-1-(3-{1-[(3-methylphenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	33	m/z 469 $[MH]^+$ RT 3.54 min
27	 8-chloro-1-(3-{1-[(4-fluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	42	m/z 473 $[MH]^+$ RT 3.44 min

*after additional purification by MDAP.

NMR details for selected examples from Table 2

Example 24: 8-chloro-3-pentyl-1-{3-[1-(phenylmethyl)-1*H*-pyrazol-4-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione; ^{1}H NMR (DMSO-d_6) 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).

Example 28: 8-Chloro-1-(3-{1-[(2-chlorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

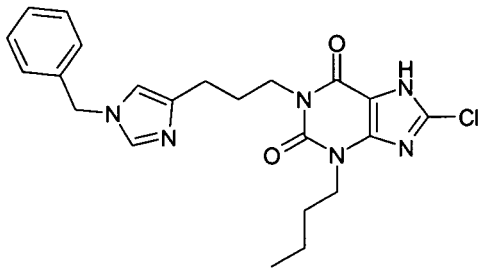


Prepared by the method for 8-chloro-1-(3-{1-[(2,4-difluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione but from 2-chlorobenzyl bromide (164mg, 0.8mmol). However, in order to complete the deprotection step further tetrakis(triphenylphosphine)palladium(0) (40mg) and 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 29: 3-Butyl-8-chloro-1-{3-[1-(phenylmethyl)-1*H*-imidazol-4-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

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

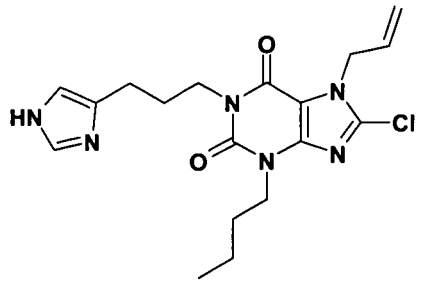


A solution of 3-butyl-8-chloro-1-[4-(1*H*-imidazol-4-yl)butyl]-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (300mg, 0.77mmol) in anhydrous THF (5ml) was treated with benzyl bromide (144mg, 0.84mmol) and DIPEA (147µl, 0.84mmol). The mixture was left to stir at rt under nitrogen for 4 days. The mixture was partitioned between EtOAc and 2M HCl (aq). The organic layer was separated, washed with brine, dried ($MgSO_4$) 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 $Pd(PPh_3)_4$ (88mg, 0.077mmol) and morpholine (670µl, 7.67mmol) were added and the mixture left to stir at rt under nitrogen for 3h. 88mg of $Pd(PPh_3)_4$ (0.077mmol) was added and the mixture was left to stir at rt under nitrogen for 16h. The mixture was partitioned between EtOAc and H_2O. The organic layer was separated and the aqueous layer was extracted with EtOAc (x2). The organic layers were combined, washed with brine, dried ($MgSO_4$) 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-d_6) 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).

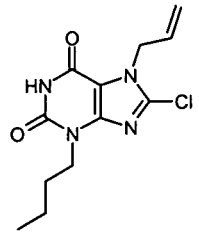
b) 3-Butyl-8-chloro-1-[3-(1*H*-imidazol-4-yl)propyl]-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



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-(1*H*-imidazol-4-yl)-1-propanol (1.5g, 12mmol) in anhydrous THF (10ml) and PPh_3 (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 H_2O. The aqueous layer was extracted and washed with EtOAc. The organic layers were combined, washed with brine, dried ($MgSO_4$) 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.

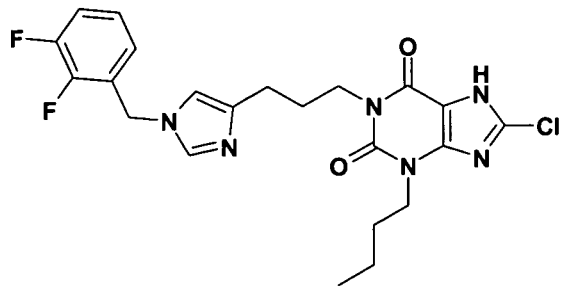
c) 3-Butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



To a solution of 3-butyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-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 combined solids were dried under vacuum to afford the title compound (2.42g, 64%).

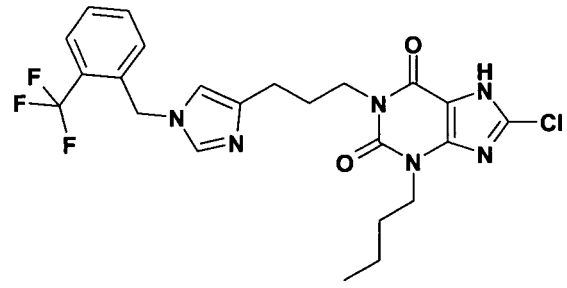
LC/MS: m/z 283 $[MH]^+$.

Example 30: 3-Butyl-8-chloro-1-(3-{1-[(2,3-difluorophenyl)methyl]-1*H*-imidazol-4-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 3-butyl-8-chloro-1-[4-(1*H*-imidazol-4-yl)butyl]-7-(2-propen-1-yl)-3,7-dihydro-1*H*-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 ($MgSO_4$) 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 $Pd(PPh_3)_4$ (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.

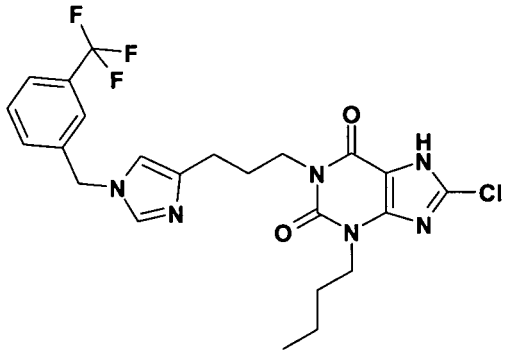
Example 31 : 3-Butyl-8-chloro-1-[3-(1-{[2-(trifluoromethyl)phenyl]methyl}-1*H*-imidazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 3-butyl-8-chloro-1-[4-(1*H*-imidazol-4-yl)butyl]-7-(2-propen-1-yl)-3,7-dihydro-1*H*-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 ($MgSO_4$) 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 $Pd(PPh_3)_4$ (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.

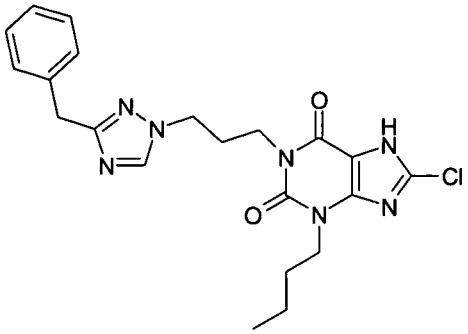
Example 32 : 3-Butyl-8-chloro-1-[3-(1-{[3-(trifluoromethyl)phenyl]methyl}-1*H*-imidazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 3-butyl-8-chloro-1-[4-(1*H*-imidazol-4-yl)butyl]-7-(2-propen-1-yl)-3,7-dihydro-1*H*-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 ($MgSO_4$) 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 $Pd(PPh_3)_4$ (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 33 : 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) 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

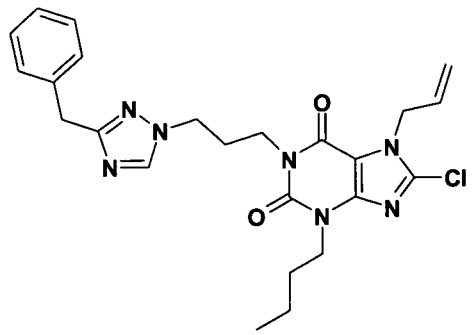


A solution of 3-butyl-8-chloro-1-{3-[3-(phenylmethyl)-1*H*-1,2,4-triazol-1-yl]propyl}-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (669mg, 1.39mmol) in THF (7ml) was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (160mg, 0.14mmol) was added and the mixture degassed 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 ($MgSO_4$) 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).

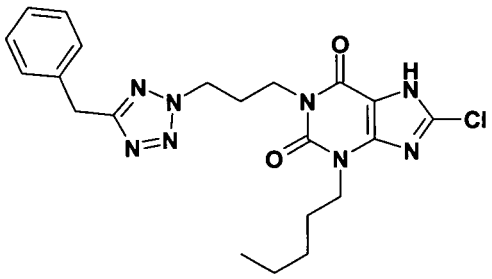
b) 3-Butyl-8-chloro-1-{3-[3-(phenylmethyl)-1*H*-1,2,4-triazol-1-yl]propyl}-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



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

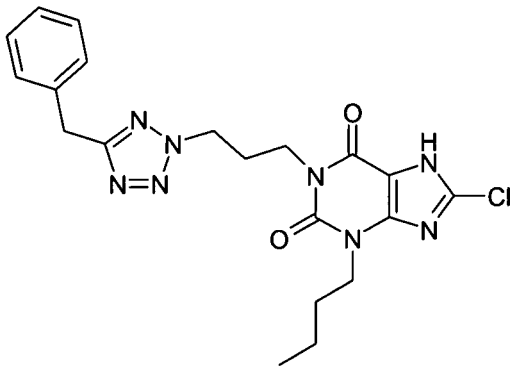
EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated, giving an oily residue (1.0g). To this was added butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (917mg, 3.2mmol) and Cs_2CO_3 (1.2g, 3.6mmol). DMF (15ml) was added and the mixture was stirred at 50°C for 20h then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) 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 34 : 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-1H-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 ($MgSO_4$) 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 Cs_2CO_3 (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. $Pd(PPh_3)_4$ (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 = 7Hz), 1.21-1.34 (m, 4H), 1.62 (m, 2H), 2.22 (m, 2H), 3.88 (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).

Example 35: 3-Butyl-8-chloro-1-{3-[5-(phenylmethyl)-2*H*-tetrazol-2-yl]propyl}-3,7-dihydro-1*H*-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 Companion™ 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)-2*H*-tetrazole) which was taken on crude in the next step.

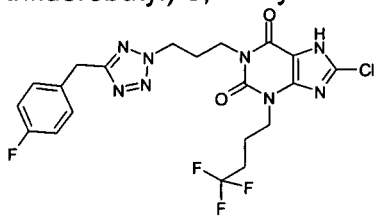
A mixture of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.74g, 6.1mmol), crude 2-(3-bromopropyl)-5-(phenylmethyl)-2*H*-tetrazole) (1.9g, 6.8mmol), Cs_2CO_3 (2.2g, 6.8mmol) and DMF (60ml) was stirred at 45°C under nitrogen for 24h. The mixture was degassed by applying a vacuum 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 Et_2O 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.

^1H NMR (DMSO-d_6) 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).

Example 36: 8-Chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2*H*-tetrazol-2-yl}propyl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione

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

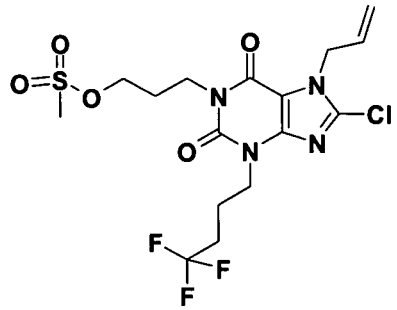


5-[(4-Fluorophenyl)methyl]-1H-tetrazole (75mg, 0.4mmol) was treated with potassium carbonate (100mg, 0.7mmol) and DMF (3ml). The mixture was treated with a solution of 3-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-2,3,6,7-tetrahydro-1H-purin-1-yl]propyl methanesulfonate (100mg, 0.2mmol) 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 (2cm^3). 1cm^3 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%).

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

^{1}H 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).

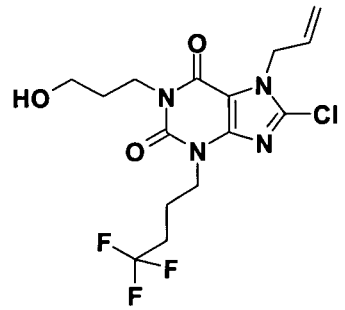
b) 3-[8-Chloro-2,6-dioxo-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-2,3,6,7-tetrahydro-1H-purin-1-yl]propyl methanesulfonate



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.

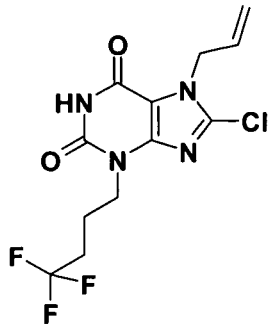
c) 8-Chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione



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.

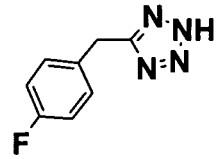
d) 8-Chloro-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione



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 ($MgSO_4$), 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



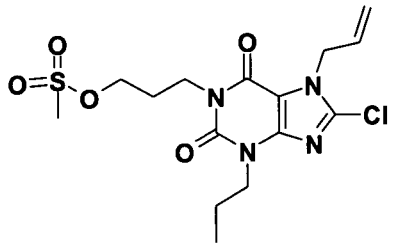
A mixture of triethylammonium chloride (4.14g, 30mmol) and sodium azide (1.95g, 30mmol) was treated with a solution of (4-fluorophenyl)acetonitrile (1.35g, 10mmol) in toluene (14ml) and the mixture was stirred and heated at 100°C for 5h. The cooled mixture was treated with water (10ml) and the mixture 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 36: 8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione, with the appropriate methanesulfonate and tetrazole. MDAP was employed to further purify those compounds insufficiently pure following normal phase chromatography.

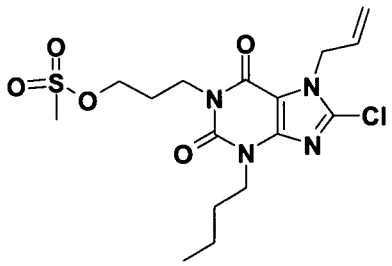
Methanesulfonates intermediates and their precursor alcohols were prepared according to the following procedures:

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



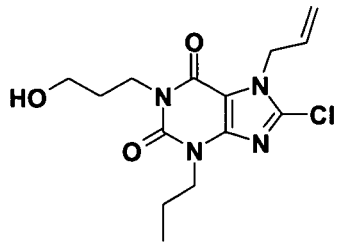
A solution of 8-chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione (1.99g, 6.1mmol) in DCM (50ml) was treated with triethylamine (1.2ml, 8.6mmol) and methanesulfonic anhydride (1.2g, 6.9mmol). After 1.5h the mixture was treated with water (50ml). The mixture was separated and the aqueous phase extracted with DCM (25ml), the combined organic phases dried ($MgSO_4$), filtered and 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.

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



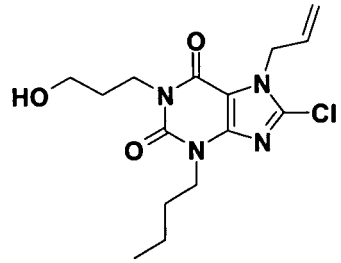
Prepared according to the method used for 3-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl]propyl methanesulfonate to give the title compound as a pale yellow oil (2.44g).
LC/MS: m/z 419 $[MH]^+$, RT 3.14min.

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



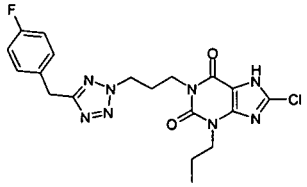
A solution of 8-chloro-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione (3.0g, 11.1mmol) in DMF (20ml) was treated with caesium carbonate (3.7g, 11.4mmol) and 3-bromo-1-propanol (1.6g, 11.5mmol). The mixture was heated at 60°C for 4h and then cooled and evaporated. The residue was partitioned between EtOAc (60ml) and saturated aqueous sodium bicarbonate (50ml). The aqueous phase was extracted with EtOAc (60ml), the combined organic phases were dried ($MgSO_4$), 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.

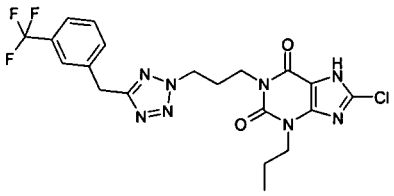
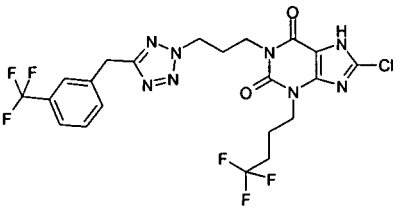
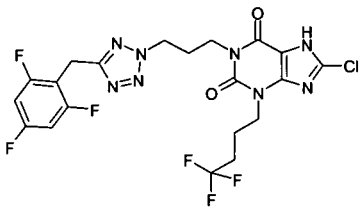
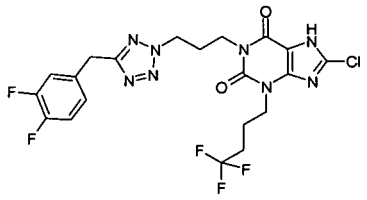
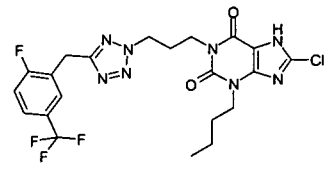
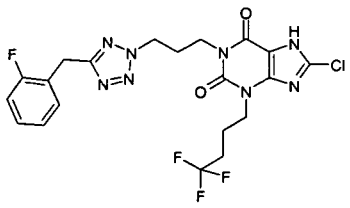
3-Butyl-8-chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione

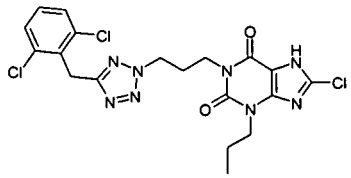
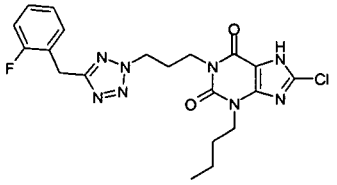
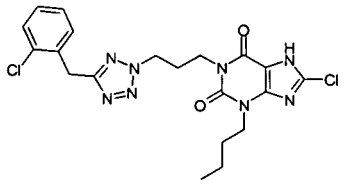
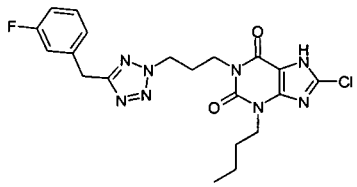
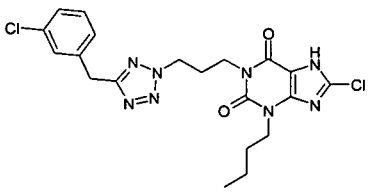
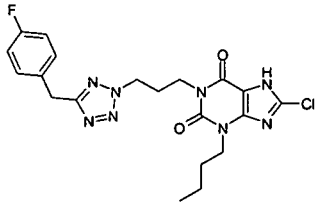


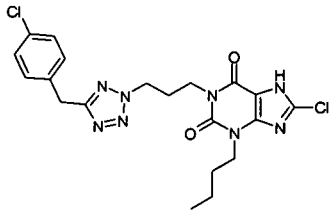
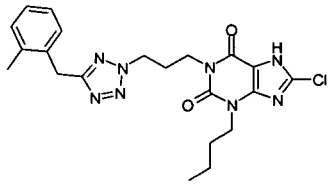
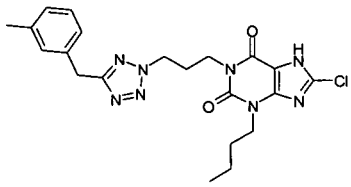
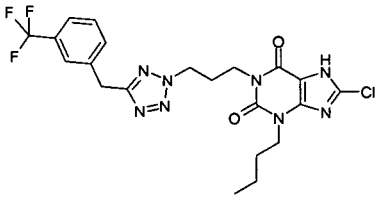
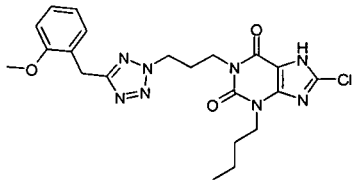
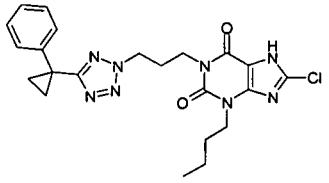
Prepared according to the method used for 8-chloro-1-(3-hydroxypropyl)-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione to give the title compound as a colourless oil (2.3g).
LC/MS: m/z 341 $[MH]^+$, RT 2.85min.

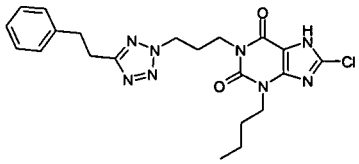
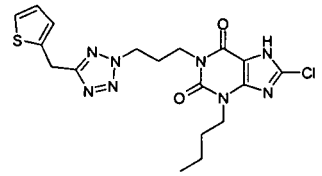
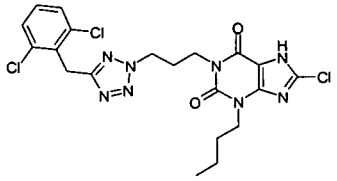
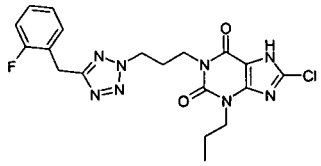
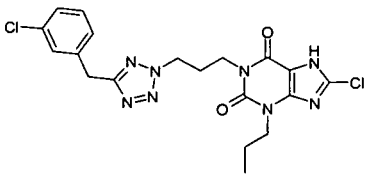
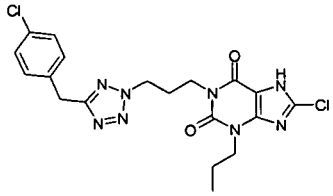
Table 3

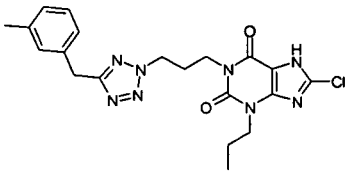
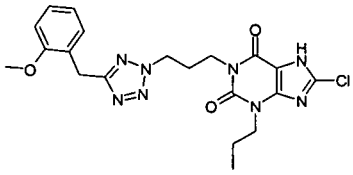
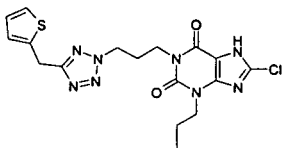
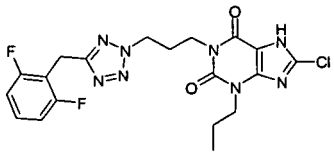
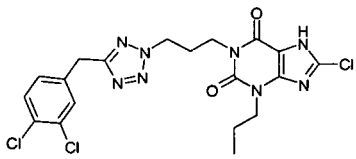
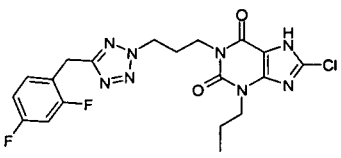
#	Structure	Name	Yield	LC/MS:
37		8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	12.4mg (14%)	m/z 447 $[MH]^+$ RT 3.14 min

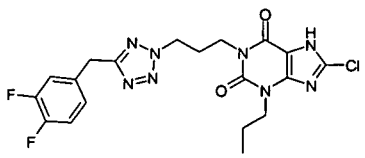
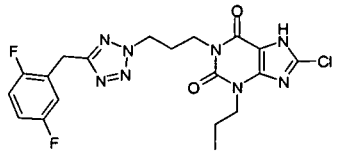
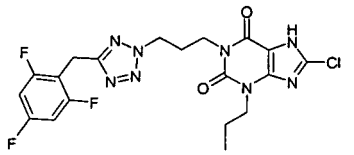
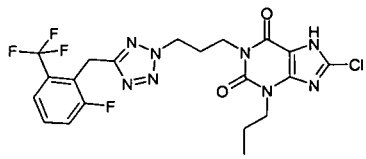
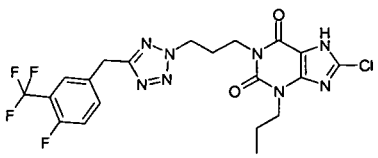
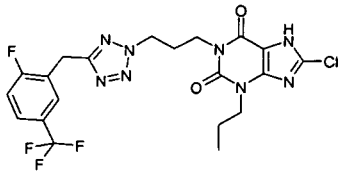
38		8-chloro-3-propyl-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	8.0mg (8%)	m/z 497 $[MH]^+$ RT 3.36 min
39		8-chloro-3-(4,4,4-trifluorobutyl)-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	21.0mg (19%)	m/z 565 $[MH]^+$ RT 3.34 min
40		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
41		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
42		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
43		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

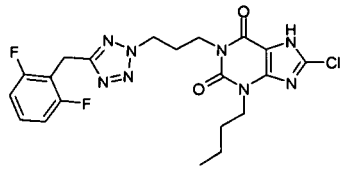
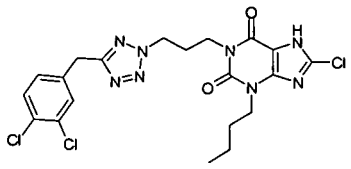
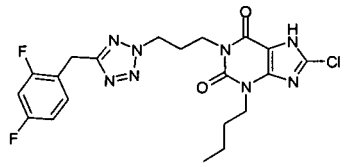
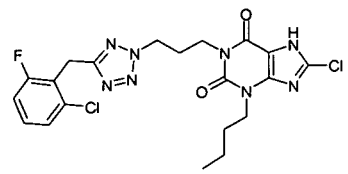
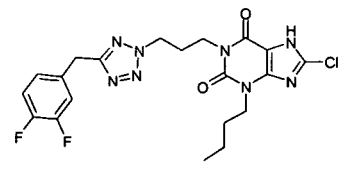
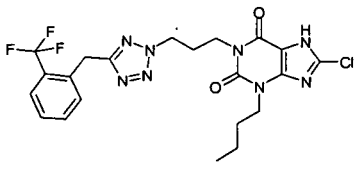
44		8-chloro-1-(3-{5-[(2,6-dichlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	50.7mg (51%)	m/z 497 $[MH]^+$ RT 3.33 min
45		3-butyl-8-chloro-1-(3-{5-[(2-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	46.4mg (48%)	m/z 461 $[MH]^+$ RT 3.27 min
46		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
47		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
48		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
49		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

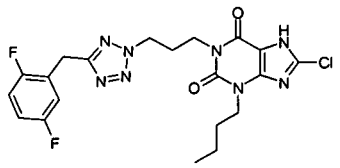
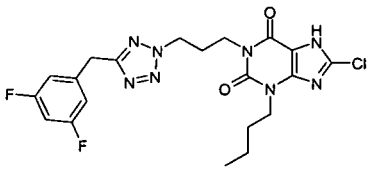
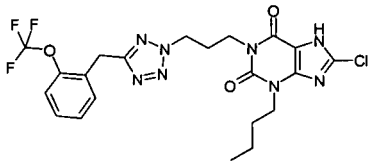
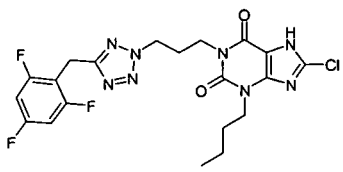
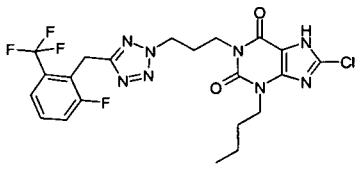
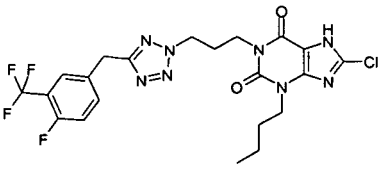
50		3-butyl-8-chloro-1-(3-{5-[(4-chlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	33.1mg (35%)	m/z 477 $[MH]^+$ RT 3.46 min
51		3-butyl-8-chloro-1-(3-{5-[(2-methylphenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	39.5mg (43%)	m/z 457 $[MH]^+$ RT 3.37 min
52		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
53		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
54		3-butyl-8-chloro-1-[3-(5-{[2-(methyloxy)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
55		3-butyl-8-chloro-1-{3-[5-(1-phenylcyclopropyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	44.2mg (47%)	m/z 469 $[MH]^+$ RT 3.41 min

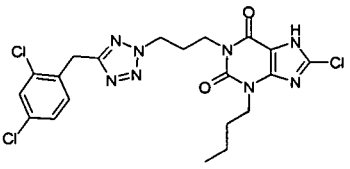
56		3-butyl-8-chloro-1-{3-[5-(2-phenylethyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	39.2mg (43%)	m/z 457 $[MH]^+$ RT 3.36 min
57		3-butyl-8-chloro-1-{3-[5-(2-thienylmethyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	33.4mg (37%)	m/z 449 $[MH]^+$ RT 3.20 min
58		3-butyl-8-chloro-1-(3-{5-[(2,6-dichlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	36.4mg (36%)	m/z 511 $[MH]^+$ RT 3.49 min
59		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
60		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
61		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

62		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
63		8-chloro-1-[3-(5-{[2-(methyloxy)phenyl]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
64		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
65		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
66		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
67		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

68		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
69		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
70		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
71		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
72		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
73		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

74		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
75		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
76		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
77		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
78		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
79		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

80		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
81		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
82		3-butyl-8-chloro-1-{3-[5-({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
83		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
84		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
85		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

86		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 37: 8-Chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2*H*-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H NMR ($CDCl_3$) 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 40 : 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 : ^{1}H 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).

Example 41: ^{1}H 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).

Example 44: ^{1}H 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).

Example 45: ^{1}H 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).

Example 46: ^{1}H 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).

Example 47: 3-Butyl-8-chloro-1-(3-{5-[(3-fluorophenyl)methyl]-2*H*-tetrazol-2-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H 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).

Example 48: ^{1}H 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).

Example 49: 3-Butyl-8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2*H*-tetrazol-2-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione

^{1}H 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).

Example 50: 3-Butyl-8-chloro-1-(3-{5-[(4-chlorophenyl)methyl]-2*H*-tetrazol-2-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H 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).

Example 55: 3-Butyl-8-chloro-1-{3-[5-(1-phenylcyclopropyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione: ^{1}H NMR ($CDCl_3$) δ: 0.93 (t, 3H, J = 7.3Hz), 1.36 (m, 4H), 1.55 (m, 2H), 1.71 (m, 2H), 2.38 (m, 2H), 4.06 (t, 2H, J = 7.5Hz), 4.20 (t, 2H, J = 6.7Hz), 4.59 (t, 2H, J = 7.5Hz), 7.25 (m, 3H), 7.36 (m, 2H), 13.30 (br s, 1H).

Example 67: 8-Chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-2*H*-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H 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).

Example 70: 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 : ^{1}H 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 = 6.5Hz), 4.67 (t, 2H, J = 7.3Hz), 6.68 (t, 2H, J = 8.1Hz).

Example 71: ^{1}H NMR ($CDCl_3$): 0.99 (t, 3H, J=7.3Hz), 1.76-1.85 (m, 2H), 2.39-2.46 (m, 2H), 4.05-4.08 (m, 2H), 4.24 (t, 2H, J=7.1Hz), 4.39 (s, 2H), 4.64 (t, 2H, J=7.1Hz), 7.29-7.32 (m, 1H), 7.38-7.44, (m, 1H), 7.49-7.51, (m, 1H), 13.17 (bs, 1H).

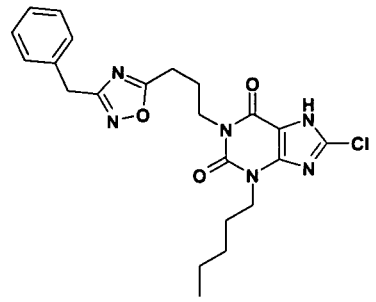
Example 78: ^{1}H NMR ($CDCl_3$): 0.99 (t, 3H, J=7.6Hz), 1.36-1.45 (m, 2H), 1.71-1.79 (m, 2H), 2.42-2.49 (m, 2H), 4.09 (t, 2H, J=7.5Hz), 4.17 (s, 2H), 4.24 (t, 2H, J=7.5Hz), 4.71 (t, 2H, J=7.3Hz), 7.00-7.14 (m, 3H), 13.07 (bs, 1H).

Example 80: ^{1}H NMR ($CDCl_3$): 0.96 (t, 3H, J=7.2Hz), 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).

Example 83: 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 : ^{1}H NMR ($CDCl_3$) δ: 0.97 (t, 3H, J = 7.3Hz), 1.41 (m, 2H), 1.75 (m, 2H), 2.44 (m, 2H), 4.10 (t, 2H, J = 7.5Hz), 4.20 (s, 2H), 4.25 (t, 2H , J = 6.5Hz), 4.67 (t, 2H, J = 7.4Hz), 6.67 (t, 2H, J = 8.0Hz), 13.25 (br s, 1H).

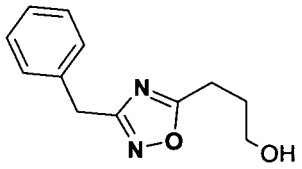
Example 87 : 8-Chloro-3-pentyl-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

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



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-1*H*-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. $Pd(PPh_3)_4$ (39mg, 0.034mmol) was added and the mixture degassed once more. Morpholine (294µl, 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 $[MH]^+$, RT 3.4min.
^1H NMR (DMSO-d_6) δ: 0.85 (t, 3H, J = 7Hz), 1.22-1.34 (m, 4H), 1.62 (m, 2H), 2.02 (m, 2H), 2.91 (t, 2H, J = 7Hz), 3.88 (t, 2H, J = 7Hz), 3.95-4.00 (m, 4H), 7.22-7.33 (m, 5H), 14.5 (br s, 1H).

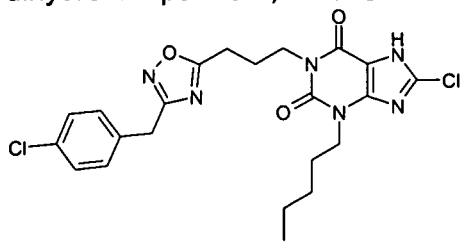
b) 3-[3-(Phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-propanol



A mixture of γ-butyrolactone (223µl, 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 Companion™ system to give a pale yellow oil (143mg, 23%).
LC/MS: m/z 219 $[MH]^+$, RT 2.4min.

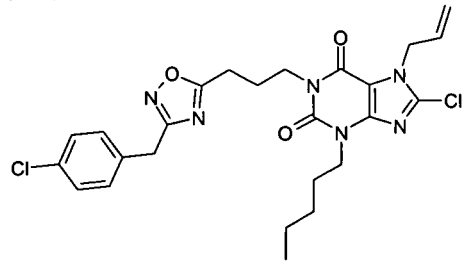
Example 88 : 8-Chloro-1-(3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-1-(3-{3-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-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-1*H*-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 $Pd(PPh_3)_4$ (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 $[MH]^+$, 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



i)

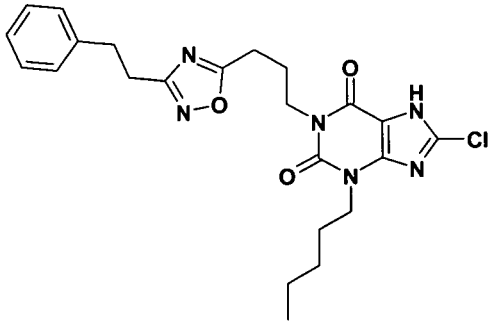
i) A mixture of γ-butyrolactone (8ml, 104mmol), 4-chlorobenzamidine oxime (3.0g, 16.25mmol), 30% solution of NaOMe in MeOH (5ml) and MeOH (80ml) was refluxed for 30h, cooled and concentrated. The residues were purified by flash chromatography over silica eluting with DCM/EtOH/0.88 aq ammonia (200:8:1) to provide a yellow oil (13g). This material was dissolved in DCM (150ml) and washed with 2M sodium 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.

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/Et_2O mixtures to yield the title

compound contaminated with dibenzylazodicarboxylate by-products (0.18g). Material used crude in deprotection step.
LC/MS: m/z 531 $[MH]^+$, RT 3.83min.

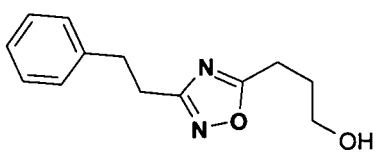
Example 89 : 8-Chloro-3-pentyl-1-{3-[3-(2-phenylethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

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



A solution of 3-[3-(2-phenylethyl)-1,2,4-oxadiazol-5-yl]-1-propanol (150mg, 0.65mmol) in THF (6ml) was treated with 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (160mg, 0.54mmol) and PPh_3 (183mg, 0.70mmol) under nitrogen. DBAD (161mg, 0.70mmol) was added in one portion and the reaction left to react for 18h. The mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (39mg, 0.034mmol) was added and the mixture degassed once more. Morpholine (294µl, 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 residue was taken up into MeOH and purified by passing down an aminopropyl SPE, the product eluted with 2-5% AcOH/MeOH. The title compound was obtained as an off-white solid (185mg, 73%).
LC/MS: m/z 471 $[MH]^+$, RT 3.6min.
^{1}H NMR; (DMSO-d_6) δ: 0.85 (t, 3H, J = 7Hz), 1.23-1.34 (m, 4H), 1.63 (m, 2H), 2.06 (m, 2H), 2.87 (m, 4H), 2.93 (t, 2H, J = 7Hz), 3.89 (t, 2H, J = 7Hz), 4.00 (t, 2H, J = 6.5Hz), 7.16-7.29 (m, 5H), 14.5 (br s, 1H).

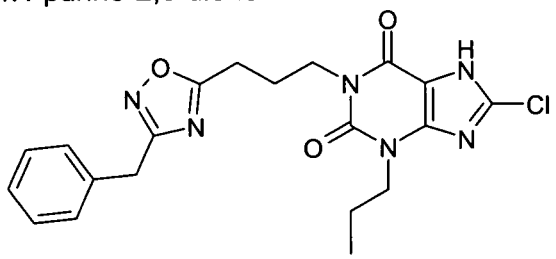
b) 3-[3-(2-Phenylethyl)-1,2,4-oxadiazol-5-yl]-1-propanol



A mixture of γ-butyrolactone (426µl, 5.5mmol), phenethylamidine oxime (1.0g, 6.1mmol), 21% solution of NaOEt in EtOH (2ml) 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 by Si-SPE eluting with EtOAc/cyclohexane mixtures to give the title compound as a pale yellow oil (390mg, 31%).
LC/MS: m/z 233 $[MH]^+$, RT 2.5min.

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

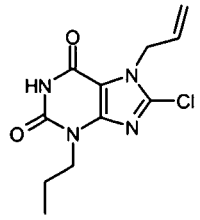
a) 8-Chloro-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione



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 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. 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 $Pd(PPh_3)_4$ (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 ($MgSO_4$) 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.

^{1}H 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).

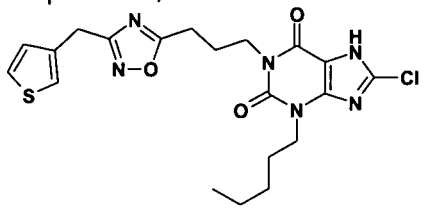
b) 8-Chloro-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione



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 ($MgSO_4$) 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 $[MH]^+$.

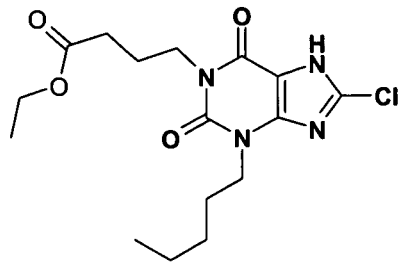
Example 91: 8-Chloro-3-pentyl-1-{3-[3-(3-thienylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

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.

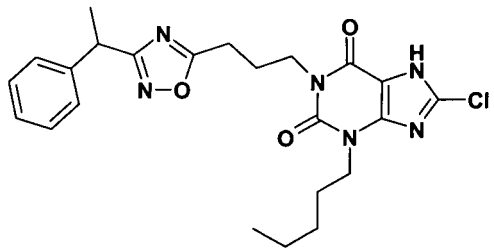
b) Ethyl 4-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate



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 Cs_2CO_3 (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. $Pd(PPh_3)_4$ (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 ($MgSO_4$) 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 92 : 8-Chloro-3-pentyl-1-{3-[3-(1-phenylethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

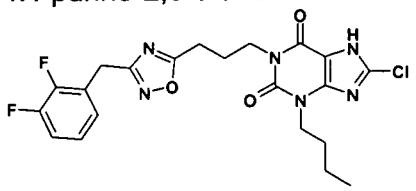


A mixture of ethyl 4-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (70mg, 0.19mmol), *N*-hydroxy-2-phenylpropanimidamide (38mg, 0.23mmol), 21% solution of NaOEt in EtOH (78µl, 0.21mmol) and EtOH (1.5ml) was heated in the microwave at 140°C for 10min. After cooling the reaction 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 the MDAP. The title compound was freeze dried from 1,4-dioxane to give a white solid (44mg, 49%).

LC/MS: m/z 471 $[MH]^+$, RT 3.6min.

Example 93 : 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

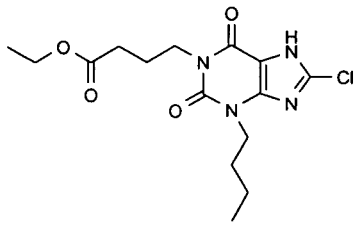


2,3-Difluorophenylacetonitrile (23mg, 0.15mmol) was dissolved in EtOH (1ml). Hydroxylamine hydrochloride (14mg, 0.20mmol) was added, followed by water (0.5ml) and potassium carbonate (41mg, 0.3mmol). The mixture was heated at reflux overnight and then cooled and partitioned between EtOAc and brine. The organic phase was evaporated and the crude amidoxime thus obtained was dissolved in EtOH (1ml). Ethyl 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).

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

^{1}H 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).

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



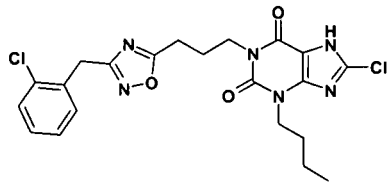
To 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (6.0g, 21.24mmol) in dry DMF (100ml) was added Cs_2CO_3 (7.62g, 23.36mmol) followed by ethyl 4-bromobutyrate (4.556g, 23.36mmol). The mixture was heated at 55°C for 18h and allowed to cool then degassed by repeatedly evacuating and 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 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 (d^4 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).

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

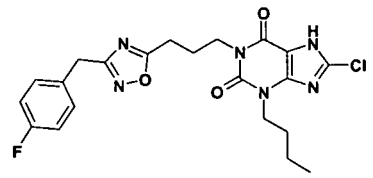


Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (53mg, 0.15mmol) and (1*Z*)-2-(2-chlorophenyl)-*N*-hydroxyethanimidamide (30mg, 0.18mmol; Entry **1**, table 7) were heated in EtOH (0.75ml) with 21% ethanolic sodium ethoxide (0.083ml, 0.22mmol) at 140°C for 10min. The 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).

LC/MS: m/z 477 $[MH]^+$, RT 3.59min.

^1H NMR (d^6 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).

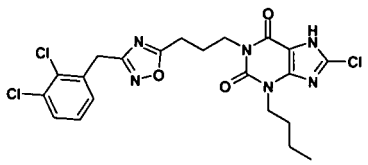
Example 95 : 3-Butyl-8-chloro-1-{3-[3-(4-fluorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



Starting from (1*Z*)-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.

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

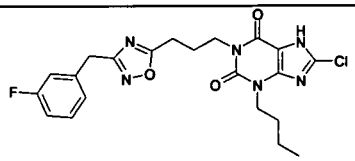
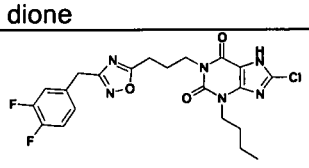


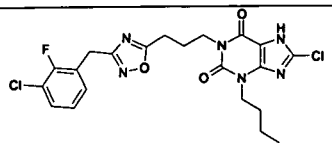
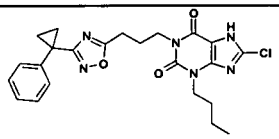
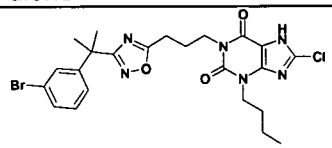
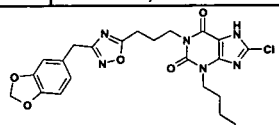
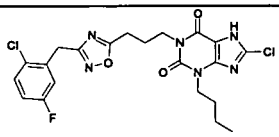
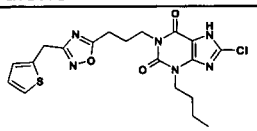
Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (53mg, 0.15mmol) and (1*Z*)-2-(2,3-dichlorophenyl)-*N*-hydroxyethanimidamide (36mg, 0.165mmol; Entry **3**, Table 7) and 21% ethanolic sodium ethoxide (0.083ml, 0.22mmol) were heated together in EtOH (0.75ml) in the microwave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

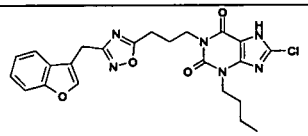
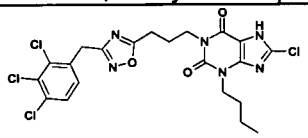
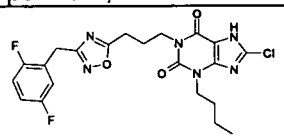
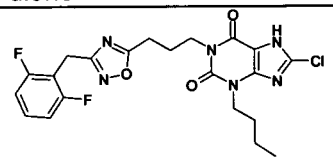
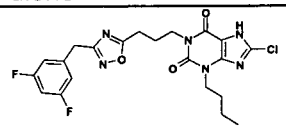
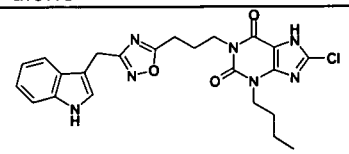
LC/MS: m/z 511, 513, 515 (isotopes) $[MH]^+$, RT 3.66min.

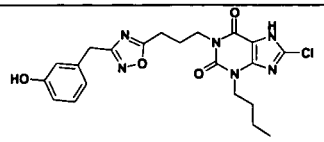
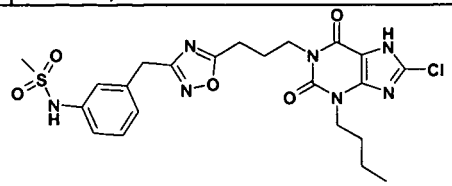
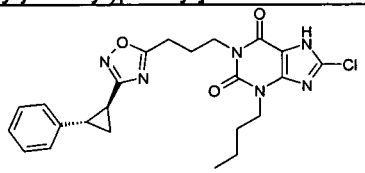
The following compounds (Table 4) were prepared using a method analogous to that for Example 96, using the appropriate amidoxime, (with the exceptions that for Example **110** (Table 4) during workup the pH was adjusted to 5 prior to extraction with EtOAc; and in the case of Example **111** (Table 4) the crude product was stirred for 18h with EtOH (1ml) and 2M NaOH (0.5ml) and Example **112** (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 :
97	 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	**4**	28	32.4	m/z 461 $[MH]^+$ RT 3.41 min
98	 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	**5**	31	28.3	m/z 479 $[MH]^+$ RT 3.46 min

99	 3-butyl-8-chloro-1-{3-[3-(3-chloro-2-fluorobenzyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	**6**	33	32.3	m/z 495 $[MH]^+$ RT 3.55 min
100	 3-butyl-8-chloro-1-{3-[3-(1-phenylcyclopropyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	**8**	29	3.5	m/z 469 $[MH]^+$ RT 3.43 min
101	 1-(3-{3-[1-(3-bromophenyl)-1-methylethyl]-1,2,4-oxadiazol-5-yl}propyl)-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione	**9**	42	2.6	m/z 551 $[MH]^+$ RT 3.71 min
102	 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	**10**	32	30.5	m/z 487 $[MH]^+$ RT 3.27 min
103	 3-butyl-8-chloro-1-(3-{3-[(2-chloro-5-fluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	**19**	33	26.2	m/z 495 $[MH]^+$ RT 3.47 min
104	 3-butyl-8-chloro-1-{3-[3-(2-thienylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	**21**	26	33.4	m/z 449 $[MH]^+$ RT 3.23 min

105	 1-{3-[3-(1-benzofuran-3-ylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione	**22**	31	27.3	m/z 483 $[MH]^+$ RT 3.47 min
106	 3-butyl-8-chloro-1-(3-{3-[(2,3,4-trichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	**15**	42	29.8	m/z 545 $[MH]^+$ RT 3.79 min
107	 3-butyl-8-chloro-1-(3-{3-[(2,5-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	**16**	31	34.8	m/z 479 $[MH]^+$ RT 3.35 min
108	 3-butyl-8-chloro-1-(3-{3-[(2,6-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	**17**	31	38.2	m/z 479 $[MH]^+$ RT 3.31 min
109	 3-butyl-8-chloro-1-(3-{3-[(3,5-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	**18**	31	35.4	m/z 479 $[MH]^+$ RT 3.39 min
110	 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	**20**	31	16.1	m/z 482 $[MH]^+$ RT 3.31 min

111	 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	**7**	28	10	m/z 459 $[MH]^+$ RT 3.07 min
112	 *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	**25**	40	28.4	m/z 536 $[MH]^+$ RT 3.03 min
113	 3-butyl-8-chloro-1-(3-{3-[(1*S*,2*S*)-2-phenylcyclopropyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	(1*S*,2*S*)-*N*-hydroxy-2-phenylcyclopropanecarboximidamide	29	29.6	m/z 469 $[MH]^+$ RT 3.51 min

NMR details for selected examples from Table 4:

Example 97: 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

^{1}H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.25-1.36 (m, 2H), 1.56-1.67 (m, 2H), 2.0-2.1 (m, 2H), 2.94 (t, 2H, J = 7Hz), 3.90 (t, 2H, J = 7 Hz), 3.98 (t, 2H, J = 7Hz), 4.02 (s, 2H), 7.05-7.15 (m, 3H), 7.32-7.40 (m, 1H).

Example 98: 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

^{1}H NMR (DMSO-d_6) δ: 0.89 (t, 3H, J = 7.5Hz), 1.25-1.34 (m, 2H), 1.56-1.65 (m, 2H), 1.99-2.07 (m, 2H), 2.92 (t, 2H, J = 7Hz), 3.89 (t, 2H, J = 7 Hz), 3.98 (t, 2H, J = 7Hz), 4.02 (s, 2H), 7.10-7.15 (m, 1H), 7.32-7.39 (m, 2H), 14.45 (br s, 1H).

Example 100: 3-butyl-8-chloro-1-{3-[3-(1-phenylcyclopropyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

^{1}H NMR (MeOH-d_4) δ: 0.95 (t, 3H, J = 7Hz), 1.25-1.30 (m, 2H), 1.30-1.45 (m, 4H), 1.64-1.75 (m, 2H), 2.15-2.25 (m, 2H), 2.94 (t, 2H, J = 7Hz), 3.98 (t, 2H, J = 7Hz), 4.10 (t, 2H, J = 7Hz), 7.20-7.37 (m, 5H).

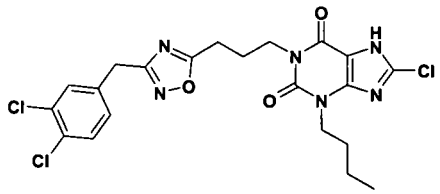
Example 102: 1-{3-[3-(1,3-benzodioxol-5-ylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.25-1.36 (m, 2H), 1.58-1.68 (m, 2H), 1.98-2.09 (m, 2H), 2.92 (t, 2H, J = 7Hz), 3.88-3.95 (m, 4H), 3.99 (t, 2H, J = 7Hz), 5.98 (s, 2H), 6.70-6.86 (m, 3H).

Example 110: 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
^{1}H NMR (DMSO-d_6) δ: 0.89 (t, 3H, J = 7Hz), 1.23-1.36 (m, 2H), 1.56-1.67 (m, 2H), 1.96-2.08 (m, 2H), 2.90 (t, 2H, J = 7Hz), 3.90 (t, 2H, J = 7 Hz), 3.99 (t, 2H, J = 7Hz), 4.04 (s, 2H), 6.92-7.50 (m, 5H), 10.95 (s, 1H).

Example 111: 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
^{1}H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.25-1.38 (m, 2H), 1.57-1.68 (m, 2H), 1.96-2.07 (m, 2H), 2.92 (t, 2H, J = 7Hz), 3.86 (s, 2H), 3.89 (t, 2H, J = 7Hz), 3.99 (t, 2H, J = 7Hz), 6.58-6.68 (m, 3H), 7.08 (m, 1H), 9.40 (s,1H).

Example 112: *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
^{1}H NMR (DMSO-d_6) δ: 0.89 (t, 3H, J = 7.5Hz), 1.24-1.34 (m, 2H), 1.56-1.65 (m, 2H), 1.97-2.06 (m, 2H), 2.91 (t, 2H, J = 7.5Hz), 2.97 (s, 3H), 3.90 (t, 2H, J = 7.5Hz), 3.96 (s, 2H), 3.97 (t, 2H, J = 7Hz), 6.96-6.99 (m, 1H), 7.06-7.13 (m, 2H), 7.26 (t, 1H, J = 8Hz), 9.75 (s, 1H), 14.45 (br s, 1H).

Example 114: 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

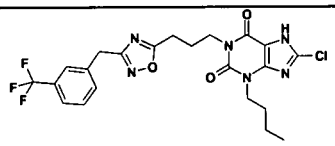
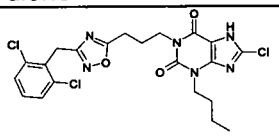
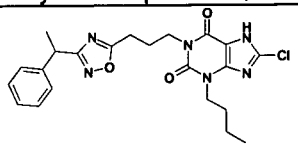
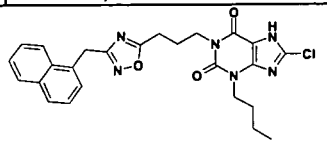


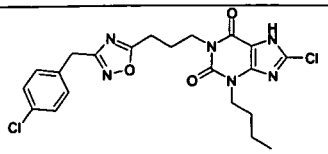
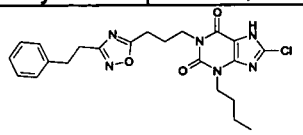
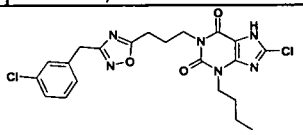
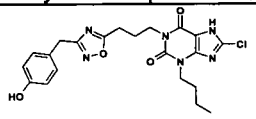
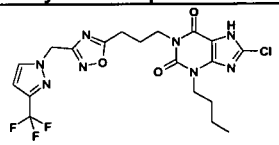
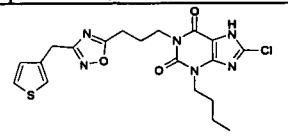
Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (71mg, 0.2mmol), (1*Z*)-2-(3,4-dichlorophenyl)-*N*-hydroxyethanimidamide (48mg, 0.22mmol) and 21% by wt. ethanolic sodium ethoxide (0.111ml, 0.3mmol) were heated together in EtOH (1ml) in the microwave reactor at 140°C for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

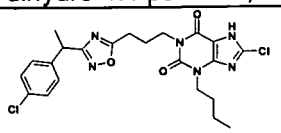
LC/MS: m/z 511, 513 $[MH]^+$, RT 3.65min.

The following compounds (Table 5) were prepared using a method analogous to that for Example 114, using the appropriate amidoxime (with the exception that for Example **115** and Example **125**, 0.185ml, (0.5mmol) of 21% sodium ethoxide was added in order to allow for the amidoximes being the hydrochloride salts).

Table 5

Example	Structure	Amidoxime	Wt of amidoxime mg	Yield mg	LC/MS:
115	 3-butyl-8-chloro-1-[3-(3-{[3-(trifluoromethyl)phenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	(1*Z*)-*N*-hydroxy-2-[3-(trifluoromethyl)phenyl]ethanimidamide hydrochloride	56	46.5	m/z 511 $[MH]^+$ RT 3.63 min
116	 3-butyl-8-chloro-1-(3-{3-[(2,6-dichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	(1*Z*)-2-(2,6-dichlorophenyl)-*N*-hydroxyethanimidamide	48	53.8	m/z 511 $[MH]^+$ RT 3.64 min
117	 3-butyl-8-chloro-1-{3-[3-(1-phenylethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	(1*Z*)-*N*-hydroxy-2-phenylpropanimidamide	36	45.4	m/z 457 $[MH]^+$ RT 3.51 min
118	 3-butyl-8-chloro-1-{3-[3-(1-naphthalenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	(1*Z*)-*N*-hydroxy-2-(1-naphthalenyl)ethanimidamide	44	48.6	m/z 493 $[MH]^+$ RT 3.67 min

119	 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	(1*Z*)-2-(4-chlorophenyl)-*N*-hydroxyethanimidamide	41	35.6	m/z 477 $[MH]^+$ RT 3.60 min
120	 3-butyl-8-chloro-1-{3-[3-(2-phenylethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	(1*Z*)-*N*-hydroxy-3-phenylpropanimidamide	36	29.6	m/z 457 $[MH]^+$ RT 3.55 min
121	 3-butyl-8-chloro-1-(3-{3-[(3-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	(1*Z*)-2-(3-chlorophenyl)-*N*-hydroxyethanimidamide	41	39.4	m/z 477 $[MH]^+$ RT 3.64 min
122	 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	(1*Z*)-*N*-hydroxy-2-(4-hydroxyphenyl)ethanimidamide	36	53.5	m/z 459 $[MH]^+$ RT 3.08 min
123	 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	(1*Z*)-*N*-hydroxy-2-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanimidamide	46	58.1	m/z 501 $[MH]^+$ RT 3.33 min
124	 3-butyl-8-chloro-1-{3-[3-(3-thienylmethyl)-1,2,4-	(1*Z*)-*N*-hydroxy-2-(3-thienyl)ethanimidamide	34	32.6	m/z 449 $[MH]^+$ RT 3.31 min

	oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione				
125	 3-butyl-8-chloro-1-(3-{3-[1-(4-chlorophenyl)ethyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	(1*Z*)-2-(4-chlorophenyl)-*N*-hydroxypropanimidamide hydrochloride	52	30.3	m/z 491 $[MH]^+$ RT 3.67 min

NMR details for selected examples from Table 5

Example 115: ^{1}H NMR (d^6 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 117: 3-butyl-8-chloro-1-{3-[3-(1-phenylethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H NMR (DMSO-d_6) δ: 0.89 (t, 3H, J = 7Hz), 1.22-1.35 (m, 2H), 1.52 (d, 3H, J = 8Hz), 1.56-1.68 (m, 2H), 1.95-2.08 (m, 2H), 2.91 (t, 2H, J = 7Hz), 3.89 (t, 2H, J = 7Hz), 3.95 (t, 2H, J = 7Hz), 4.18 (q, 1H, J = 8Hz), 7.17-7.32 (m, 5H).

Example 119: 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
^{1}H NMR (DMSO-d_6) 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).

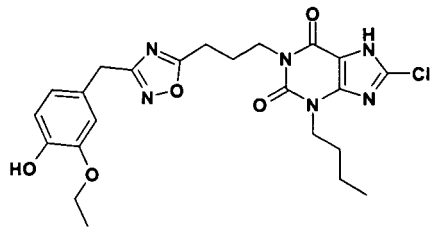
Example 122: 3-butyl-8-chloro-1-(3-{3-[(4-hydroxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione
^{1}H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.23-1.37 (m, 2H), 1.57-1.68 (m, 2H), 1.96-2.08 (m, 2H), 2.90 (t, 2H, J = 7Hz), 3.82 (s, 2H), 3.90 (t, 2H, J = 7Hz), 3.98 (t, 2H, J = 7Hz), 6.68 (d, 2H, J = 9Hz), 7.04 (d, 2H, J = 9Hz), 9.32 (s, 1H).

Example 123: 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
^{1}H NMR (DMSO-d_6) 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 125: 3-butyl-8-chloro-1-(3-{3-[1-(4-chlorophenyl)ethyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione

^{1}H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.23-1.38 (m, 2H), 1.51 (d, 3H, J = 6Hz), 1.55-1.69 (m, 2H), 1.96-2.10 (m, 2H), 2.92 (t, 2H, J = 7Hz), 3.89 (t, 2H, J = 7Hz), 3.98 (t, 2H, J = 7Hz), 4.24 (q, 1H, J = 6Hz), 7.27-7.40 (m, 4H).

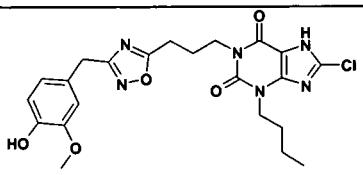
Example 126 : 3-Butyl-8-chloro-1-[3-(3-{[3-(ethyloxy)-4-hydroxyphenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione

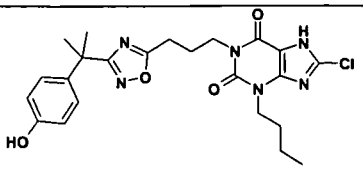
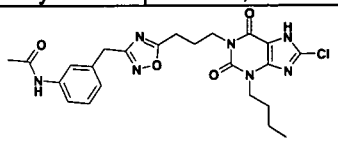


Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (53mg, 0.15mmol) and (1*Z*)-2-[3-(ethyloxy)-4-hydroxyphenyl]-*N*-hydroxyethanimidamide (35mg, 0.165mmol; entry 11, Table 7) were mixed in EtOH (0.75ml). Ethanolic sodium ethoxide (21% by wt., 0.083ml, 0.22mmol) was added 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 126, using the appropriate amidoxime (with the exception that for Example **127** (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:
127	 3-butyl-8-chloro-1-[3-(3-{[4-hydroxy-3-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	**12**	32	19.3	m/z 489 $[MH]^+$ RT 2.98 min

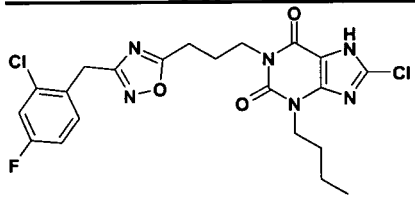
128	 3-butyl-8-chloro-1-(3-{3-[1-(4-hydroxyphenyl)-1-methylethyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	13	32	37.2	m/z 487 $[MH]^+$ RT 3.23 min
129	 *N*-[3-({5-[3-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]-1,2,4-oxadiazol-3-yl}methyl)phenyl]acetamide	14	34	23.6	m/z 500 $[MH]^+$ RT 2.94 min

NMR details for selected examples from Table 6

Example 129: *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]acetamide

^{1}H 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).

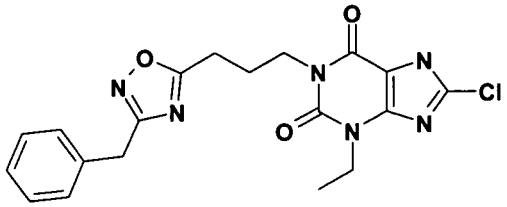
Example 130: 3-Butyl-8-chloro-1-(3-{3-[(2-chloro-4-fluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



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

Example 131 : 8-Chloro-3-ethyl-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

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

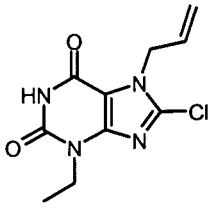


A solution of 8-chloro-3-ethyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (150mg, 0.59mmol) in anhydrous THF (4ml) was treated with 3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-propanol (154mg, 0.71mmol) and triphenylphosphine (200mg, 0.76mmol). DBAD (162mg, 0.71mmol) was added in one portion and the mixture was left to stir at rt, under nitrogen for 18h. The mixture was degassed by high vacuum then $Pd(PPh_3)_4$ (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 ($MgSO_4$) 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

^1H NMR; (DMSO-d_6) 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).

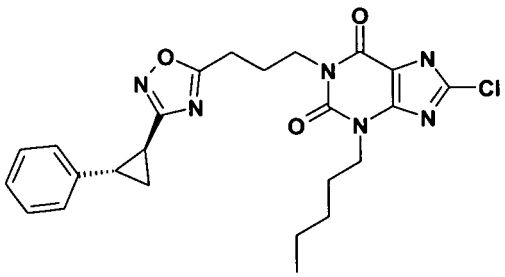
b) 8-Chloro-3-ethyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



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 Na_2CO_3 (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

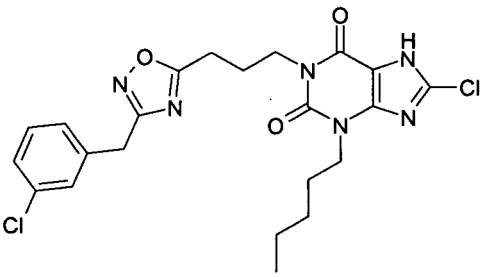
brine, dried ($MgSO_4$) and concentrated. The crude solid was washed with Et_2O to give the title compound as a white solid (8.37g, 75%).
LC/MS: m/z 255 $[MH]^+$, RT 2.35min.

Example 132 : 8-Chloro-3-pentyl-1-(3-{3-[(1*S*,2*S*)-2-phenylcyclopropyl]-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 (1.5ml). The solution was treated with a 21% solution of NaOEt in EtOH (78µl, 0.21mmol) and (1*S*,2*S*)-*N*-hydroxy-2-phenylcyclopropanecarboximidamide (37mg, 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 separated and concentrated, the resulting crude product was purified by MDAP. The product fractions were combined and concentrated to give the title compound as a white solid (35mg, 38%).
LC/MS: m/z 483 $[MH]^+$, RT 3.67min.

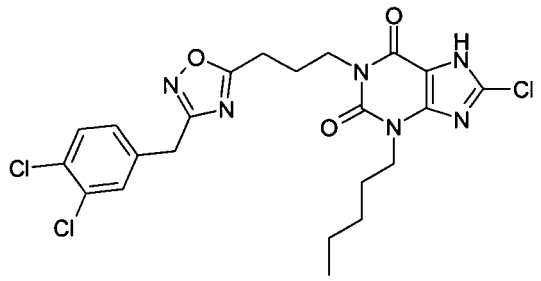
Example 133 : 8-Chloro-1-(3-{3-[(3-chlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



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-(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%).

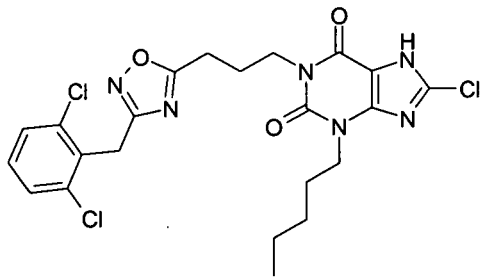
LC/MS: m/z 491 $[MH]^+$, RT 3.64min.
^1H NMR (DMSO-d_6) δ: 0.85 (t, 3H, J = 7Hz), 1.27 (m, 4H), 1.62 (m, 2H), 2.02 (m, 2H), 2.92 (t, 2H, J = 7.5Hz), 3.88 (t, 2H, J=7 Hz), 3.97 (t, 2H, J = 6.5Hz), 4.02 (s, 2H), 7.23 (d, 1H, J = 7Hz), 7.34 (m, 3H).

Example 134: 8-Chloro-1-(3-{3-[(3,4-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-(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.

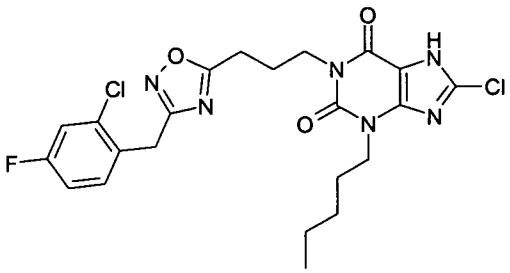
Example 135 : 8-Chloro-1-(3-{3-[(2,6-dichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



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

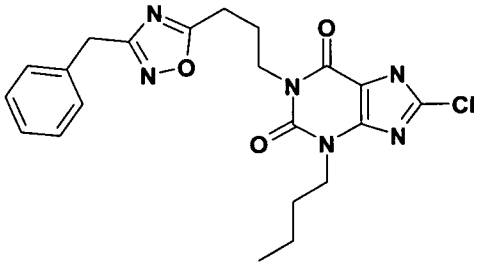
product was purified on the MDAP. The product fractions were combined and concentrated to give the title compound as a white solid (80mg, 80%).
LC/MS: m/z 526 $[MH]^+$, RT 3.6 min.

Example 136 : 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-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 (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 137 : 3-Butyl-8-chloro-1-{3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



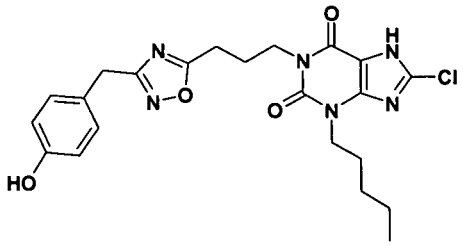
A solution of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (205mg, 0.73mmol) in anhydrous THF (4ml) was treated with 3-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-propanol (190mg, 0.87mmol) and PPh_3 (247mg, 0.94mmol). DBAD (217mg, 0.94mmol) was added in one portion and the mixture was stirred at rt under nitrogen for 18h. The mixture was degassed by high vacuum then $Pd(PPh_3)_4$ (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 ($MgSO_4$) 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-d_6) 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).

Example 138: 8-Chloro-1-(3-{3-[(4-hydroxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

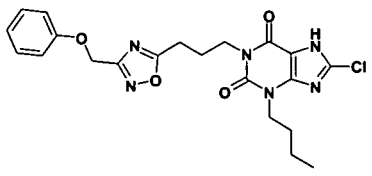


Ethyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (29mg, 0.078mmol) and (1*Z*)-*N*-hydroxy-2-(4-hydroxyphenyl)ethanimidamide (14mg, 0.084mmol) were heated in EtOH (1ml) with 21% ethanolic sodium ethoxide (0.043ml, 0.117mmol) under microwave irradiation at 140°C for 10min. 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 afforded the title compound (6.5mg).

LC/MS: m/z 473 $[MH]^+$, RT 3.34min.

^1H NMR (MeOH-d_4) 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).

Example 139: 3-Butyl-8-chloro-1-(3-{3-[(phenyloxy)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



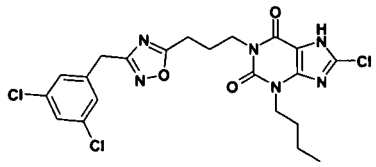
To ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (26mg, 0.073mmol) and (1*Z*)-*N*-hydroxy-2-(phenyloxy)ethanimidamide hydrochloride (16mg, 0.079mmol) in EtOH (1ml) was added 21%wt. ethanolic sodium ethoxide solution (0.068 ml, 0.183mmol) and the mixture was heated under microwave

irradiation at 140°C for 10min. The mixture was partitioned between EtOAc and 2M HCl, the organic phase dried (Na_2SO_4) 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-d_6) 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).

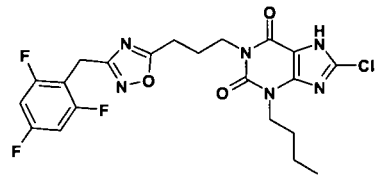
Example 140: 3-Butyl-8-chloro-1-(3-{3-[(3,5-dichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



To ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (185mg, 0.52mmol) and (1*Z*)-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.

Example 141: 3-Butyl-8-chloro-1-(3-{3-[(2,4,6-trifluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



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

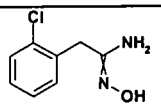
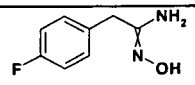
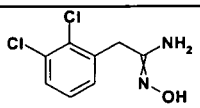
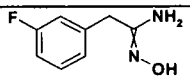
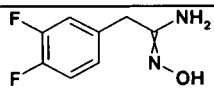
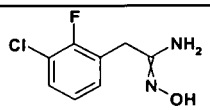
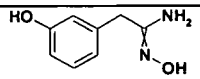
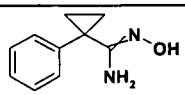
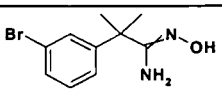
LC/MS: m/z 497 $[MH]^+$, RT 3.39min.

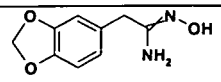
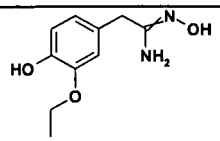
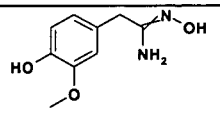
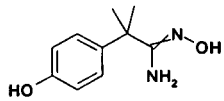
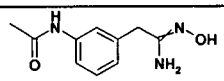
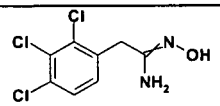
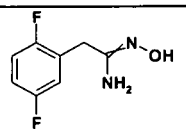
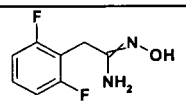
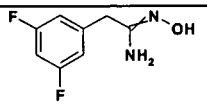
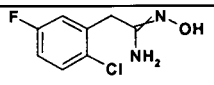
^1H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 7Hz), 1.24-1.36 (m, 2H), 1.55-1.66 (m, 2H), 1.96-2.06 (m, 2H), 2.91 (t, 2H, J = 8Hz), 3.91 (t, 2H, J = 8 Hz), 3.94 – 4.02 (m, 4H), 7.18-7.28 (m, 2H).

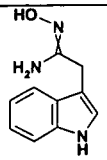
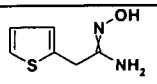
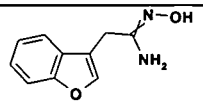
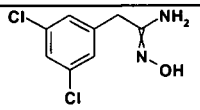
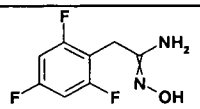
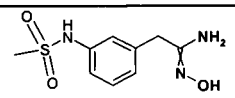
Amidoximes:

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

Table 7 (Intermediates)

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

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

20		**(1Z)-*N*-hydroxy-2-(1*H*-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

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.

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.

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

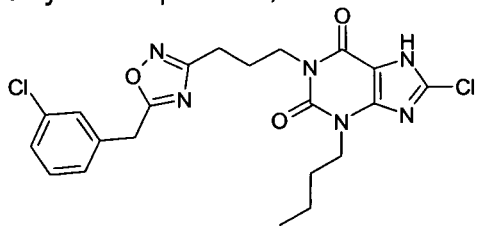
Method F
Similar to Method A except that the scale was 1.5mmol of nitrile and purification was on a 10g SCX cartridge.

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

It should be noted that the above assignment of (Z)-stereochemistry 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. Journal of Organic Chemistry (1975), 40(20), 2979-80)

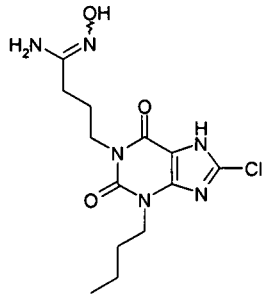
Example 142: 3-Butyl-8-chloro-1-(3-{5-[(3-chlorophenyl)methyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione

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



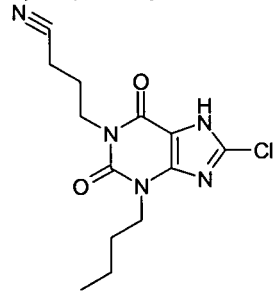
(3-Chlorophenyl)acetic acid (0.1mmol), *N*-[3-(dimethylamino)propyl]-*N'*-ethylcarbodiimide hydrochloride (21mg, 0.11mmol) and 1*H*-1,2,3-benzotriazol-1-ol (15mg, 0.11mmol) were stirred in 1-methyl-2-pyrrolidinone (1ml). To this was added (1*Z*)-4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxybutanimidamide (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%).
LC/MS: m/z 477, 479 $[MH]^+$, RT 3.5min.
^{1}H NMR ($CDCl_3$) 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).

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



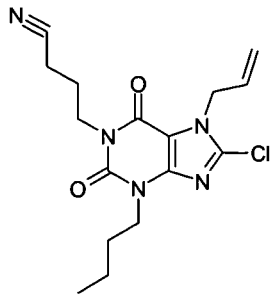
4-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butanenitrile (1g, 0.0032mol) was stirred in EtOH (3.5ml) and water (1.8ml). Hydroxylamine hydrochloride (344mg, 0.0049mol) and potassium carbonate (652mg, 0.0049mol) were added and the mixture heated at 80°C for 3 days. After cooling the crude reaction mixture was evaporated. The crude product was dissolved in water, neutralised to pH7 with HCl, and loaded onto an Oasis™ 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-1*H*-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-1*H*-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 Cs_2CO_3 (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 ($MgSO_4$) 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 142, 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.

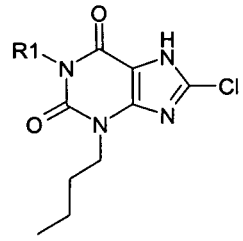
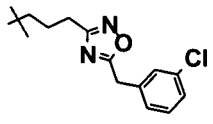
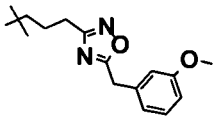
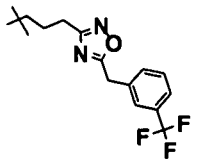
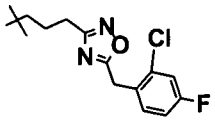
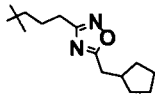
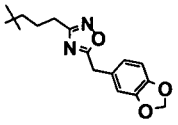
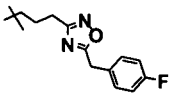
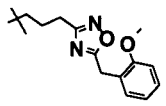
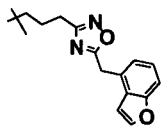


Table 8

Example		Compound: R1 =	Yield %	LC/MS:
143	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		27	m/z 477 $[MH]^+$ RT 3.5 min
144	3-butyl-8-chloro-1-[3-(5-{[3-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione		22	m/z 473 $[MH]^+$ RT 3.3 min

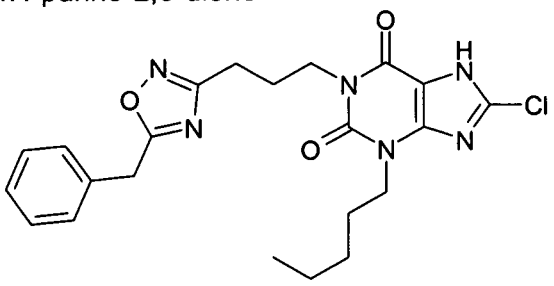
Example		Compound: R1 =	Yield %	LC/MS:
145	3-butyl-8-chloro-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione		23	m/z 511 $[MH]^+$ RT 3.5 min
146	3-butyl-8-chloro-1-(3-{5-[(2-chloro-4-fluorophenyl)methyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione		28	m/z 495 $[MH]^+$ RT 3.5 min
147	3-butyl-8-chloro-1-{3-[5-(cyclopentylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione		15	m/z 435 $[MH]^+$ RT 3.5 min
148	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
149	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
150	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
151	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 145: ^{1}H NMR ($CDCl_3$) 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).

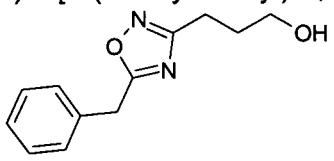
Example 152: 8-Chloro-3-pentyl-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

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



To a stirred solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-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 $Pd(PPh_3)_4$ (75mg, 0.067mmol) and morpholine (600µl, 6.7mmol) were added and stirred for at rt under nitrogen for a further 3h. 75mg of $Pd(PPh_3)_4$ 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 ($MgSO_4$) 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



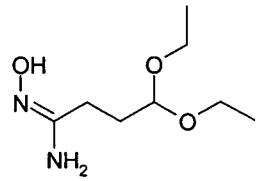
A mixture of (1*E*)-4,4-bis(ethyloxy)-*N*-hydroxybutanimidamide (3.2g, 16.8mmol), ethyl phenylacetate (2.3ml, 14.4mmol) and sodium ethoxide (21% solution in EtOH, 6.4ml) was heated in a microwave at 140°C for 10min. The material was combined with that from a second reaction (using 1.2g of (1*E*)-4,4-bis(ethyloxy)-*N*-hydroxybutanimidamide 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 $[MH]^+$.

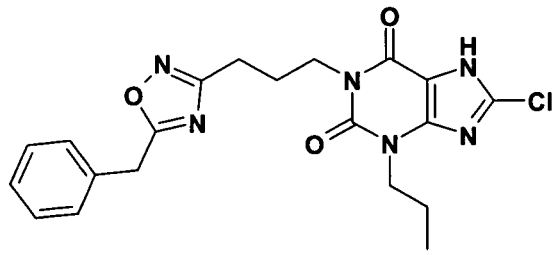
c) (1*E*)-4,4-bis(ethyloxy)-*N*-hydroxybutanimidamide



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 brine, dried and concentrated to provide the title compound as a colourless oil contaminated with ~20% starting nitrile (6.03g, 81%).

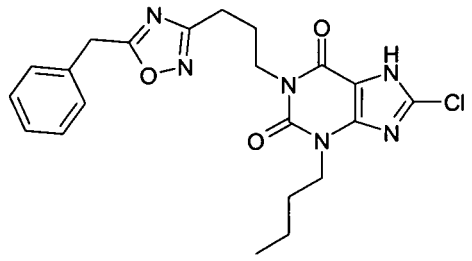
LC/MS: m/z 191 $[MH]^+$.

Example 153 : 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 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 (460µl, 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 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.
^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).

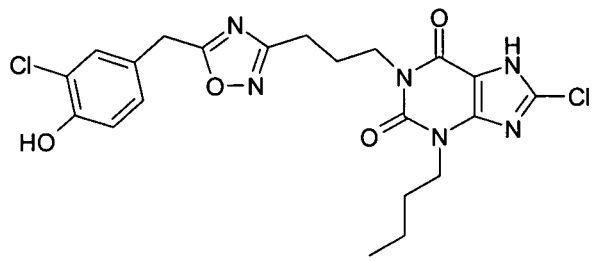
Example 154 : 3-Butyl-8-chloro-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



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-1*H*-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.

^{1}H 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).

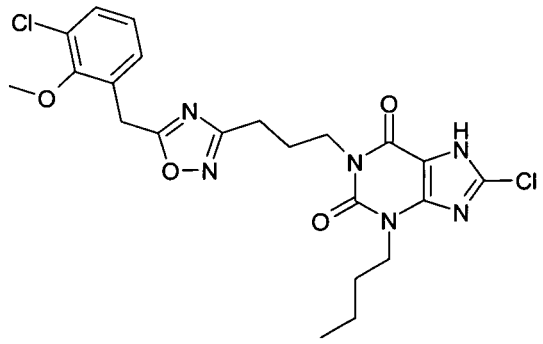
Example 155 : 3-Butyl-8-chloro-1-(3-{5-[(3-chloro-4-hydroxyphenyl)methyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



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. (1*Z*)-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%).

LC/MS: m/z 493 $[MH]^+$, RT 3.2min.

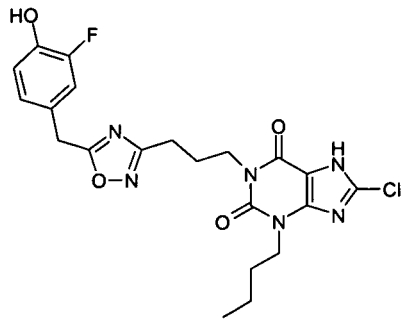
Example 156 : 3-Butyl-8-chloro-1-[3-(5-{[3-chloro-2-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione



A mixture of [3-chloro-2-(methyloxy)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%).

LC/MS: m/z 507 $[MH]^+$, RT 3.5min.

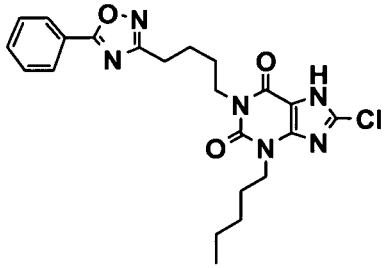
Example 157 : 3-Butyl-8-chloro-1-(3-{5-[(3-fluoro-4-hydroxyphenyl)methyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



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.

Example 158 : 8-chloro-3-pentyl-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione

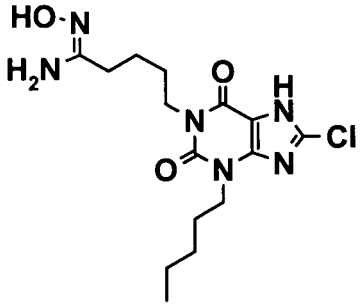
a) Preparation of 8-chloro-3-pentyl-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione



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.

^{1}H 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).

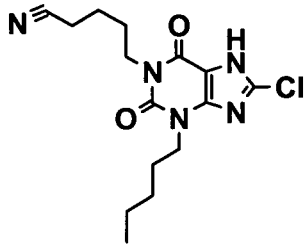
b) 5-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-hydroxypentanimidamide



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

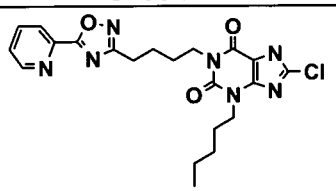
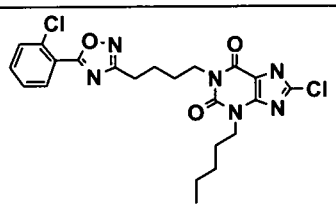
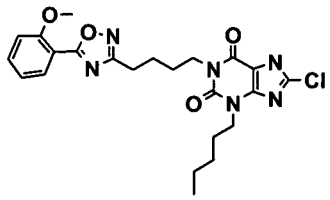
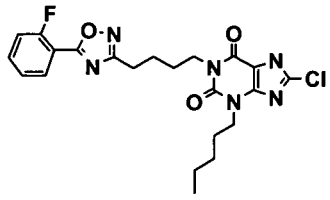


A solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (4.0g, 13.5mmol) in DMF (100ml) was treated with caesium carbonate (4.83g, 14.8mmol) and 5-bromopentanenitrile (1.73ml, 14.8mmol). The mixture was heated at 50°C in a nitrogen atmosphere for 19h and then cooled. The mixture 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 ($MgSO_4$) 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.

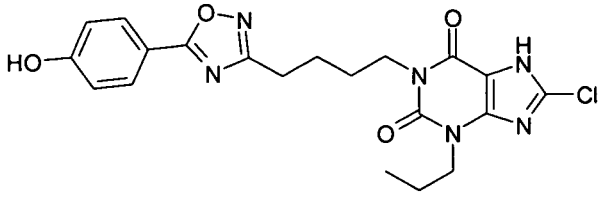
The following compounds were prepared using a method analogous to that for Example 158 (8-chloro-3-pentyl-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione) from the corresponding acids:

Table 9

#	Structure	Name	Yield	LC/MS:
159		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
160		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
161		8-chloro-1-(4-{5-[2-(methyloxy)phenyl]-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
162		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

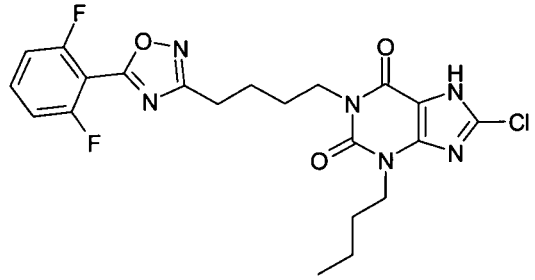
In addition Example **159**, 8-chloro-3-pentyl-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione has the following spectral data: ^1H NMR ($CDCl_3$) δ: 0.89 (t, 3H, J = 6.9Hz), 1.75 (m, 4H), 1.89 (m, 6H), 2.92 (t, 2H, J = 7.1Hz), 4.07 (t, 2H, J = 7.4Hz), 4.16 (t, 2H, J = 6.9Hz), 7.52 (m, 1H), 7.92 (m, 1H), 8.18 (m, 1H), 8.83 (m, 1H), 13.40 (br s, 1H).

Example 163: 8-Chloro-1-{4-[5-(4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione



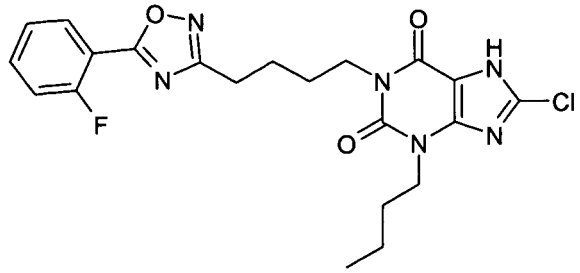
4-Hydroxybenzoic acid (18mg, 0.13mmol) and CDI (24mg, 0.15mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1*Z*)-5-(8-Chloro-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (50mg, 0.15mmol; prepared in a manner similar to (1*Z*)-5-(8-Chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide as described in Example 158(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.

Example 164 : 3-Butyl-8-chloro-1-{4-[5-(2,6-difluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



2,6-Difluorobenzoic acid (40mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1*Z*)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-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 compound as a white solid (18mg, 15%).
LC/MS: m/z 479 $[MH]^+$, RT 3.40min.

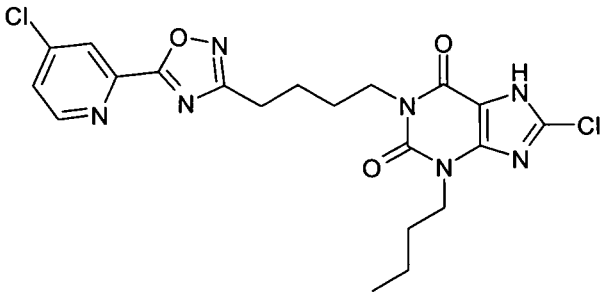
Example 165 : 3-Butyl-8-chloro-1-{4-[5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



2-Fluorobenzoic acid (36mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1*Z*)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-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%).

LC/MS: m/z 461 $[MH]^+$, RT 3.44min.

Example 166 : 3-Butyl-8-chloro-1-{4-[5-(4-chloro-2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione

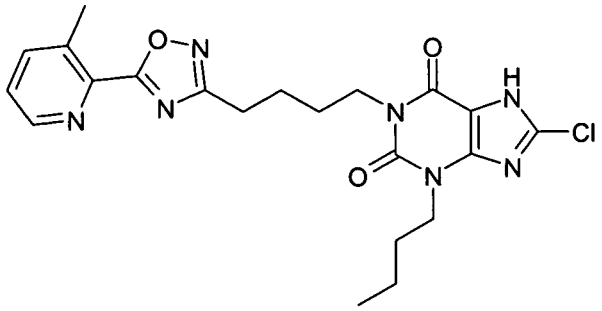


4-Chloro-2-pyridinecarboxylic acid (40mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1*Z*)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (100mg, 0.28mmol) was added and the mixture was stirred at 90°C for 16h.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

LC/MS: m/z 478 $[MH]^+$, RT 3.31min.

^{1}H NMR (DMSO-d_6) 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.

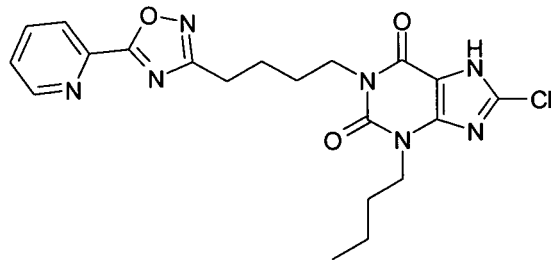
Example 167 : 3-Butyl-8-chloro-1-{4-[5-(3-methyl-2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



3-Methyl-2-pyridinecarboxylic acid (35mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1*Z*)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-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 compound as a white solid 14mg, 12%).
LC/MS: m/z 458 $[MH]^+$, RT 3.13min.

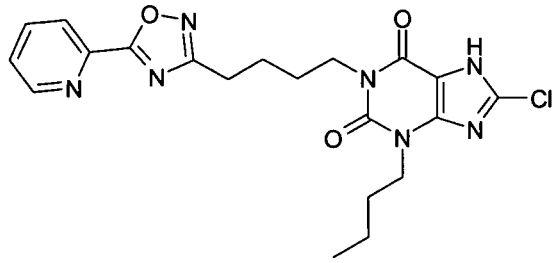
Example 168 : 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione

Method A



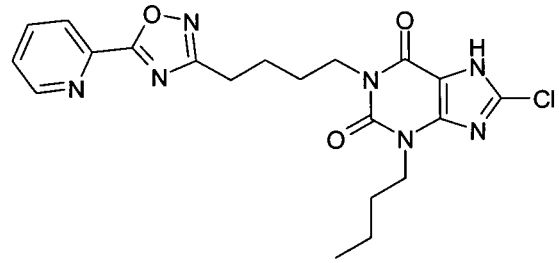
2-Pyridinecarboxylic acid (31mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.5ml) at rt for 1h. A solution of (1*Z*)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (100mg, 0.28mmol) in DMSO (0.4ml) was added and the mixture was stirred 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.
^{1}H NMR (DMSO-d_6) 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. (1*Z*)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-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. NH_4Cl(aq) solution and EtOAc. The organic layer was separated, and the aqueous solution extracted with EtOAc. The combined extracts were washed with brine, dried $MgSO_4$ and concentrated giving an orange liquid. This was purified using the Companion™ system giving two identical white solids (649mg; 240mg).
LC/MS: m/z 444 $[MH]^+$, RT 3.04min.

Method C



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 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, (1*Z*)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-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 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.

Method D

Formation of 3-Butyl-8-chloro-1-{4-[5-(2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-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-1*H*-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 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-1*H*-purine-2,6-dione (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 1hour. 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 shows solvent levels (acetone, water) to be at acceptable.

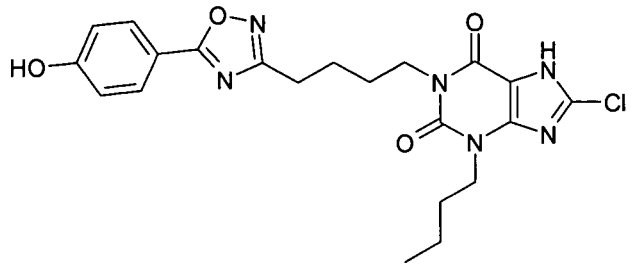
Expected yield (75-80%w/w).

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 1hour. The thin suspension is then cooled to 20-25°C and held at this temperature for a minimum of 12hours. The suspension thus formed is then cooled to 13-17°C and held at this temperature for a minimum of 1hour. The suspension is then sampled, and the solid collected by filtration in the laboratory. The solid is dried and analysed by 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)

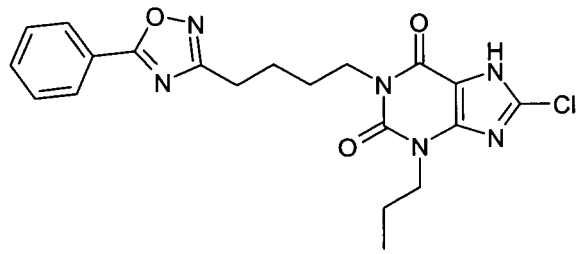
X-ray powder diffraction (XRPD) data are shown in Figures 1-3. The data were acquired on a PANalytical X'Pert Pro powder diffractometer, model PW3040/60, serial number DY1850 using an X'Celerator detector. The acquisition conditions were: radiation: Cu Kα, generator tension: 40 kV, generator current: 45 mA, start angle: 2.0°2θ, end angle: 40.0°2 θ, step size: 0.0167 °2 θ, time per step: 31.75 seconds. The 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 169: 3-Butyl-8-chloro-1-{4-[5-(4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



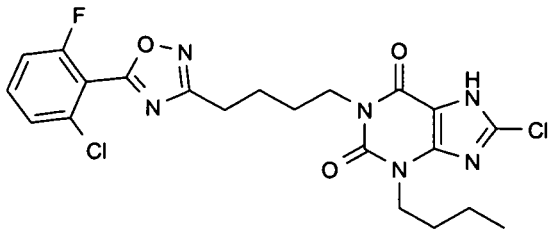
4-Hydroxybenzoic acid (35mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1*Z*)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (100mg, 0.28mmol) was added and the mixture was stirred at 90°C for 16h. The mixture was purified by MDAP to give the title compound as a white solid (5mg, 4%).
LC/MS: m/z 459 $[MH]^+$, RT 3.24min.

Example 170 : 8-Chloro-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione



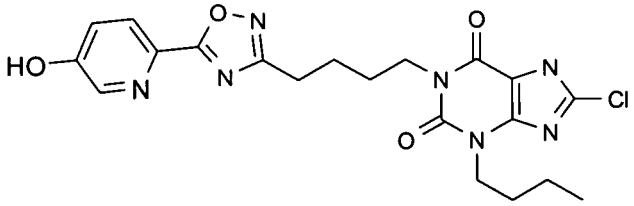
Benzoic acid (9mg, 0.074mmol) and CDI (13mg, 0.081mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1*Z*)-5-(8-Chloro-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (28mg, 0.081mmol) was added and the mixture was stirred at 80°C for 4h. The mixture was purified by MDAP to give the title compound as a white solid (0.6mg, 2%).
LC/MS: m/z 429 $[MH]^+$, RT 3.21min.
^{1}H NMR (MeOH-d_4) 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).

Example 171: 3-Butyl-8-chloro-1-{4-[5-(2-chloro-6-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



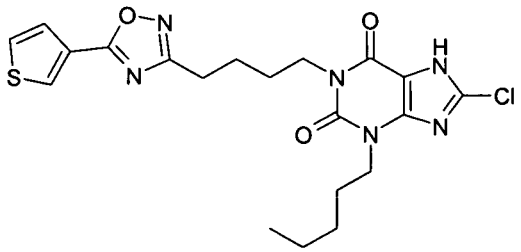
2-Chloro-6-fluorobenzoic acid (44mg, 0.25mmol) and CDI (45mg, 0.28mmol) were stirred in anhydrous DMSO (0.9ml) at rt for 1h. (1Z)-5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (100mg, 0.28mmol) was added and the mixture was stirred at 90°C for 16h. The mixture 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.

Example 172: 3-Butyl-8-chloro-1-{4-[5-(5-hydroxy-2-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-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-1*H*-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.

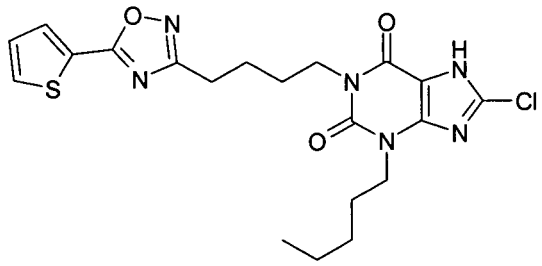
Example 173: 8-Chloro-3-pentyl-1-{4-[5-(3-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



A solution of (1Z)-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (50mg, 0.13mmol) in EtOH (1ml) was treated with a 21%

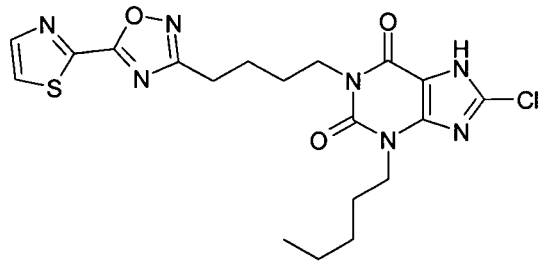
solution of NaOEt in EtOH (55µl, 0.21mmol) and ethyl 3-thiophenecarboxylate (18µl, 0.13mmol). The mixture was heated in the microwave at 150°C for 10min. After cooling, the reaction was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated and the aqueous extracted again with EtOAc. 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 174 : 8-Chloro-3-pentyl-1-{4-[5-(2-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-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, (1*Z*)-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-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 175: 8-Chloro-3-pentyl-1-{4-[5-(1,3-thiazol-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione

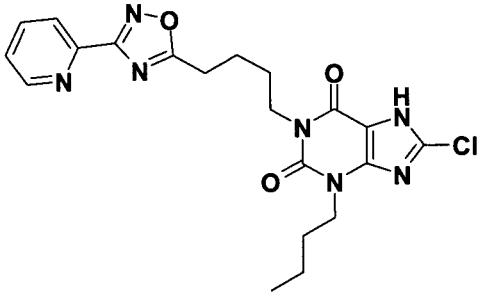


A solution of (1*Z*)-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (50mg, 0.13mmol) in EtOH (1.5ml) was treated with a 21% solution of NaOEt in EtOH (50µl, 0.13mmol) and ethyl 1,3-thiazole-2-carboxylate (18mg, 0.11mmol). The mixture was heated in the microwave 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 ($DMSO-d_6$) 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).

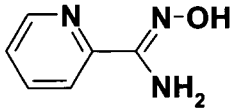
Example 176: 3-butyl-8-chloro-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione

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 ($CDCl_3$) 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

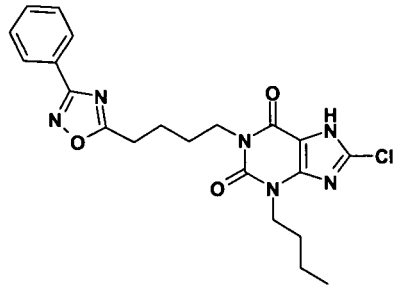
to dryness. The residue was treated with water (100ml) and the suspended solid product filtered off, washed with water and dried to yield the title compound as a white solid (2.28g, 57%).

^{1}H NMR (DMSO-d_6) 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 177: 3-Butyl-8-chloro-1-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-3,7-dihydro-1*H*-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

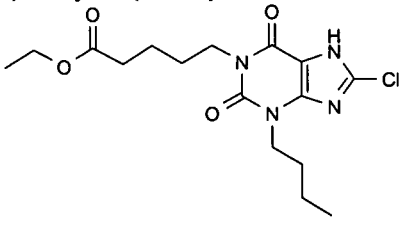


Ethyl 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (74mg, 0.2mmol) and benzamidoxime (30mg, 0.22mmol) were suspended in dry EtOH (1ml) and ethanolic sodium ethoxide (21% by wt., 0.111ml, 0.3mmol) was added. The mixture was gently warmed until solids were dissolved and then 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 (Na_2SO_4) and evaporated. MDAP afforded the pure title compound (40.7mg).

LC/MS: m/z 443 $[MH]^+$, RT 3.67min.

^{1}H NMR (DMSO-d_6) 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

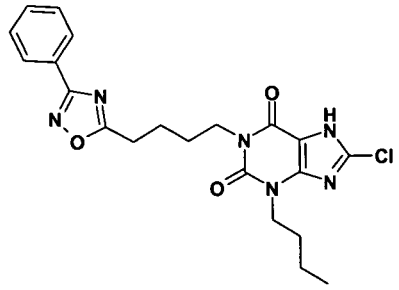


To 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.5g, 5.31mmol) in dry DMF (25ml) was added Cs_2CO_3 (1.905g, 5.84mmol), followed by ethyl 5-bromovalerate (1.46g, 6.99mmol). The mixture was heated at 55°C for 18h then allowed to cool. It was degassed by repeatedly evacuating 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 (Na_2SO_4) 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

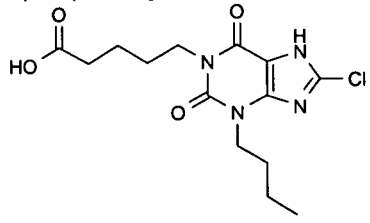
Method B

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



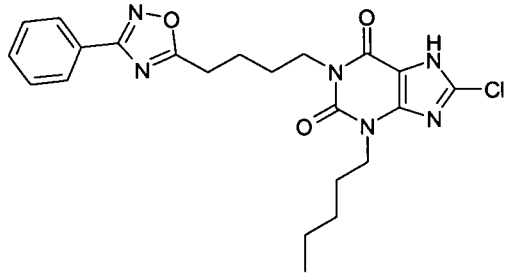
CDI (0.98g, 6.1mmol) was added to a solution of 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (1.89g, 5.5mmol) in DMF (15ml) and stirred under nitrogen for 1.5h. Benzamidoxime (0.91g, 6.1mmol) was added and the mixture stirred at 110°C overnight. The reaction mixture was partitioned between EtOAc and 2M HCl. The organic layer was separated, washed with brine, dried ($MgSO_4$) 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.
^{1}H NMR (MeOH-d_4) 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-1*H*-purin-1-yl)pentanoic acid



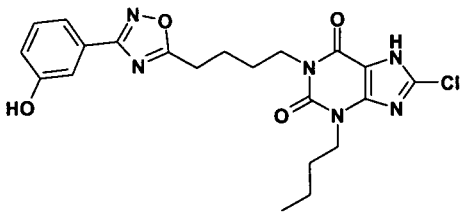
A mixture of ethyl 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate (2.8g, 7.55mmol), LiOH (542mg, 22.7mmol), water (2.5ml) and methanol (50ml) was stirred at rt for for 60h. The mixture was portioned between water and EtOAc and the pH of the aqueous phase adjusted to pH 4-5. The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated to give the title compound as a white solid (2.18g).
LC/MS: m/z 343 $[MH]^+$, RT 2.69min.

Example 178 : 8-Chloro-3-pentyl-1-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione



A mixture of methyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-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 ($MgSO_4$) 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-d_6) 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).

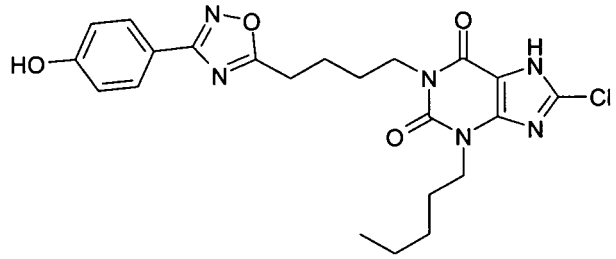
Example 179: 3-Butyl-8-chloro-1-{4-[3-(3-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione



A mixture of ethyl 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-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

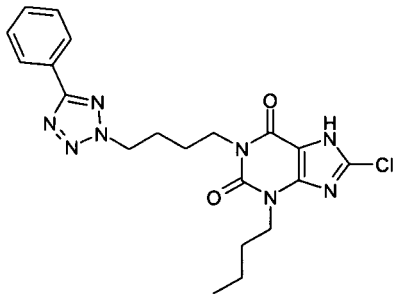
175°C for 30min. After cooling the reaction was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, concentrated and purified by the MDAP. The title compound was obtained as an off-white solid (20mg, 32%).
LC/MS: m/z 459 $[MH]^+$, RT 3.3min.

Example 180 : 8-Chloro-1-{4-[3-(4-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-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%).
LC/MS: m/z 473 $[MH]^+$,RT 3.5min.

Example 181: 3-Butyl-8-chloro-1-[4-(5-phenyl-2*H*-tetrazol-2-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione



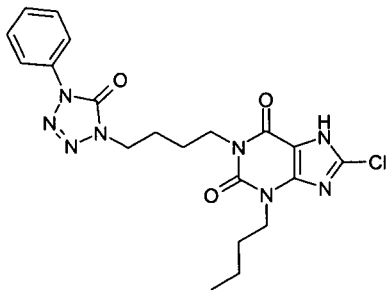
A mixture of 4-[3-butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]butyl methanesulfonate (50mg, 0.12mmol), Cs_2CO_3 (45mg, 0.14mmol) and DMF (3ml) was treated with 5-phenyl-1*H*-tetrazole (20mg, 0.14mmol) and stirred for 60h at 50°C. After cooling, the mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (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 NH_2-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.

^{1}H NMR (DMSO-d_6) δ: 0.86 (t, 3H, J = 7Hz), 1.26 (m, 2H), 1.59 (m, 4H), 1.97 (m, 2H), 3.90 (m, 4H), 4.76 (t, 2H, J = 7Hz), 7.54 (m, 3H), 8.02 (m, 2H), 14.4 (br s, 1H).

Example 182 : 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



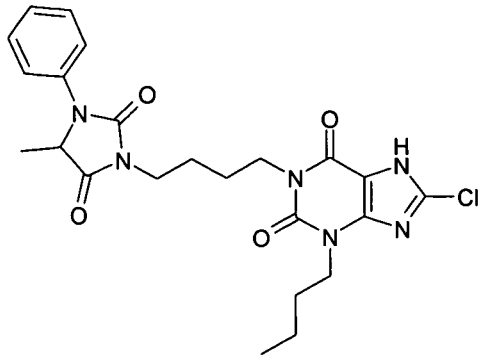
A mixture of 4-[3-butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]butyl methanesulfonate (50mg, 0.12mmol), Cs_2CO_3 (45mg, 0.14mmol) and DMF (3ml) was treated with 1-phenyl-1,2-dihydro-5*H*-tetrazol-5-one (23mg, 0.14mmol) and stirred for 60h at 50°C. After cooling, the mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (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.

^{1}H NMR (DMSO-d_6) 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).

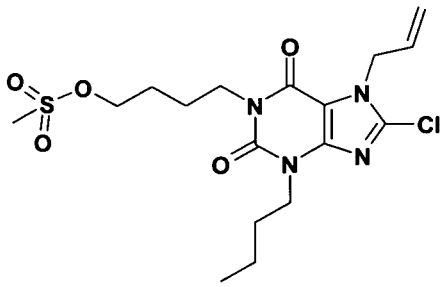
Example 183 : 3-Butyl-8-chloro-1-[4-(4-methyl-2,5-dioxo-3-phenyl-1-imidazolidinyl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione

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



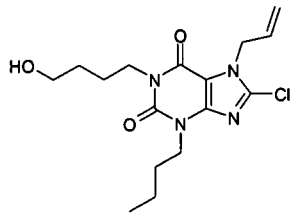
A mixture of 4-[3-butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]butyl methanesulfonate (88mg, 0.20mmol), Cs_2CO_3 (80mg, 0.24mmol) and DMF (2ml) was treated with 5-methyl-1-phenyl-2,4-imidazolidinedione (46mg, 0.24mmol) and stirred for 18h at 70°C. After cooling, the mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (25mg, 0.022mmol) was added and the mixture degassed once more. Morpholine (174µL, 2.0mmol) was added and the mixture was stirred under nitrogen for 5h, 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 SPE with the product eluting with 2% AcOH/MeOH. Further purification by MDAP gave the title compound as a solid (70mg, 71%).
LC/MS: m/z 487 $[MH]^+$, RT 3.2min.

b) 4-[3-Butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]butyl methanesulfonate



A solution of 3-butyl-8-chloro-1-(4-hydroxybutyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.30g, 3.66mmol) in DCM (10ml) was treated with triethylamine (0.77ml, 5.50mmol) followed by portionwise addition of methanesulfonic anhydride (702mg, 4.03mmol). CARE, effervescence. The reaction mixture was stirred at rt for 10min then partitioned between sat. $NaHCO_3$ (aq) solution and DCM. The organic layer was separated and washed with 1M HCl (aq) and then brine. It was dried ($MgSO_4$) and concentrated, giving the title compound as a viscous oil (1.60g, quant.).
LC/MS: m/z 433 $[MH]^+$, RT 3.3min.

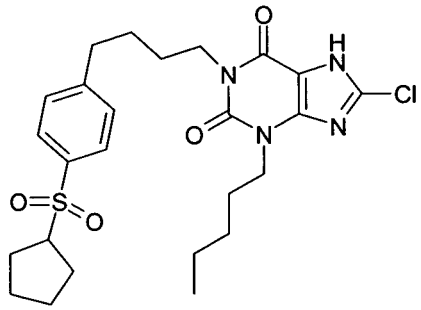
c) 3-Butyl-8-chloro-1-(4-hydroxybutyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



A stirred solution of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (5.0g, 17.7mmol) in DMF (100ml) was treated with Cs_2CO_3 (6.3g, 19.5mmol) and 4-bromo-1-butanol (3.0ml, 21.2mmol). The mixture was heated at 50°C for 5h then partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated, giving a yellow solid. Purification by silica SPE (EtOAc/cyclohexane mixtures as the eluent) and then by the Companion™ system (IPA/DCM mixtures as the eluent) gave the title compound as a colourless oil (1.35g, 21%).

LC/MS: m/z 355 $[MH]^+$, RT 2.9min.

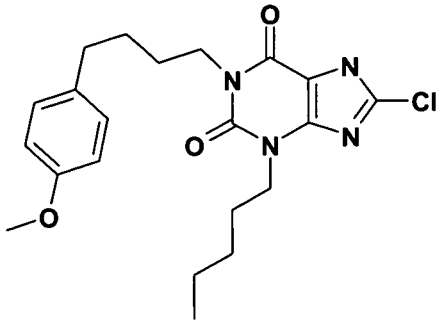
Example 184 : 8-Chloro-1-{4-[4-(cyclopentylsulfonyl)phenyl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



8-Chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.34mmol) was dissolved in DMF (1ml) and sequentially treated with 4-[4-(cyclopentylsulfonyl)phenyl]-1-butanol (105mg, 0.37mmol), PPh_3 (404µl of a 1M solution in DMF) and DBAD (404µl of a 1M solution in DMF). After stirring for 24h under nitrogen, the mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (39mg, 0.034mmol) was added and the mixture degassed once more. Morpholine (297µl, 3.4mmol) was added and the mixture was stirred under nitrogen for 63h, 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 SPE with the product eluting with 2% AcOH/MeOH. The product was further purified by MDAP giving the title compound as a beige solid (5mg, 3%).

LC/MS: m/z 521 $[MH]^+$, RT 3.7min.

Example 185 : 8-Chloro-1-{4-[4-(methyloxy)phenyl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 4-(4-bromobutyl)phenyl methyl ether (88mg, 0.36mmol) in DMF (3ml) was reacted with 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (90mg, 0.30mmol) and Cs_2CO_3 (109mg, 0.33mmol) for 5h at 50°C. The mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (35mg, 0.030mmol) was added and the mixture degassed once more. Morpholine (0.26ml, 3.0mmol) was added and the mixture was stirred under nitrogen for 3h. Another aliquot of $Pd(PPh_3)_4$ (35mg, 0.030mmol) was added and left for a further 3h. The mixture 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, giving a yellow residue. MeOH was added and then passed down an aminopropyl SPE with the product eluting with 3% AcOH/MeOH. The product was further purified by MDAP giving the title compound as a solid (2mg, 1.5%).

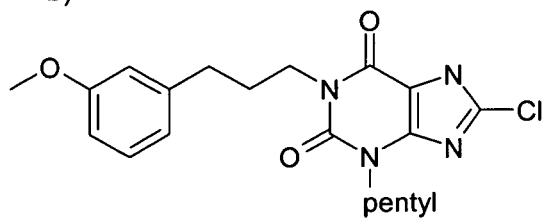
LC/MS: m/z 419 $[MH]^+$, RT 3.7min.

^1H NMR; (MeOH-d_4) δ: 0.90 (t, 3H, J = 7Hz), 1.28-1.40 (m, 4H), 1.57-1.75 (m, 6H), 2.57 (t, 2H, J = 7Hz), 3.73 (s, 3H), 3.97-4.02 (4H, m), 6.77 (m, 2H), 7.06 (m, 2H).

Example 186: 8-Chloro-3-pentyl-1-{3-[3-(methyloxy)phenyl]propyl}-3,7-dihydro-1H-purine-2,6-dione

a) 8-Chloro-3-pentyl-1-{3-[3-(methyloxy)phenyl]propyl}-3,7-dihydro-1H-purine-2,6-dione

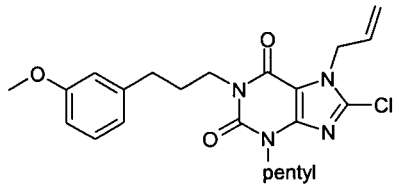
b)



8-Chloro-3-pentyl-1-{3-[3-(methyloxy)phenyl]propyl}-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (2.94g) was dissolved in anhydrous THF (40ml). The solution was

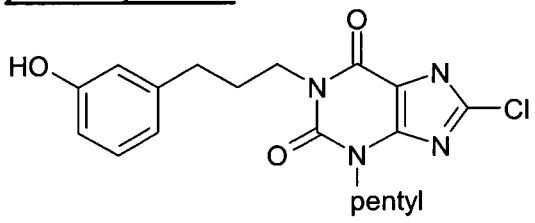
degassed using a nitrogen/vacuum purge 6 times. Tetrakis(triphenylphosphine) palladium (0.66g) was added followed by morpholine (5ml). After stirring for 18hr, the reaction mixture was diluted with EtOAc and was washed with 1N HCl and brine (x2), dried ($MgSO_4$) and evaporated *in vacuo*. This crude material was purified on an aminopropyl SPE (70g) eluting with MeOH then MeOH containing 3% AcOH to give the title compound as a pale yellow solid (1.56g).
LC/MS: m/z 405 $[MH]^+$, RT 3.51min.

b) 8-Chloro-3-pentyl-1-{3-[3-(methyloxy)phenyl]propyl}-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



8-Chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.76g, 5.94mmol) and 3-[3-(methyloxy)phenyl]-1-propanol (1.00g, 6.04mmol) were dissolved in anhydrous THF (50ml) under an atmosphere of nitrogen. After 5min triphenylphosphine (1.87g, 7.12mmol) was added. After a further 5min di-tert-butyl azodicarboxylate (1.64g, 7.1mmol) was added. The solution was stirred for 20h at rt. The cloudy solution was concentrated *in vacuo* and purified on a 50g Silica II SPE (IST) using a Biotage FlashMaster™ Personal, eluting with cyclohexane /EtOAc 5:1 the appropriate fractions were concentrated *in vacuo* to give the title compound as a pale cream oil containing minor impurities(2.94g).
LC/MS:, m/z 445 $[MH]^+$, RT 3.88min.

Example 187 : 8-Chloro-1-[3-(3-hydroxyphenyl)propyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



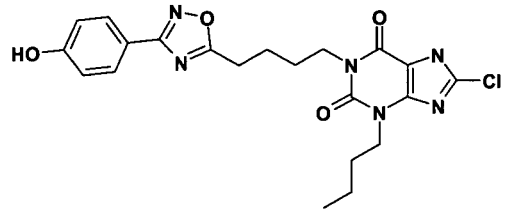
To a suspension of 8-chloro-3-pentyl-1-{3-[3-(methyloxy)phenyl]propyl}-3,7-dihydro-1H-purine-2,6-dione (1.52g, 3.86mmol) in anhydrous DCM (40ml) at -73°C was slowly added 1N borontribromide in DCM (4.6ml). The reaction mixture was stirred at -70°C for 2hours and then at rt for 96h. The reaction mixture was cooled in ice, and water (6.8ml) was added slowly. The reaction mixture was then diluted with EtOAc and water, and the organic phase was washed with saturated, sodium hydrogen carbonate (x3) and brine then dried ($MgSO_4$) and evaporated *in vacuo*. A portion of this crude material

(90mg) was purified by MDAP to give the title compound after freeze drying as a white solid (40mg).

LC/MS:, m/z 391 $[MH]^+$, RT 3.43min.

^1H NMR (DMSO-d_6) δ: 0.85 (t, 3H, J = 7Hz); 1.27 (m, 4H); 1.63 (m, 2H); 1.80 (m, 2H); 2.50 (m, 2H); 3.89 (m, 4H); 6.57 (m, 3H); 7.02 (t, 1H, J = 8Hz); 9.22 (s, 1H); 14.39 (s, 1H)

Example 188: 3-butyl-8-chloro-1-{4-[3-(4-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione

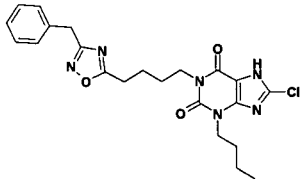


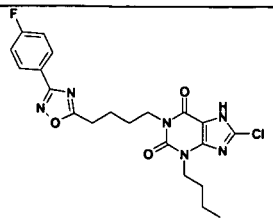
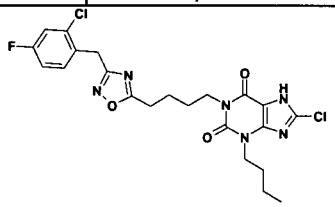
A stirred solution of 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (100mg, 0.29mmol) in DMF (4ml) was treated with CDI (52mg, 0.32mmol). After 1h, *N*,4-dihydroxybenzenecarboximidamide was added and the mixture heated at 100°C for 6h. On cooling, the reaction mixture 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.

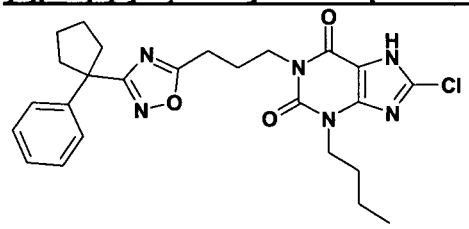
The following compounds (**Table 10**) were prepared using a method analogous to that for **Example 177**, using the appropriate amidoxime.

Table 10

Example	Structure	Yield (mg)	LC/MS
189	 3-butyl-8-chloro-1-{4-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	48.4	m/z 457 $[MH]^+$ RT 3.56min

190	 3-butyl-8-chloro-1-{4-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	35.8	m/z 461 $[MH]^+$ RT 3.74min
191	 3-butyl-8-chloro-1-(4-{3-[(2-chloro-4-fluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}butyl)-3,7-dihydro-1*H*-purine-2,6-dione	48.2	m/z 509 $[MH]^+$ RT 3.74min

Example 192: 3-Butyl-8-chloro-1-{3-[3-(1-phenylcyclopentyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

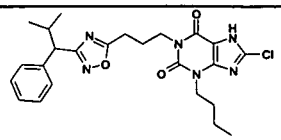
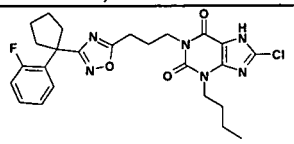
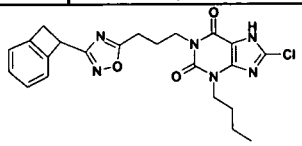
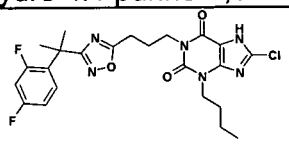
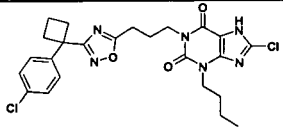
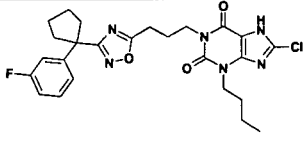


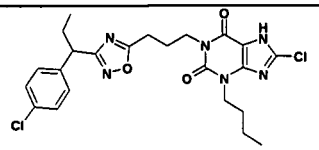
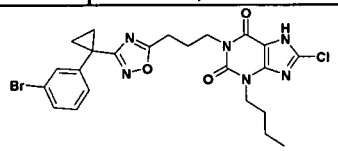
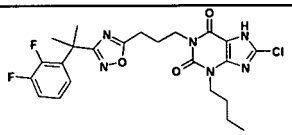
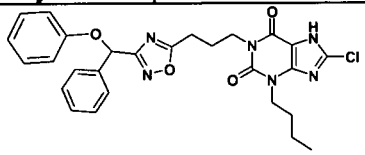
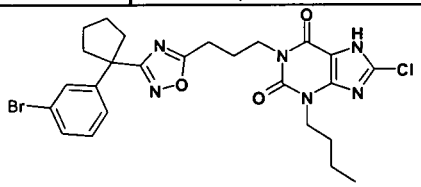
Ethyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butanoate (53mg, 0.15mmol), *N*-hydroxy-1-phenylcyclopentanecarboximidamide (34mg, 0.165mmol) and sodium methoxide (20mg, 0.37mmol) in dry MeOH (0.75ml) were heated at 140°C in the microwave reactor for 10min. The mixture was then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

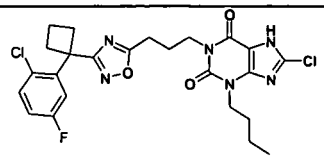
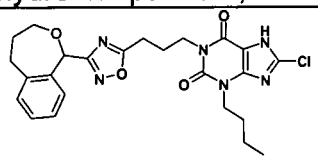
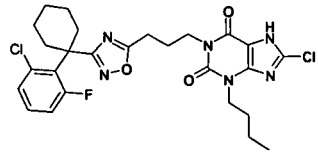
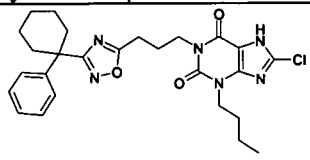
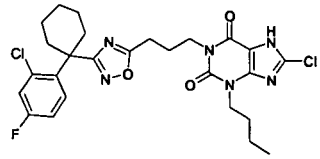
The following compounds (**Table 11**) were prepared using a method analogous to that for **Example 192**, using the appropriate amidoxime [with the exception that for **Examples 210**, **211** and **212** EtOH was used as reaction solvent; for **Examples 210**, **211** and **212** the reactions were worked up by adding 2M HCl until neutral and evaporating the solvent; for **Example 206** the scale was 32mg of starting ethyl ester; **Example 208** the scale was 42mg of starting ethyl ester].

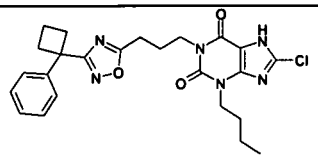
Table 11

Example	Structure	Yield	LC/MS

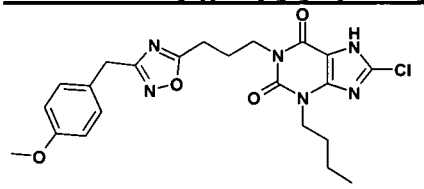
		(mg)	
193	 3-butyl-8-chloro-1-{3-[3-(2-methyl-1-phenylpropyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	17.4	m/z 485 $[MH]^+$ RT 3.74min
194	 3-butyl-8-chloro-1-(3-{3-[1-(2-fluorophenyl)cyclopentyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	33.7	m/z 515 $[MH]^+$ RT 3.73min
195	 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-1*H*-purine-2,6-dione	28.8	m/z 455 $[MH]^+$ RT 3.43min
196	 3-butyl-8-chloro-1-(3-{3-[1-(2,4-difluorophenyl)-1-methylethyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	33.4	m/z 507 $[MH]^+$ RT 3.59min
197	 3-butyl-8-chloro-1-(3-{3-[1-(4-chlorophenyl)cyclobutyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	33.8	m/z 517 $[MH]^+$ RT 3.85min
198	 3-butyl-8-chloro-1-(3-{3-[1-(3-	34.2	m/z 515 $[MH]^+$ RT 3.80min

	fluorophenyl)cyclopentyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione		
199	 3-butyl-8-chloro-1-(3-{3-[1-(4-chlorophenyl)propyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	16.3	m/z 505 $[MH]^+$ RT 3.80min
200	 1-(3-{3-[1-(3-bromophenyl)cyclopropyl]-1,2,4-oxadiazol-5-yl}propyl)-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione	34.9	m/z 549 $[MH]^+$ RT 3.72min
201	 3-butyl-8-chloro-1-(3-{3-[1-(2,3-difluorophenyl)-1-methylethyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	30.4	m/z 507 $[MH]^+$ RT 3.59min
202	 3-butyl-8-chloro-1-(3-{3-[phenoxy(phenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	3	m/z 535$[MH]^+$ RT 3.69min.
203	 1-(3-{3-[1-(3-bromophenyl)cyclopentyl]-1,2,4-oxadiazol-5-yl}propyl)-3-butyl-8-	38.8	m/z 577$[MH]^+$ RT 3.99 min.

	chloro-3,7-dihydro-1H-purine-2,6-dione		
204	 3-butyl-8-chloro-1-(3-{3-[1-(2-chloro-5-fluorophenyl)cyclobutyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	41.4	m/z 535[MH]$^+$ RT 3.79 min.
205	 3-butyl-8-chloro-1-{3-[3-(1,3,4,5-tetrahydro-2-benzoxepin-1-yl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	27.4	m/z 499[MH]$^+$ RT 3.42 min.
206	 3-butyl-8-chloro-1-(3-{3-[1-(2-chloro-6-fluorophenyl)cyclohexyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	12.9	m/z 563[MH]$^+$ RT 4.02min.
207	 3-butyl-8-chloro-1-{3-[3-(1-phenylcyclohexyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	34.8	m/z 511[MH]$^+$ RT 3.88min.
208	 3-butyl-8-chloro-1-(3-{3-[1-(2-chloro-4-fluorophenyl)cyclohexyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-	19	m/z 563[MH]$^+$ RT 4.00min.

	dihydro-1H-purine-2,6-dione		
209	 3-butyl-8-chloro-1-{3-[3-(1-phenylcyclobutyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	30.5	m/z 483[MH]$^+$ RT 3.64min.

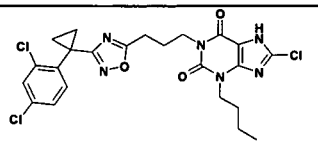
Example 210: 3-Butyl-8-chloro-1-[3-(3-{[4-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione

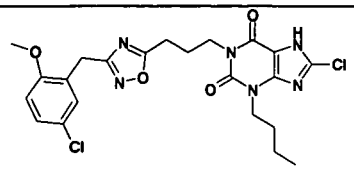
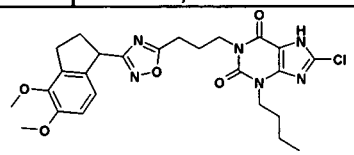
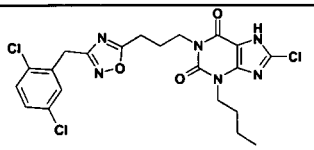
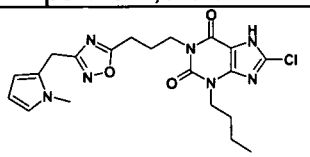
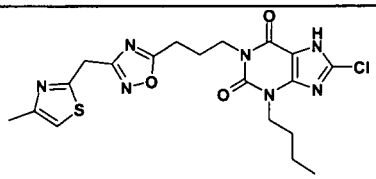


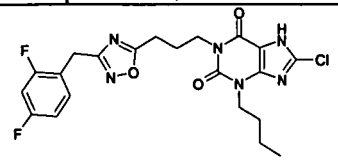
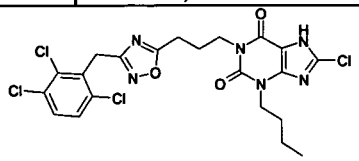
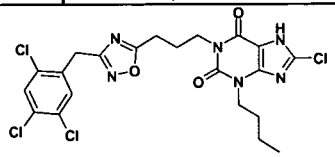
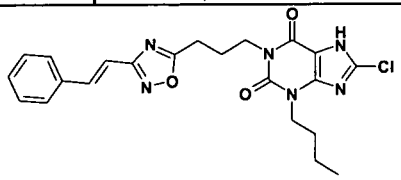
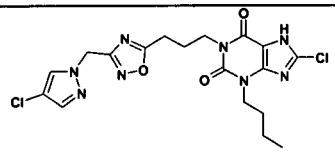
Prepared using a method analogous to that used for **Example 93**, except an additional final purification step using HPLC was employed. Yield 6.0mg.
LC/MS: m/z 473 [MH]$^+$, RT 3.27min.

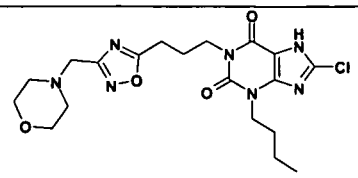
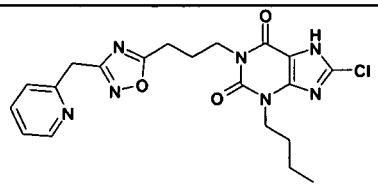
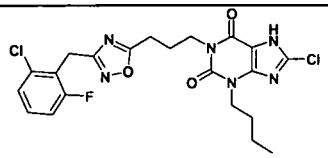
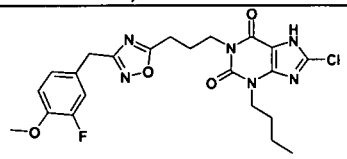
The following compounds (**Table 12**) were prepared using a method analogous to that for **Example 96**, using the appropriate amidoxime [with the exception that for **Example 211** the scale was 0.12mmol instead of 0.15mmol; for **Example 216** the crude product was stirred in EtOH (0.75ml) with 2M NaOH (0.5ml) overnight prior to the usual EtOAc/HCl workup and MDAP; **Example 218** was isolated as an impurity from the preparation of **Example 219** and was separated from it by HPLC; for **Examples 221, 222** and **223** the pH during aqueous workup was adjusted to approximately 5 prior to extraction; additionally **Example 223** was further purified by silica SPE (2g, DCM-MeOH 40:1then 20:1) after MDAP].

Table 12

Example	Structure	Yield (mg)	LC/MS
211	 3-butyl-8-chloro-1-(3-{3-[1-(2,4-	23.8	m/z 537 [MH]$^+$ RT 3.83min

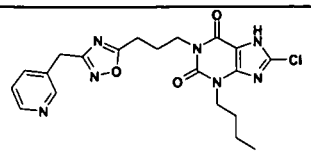
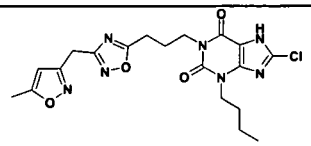
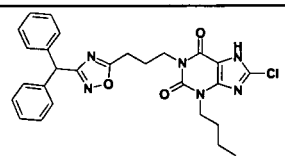
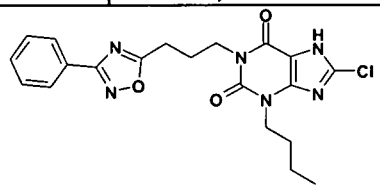
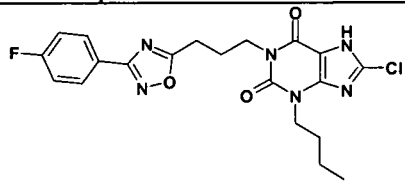
	dichlorophenyl)cyclopropyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione		
212	 3-butyl-8-chloro-1-[3-(3-{[5-chloro-2-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	39.5	m/z 507 $[MH]^+$ RT 3.58min
213	 1-(3-{3-[4,5-bis(methyloxy)-2,3-dihydro-1*H*-inden-1-yl]-1,2,4-oxadiazol-5-yl}propyl)-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione	35.8	m/z 529 $[MH]^+$ RT 3.41min
214	 3-butyl-8-chloro-1-(3-{3-[(2,5-dichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	9.7	m/z 511 $[MH]^+$ RT 3.63min
215	 3-butyl-8-chloro-1-(3-{3-[(1-methyl-1*H*-pyrrol-2-yl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	18.0	m/z 446 $[MH]^+$ RT 3.15min
216	 3-butyl-8-chloro-1-(3-{3-[(4-methyl-1,3-thiazol-2-yl)methyl]-1,2,4-	15.5	m/z 464 $[MH]^+$ RT 2.94min

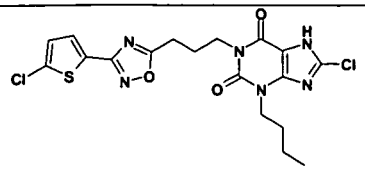
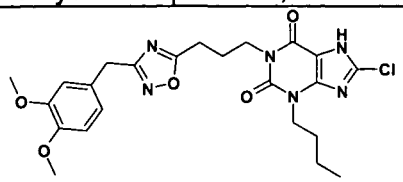
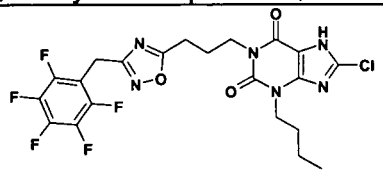
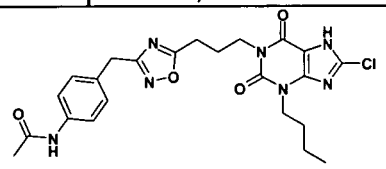
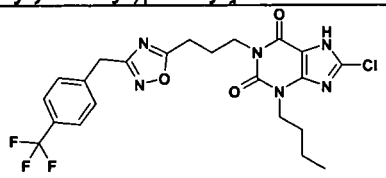
	oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione		
217	 3-butyl-8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	33.5	m/z 479 $[MH]^+$ RT 3.35min
218	 3-butyl-8-chloro-1-(3-{3-[(2,3,6-trichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	4.6	m/z 545 $[MH]^+$ RT 3.71min
219	 3-butyl-8-chloro-1-(3-{3-[(2,4,5-trichlorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	17.7	m/z 545 $[MH]^+$ RT 3.79min
220	 3-butyl-8-chloro-1-(3-{3-[(*E*)-2-phenylethenyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	17.8	m/z 455 $[MH]^+$ RT 3.49min
221	 3-butyl-8-chloro-1-(3-{3-[(4-chloro-1*H*-pyrazol-1-yl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	39.2	m/z 467 $[MH]^+$ RT 3.24min

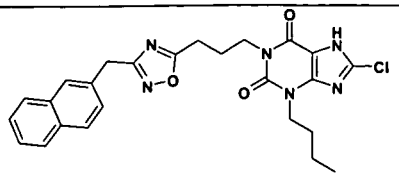
222	 3-butyl-8-chloro-1-{3-[3-(4-morpholinylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	27.0	m/z 452 $[MH]^+$ RT 2.56min
223	 3-butyl-8-chloro-1-{3-[3-(2-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	23.6	m/z 444 $[MH]^+$ RT 2.92min
224	 3-butyl-8-chloro-1-(3-{3-[(2-chloro-6-fluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	38.8	m/z 495$[MH]^+$ RT 3.43min
225	 3-butyl-8-chloro-1-[3-(3-{[3-fluoro-4-(methyloxy)phenyl]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 13**) were prepared using a method analogous to that for **Example 114**, using the appropriate amidoxime [with the exception that **Example 226** was conducted on half the scale of **Example 114** and during workup the aqueous phase was neutralised prior to extraction; **Example 227** was conducted on half the scale of **Example 114** and the crude product stirred with 2M NaOH (0.5ml) in EtOH (1ml) for 5h prior to workup and MDAP; for **Example 232** 0.185ml (0.5mmol) of 21% NaOEt was used].

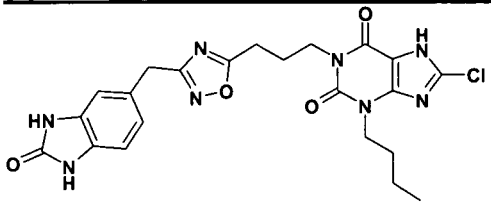
Table 13

Example	Structure	Yield (mg)	LC/MS
226	 3-butyl-8-chloro-1-{3-[3-(3-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	20	m/z 444 $[MH]^+$ RT 2.74min
227	 3-butyl-8-chloro-1-(3-{3-[(5-methyl-3-isoxazolyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	7.2	m/z 448 $[MH]^+$ RT 3.13min
228	 3-butyl-8-chloro-1-{3-[3-(diphenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	47.4	m/z 519 $[MH]^+$ RT 3.71min
229	 3-butyl-8-chloro-1-[3-(3-phenyl-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	36.7	m/z 429 $[MH]^+$ RT 3.36min
230	 3-butyl-8-chloro-1-{3-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	41.1	m/z 447 $[MH]^+$ RT 3.42min

231	 3-butyl-8-chloro-1-{3-[3-(5-chloro-2-thienyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	36.7	m/z 469 $[MH]^+$ RT 3.60min
232	 1-[3-(3-{[3,4-bis(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione	47.0	m/z 503 $[MH]^+$ RT 3.14min
233	 3-butyl-8-chloro-1-(3-{3-[(pentafluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	29.2	m/z 533 $[MH]^+$ RT 3.62min
234	 *N*-[4-({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]acetamide	29.8	m/z 500 $[MH]^+$ RT 3.01min
235	 3-butyl-8-chloro-1-[3-(3-{[4-(trifluoromethyl)phenyl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	37.7	m/z 511 $[MH]^+$ RT 3.65min

236	 3-butyl-8-chloro-1-{3-[3-(2-naphthalenylmethyl)-1,2,4-oxadiazol-5-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	47.5	m/z 493 $[MH]^+$ RT 3.69min

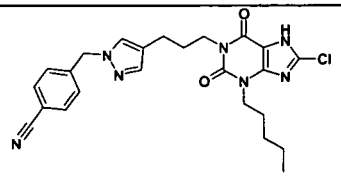
Example 237: 3-Butyl-8-chloro-1-(3-{3-[(2-oxo-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione

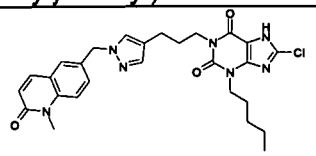
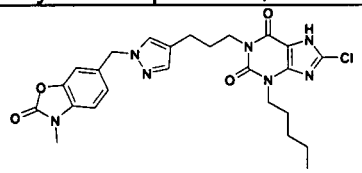
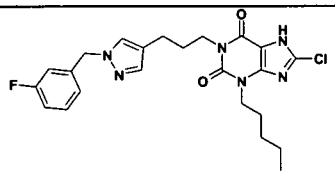
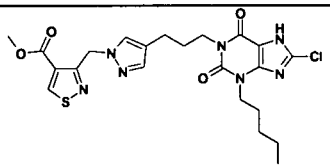


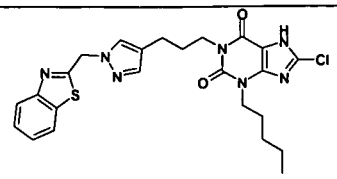
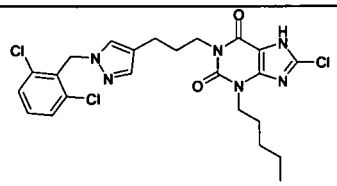
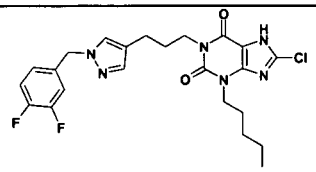
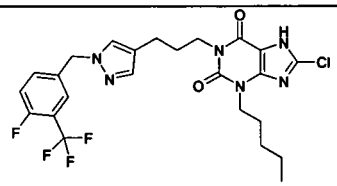
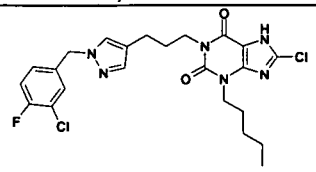
Synthesised by a method analogous to that for **Example 126** with the exception that a further 2 equivalents of 21% sodium ethoxide (0.11ml) was used, the extra heating time was 20min. and the product was isolated by filtration followed by trituration with hot MeOH. Yield 14.5mg.
LC/MS: m/z 499 $[MH]^+$, RT 2.78min.

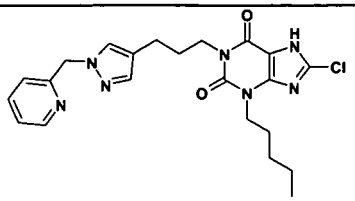
The following compounds (**Table 14**) were prepared by a method analogous to that for **Example 18** [with the exception that **Examples 238-243** were all synthesised on a scale starting from 50mg of 8-chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione; **Examples 241**, **243**, **245**, **246** and **247** were additionally purified by MDAP following aminopropyl SPE; **Example 242** was additionally purified by recrystallisation from MeOH following aminopropyl SPE; for **Example 248**, 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 241** solids which precipitated during workup were combined with the EtOAc extracts prior to SPE].

Table 14

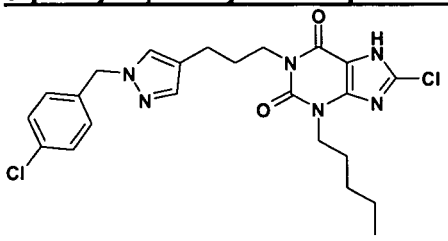
Example	Structure	Yield (mg)	LC/MS
238	 4-({4-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-	36.0	m/z 480 $[MH]^+$ RT 3.24min

	purin-1-yl)propyl]-1*H*-pyrazol-1-yl}methyl)benzonitrile		
239	 8-chloro-1-(3-{1-[(1-methyl-2-oxo-1,2-dihydro-6-quinolinyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	7.6	m/z 536 $[MH]^+$ RT 3.03min
240	 8-chloro-1-(3-{1-[(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	34.0	m/z 526 $[MH]^+$ RT 3.11min
241	 8-chloro-1-(3-{1-[(3-fluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	26.2	m/z 473 $[MH]^+$ RT 3.38min
242	 methyl 3-({4-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]-1*H*-pyrazol-1-yl}methyl)-4-isothiazolecarboxylate	16.2	m/z 520 $[MH]^+$ RT 3.12min

243	 1-{3-[1-(1,3-benzothiazol-2-ylmethyl)-1*H*-pyrazol-4-yl]propyl}-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	21.0	m/z 512 $[MH]^+$ RT 3.36min
244	 8-chloro-1-(3-{1-[(2,6-dichlorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	65.0	m/z 523, 525 [Cl isotopes MH^+] RT 3.77min
245	 8-chloro-1-(3-{1-[(3,4-difluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	35.0	m/z 491 $[MH]^+$ RT 3.61min
246	 8-chloro-1-[3-(1-{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}-1*H*-pyrazol-4-yl)propyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	17.0	m/z 541 $[MH]^+$ RT 3.76min
247	 8-chloro-1-(3-{1-[(3-chloro-4-	27.0	m/z 507 $[MH]^+$ RT 3.73min

	fluorophenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione		
248	 8-chloro-3-pentyl-1-{3-[1-(2-pyridinylmethyl)-1*H*-pyrazol-4-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	11.4	m/z 456 $[MH]^+$ RT 3.13min

Example 249: 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

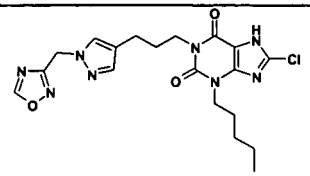
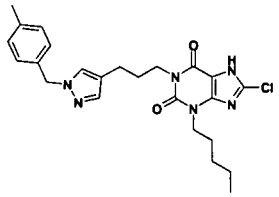
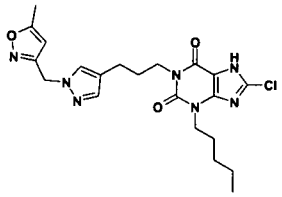
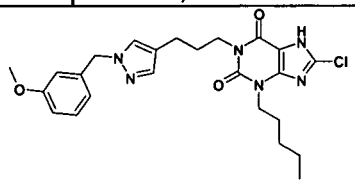
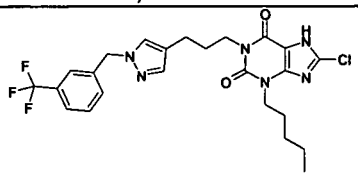


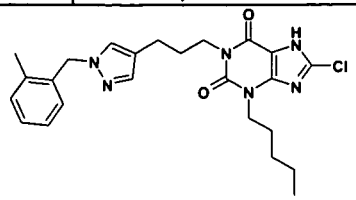
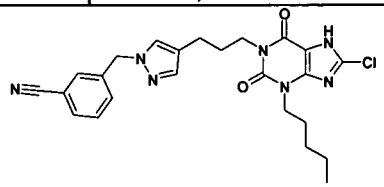
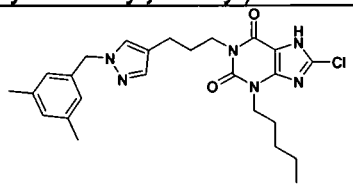
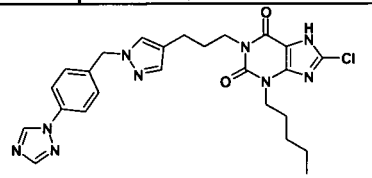
8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione (50mg, 0.123mmol) in dry DMF (1.5ml) was stirred with sodium carbonate (75mg, 0.708mmol) and 4-chlorobenzyl bromide (150mg, 0.73mmol) at 40°C for 18h. The mixture was partitioned between EtOAc and water,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

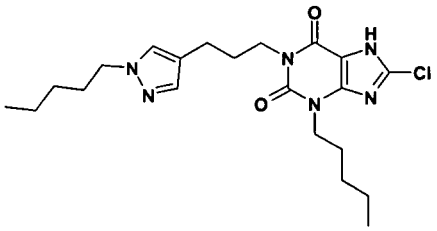
The following compounds (**Table 15**) were prepared by a method analogous to that for **Example 23** [with the exception that for **Example 250** a second portion of $Pd(PPh_3)_4$ was added after 5h, stirring was continued overnight, and final purification was achieved by HPLC; for **Example 252** required additional purification by MDAP; **Example 257** required additional purification by recrystallisation from MeOH; **Example 258** required additional purification by trituration with MeOH].

Table 15

Example	Structure	Yield (mg)	LC/MS
250	 8-chloro-1-{3-[1-(1,2,4-oxadiazol-3-ylmethyl)-1*H*-pyrazol-4-yl]propyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	7.3	m/z 447 $[MH]^+$ RT 3.06min
251	 8-chloro-1-(3-{1-[(4-methylphenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	23.7	m/z 469 $[MH]^+$ RT 3.49min
252	 8-chloro-1-(3-{1-[(5-methyl-3-isoxazolyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	29.0	m/z 460 $[MH]^+$ RT 3.10min
253	 8-chloro-1-[3-(1-{[3-(methyloxy)phenyl]methyl}-1*H*-pyrazol-4-yl)propyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	56.0	m/z 485 $[MH]^+$ RT 3.41min
254	 8-chloro-3-pentyl-1-[3-(1-{[3-(trifluoromethyl)phenyl]methyl}-1*H*-	47.0	m/z 523 $[MH]^+$ RT 3.61min

	pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione		
255	 8-chloro-1-(3-{1-[(2-methylphenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	44.0	m/z 469 $[MH]^+$ RT 3.54min
256	 3-({4-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]-1*H*-pyrazol-1-yl}methyl)benzonitrile	51.0	m/z 480 $[MH]^+$ RT 3.32min
257	 8-chloro-1-(3-{1-[(3,5-dimethylphenyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	36.7	m/z 483 $[MH]^+$ RT 3.66min
258	 8-chloro-3-pentyl-1-[3-(1-{[4-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl}-1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	21.2	m/z 522 $[MH]^+$ RT 3.09min

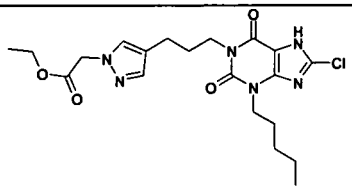
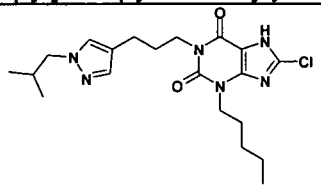
Example 259: 8-Chloro-3-pentyl-1-[3-(1-pentyl-1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione

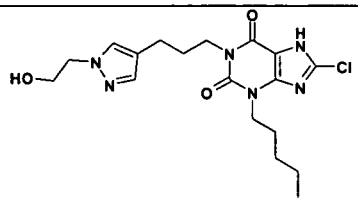
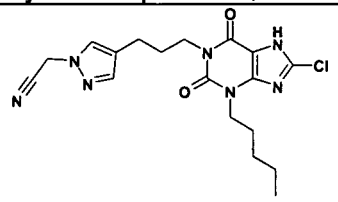


8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione (61mg, 0.15mmol) and sodium carbonate (32mg, 0.3mmol) in dry DMF (1.5ml) was heated with 1-iodopentane (238mg, 1.2mmol) in the microwave reactor at 120°C for 25min. After cooling the mixture was degassed and stirred with tetrakis(triphenylphosphine)palladium(0) (40mg, 0.0346mmol) and morpholine (0.2ml) for 7h. A further 20mg of $Pd(PPh_3)_4$ was then added and stirring continued overnight. The mixture was stirred with EtOAc and 2M HCl for 1h and the organic phase separated and evaporated. The product was purified by aminopropyl SPE (5g) washing with MeOH-THF (1:1), then MeOH, and eluting the product with DCM-MeOH (1:1) containing 5% added AcOH to give the title compound (25mg).
LC/MS: m/z 435 $[MH]^+$, RT 3.65min.

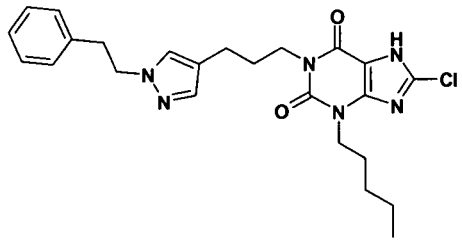
The following compounds (**Table 16**) were prepared by a method analogous to that for **Example 259** [with the exception that the compounds were purified by MDAP and for **Example 261** the total heating time in the microwave reactor was 50min].

Table 16

Example	Structure	Yield (mg)	LC/MS
260	 ethyl {4-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]-1*H*-pyrazol-1-yl}acetate	15.1	m/z 451 $[MH]^+$ RT 3.21min
261	 8-chloro-1-{3-[1-(2-methylpropyl)-1*H*-pyrazol-4-yl]propyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	1.34	m/z 421 $[MH]^+$ RT 3.48min

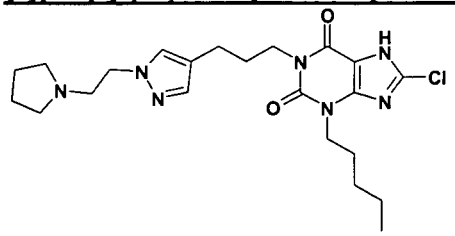
262	 8-chloro-1-{3-[1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]propyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	0.32	m/z 409 $[MH]^+$ RT 2.79min
263	 {4-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]-1*H*-pyrazol-1-yl}acetonitrile	9.6	m/z 404 $[MH]^+$ RT 3.12min

Example 264: 8-Chloro-3-pentyl-1-{3-[1-(2-phenylethyl)-1*H*-pyrazol-4-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



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 (81mg, 0.2mmol), sodium carbonate (42mg, 0.4mmol) and (2-iodoethyl)benzene (0.174ml, 1.2mmol) were heated together in dry DMF (1ml) under microwave irradiation at 120°C for 25min. Tetrakis(triphenylphosphine)palladium(0) (46mg, 0.04mmol) and morpholine (0.174ml) were added and the mixture stirred for 6h. Further quantities (46mg and 0.174ml) of these reagents were added and stirring continued for a further 60h. Workup and purification as for the examples in **Table 16** gave the title compound (15.5mg).
LC/MS: m/z 469 $[MH]^+$, RT 3.60min.

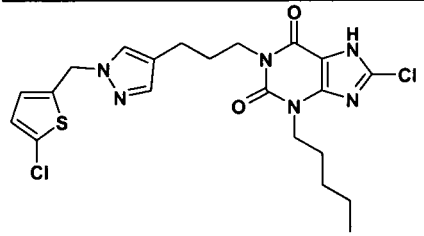
Example 265 : 8-Chloro-3-pentyl-1-(3-{1-[2-(1-pyrrolidinyl)ethyl]-1*H*-pyrazol-4-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione



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 (61mg, 0.15mmol), sodium carbonate (159mg, 1.5mmol) and 1-(2-chloroethyl)pyrrolidine hydrochloride (127mg, 0.75mmol) were heated together in dry DMF (2ml) at 80°C for 65h. Tetrabutylammonium iodide (55mg, 0.15mmol) was added and heating continued for another 18h. A further quantity of 1-(2-chloroethyl)pyrrolidine hydrochloride (127mg, 0.75mmol) was added and the mixture heated by microwaves at 120°C, then a 3rd aliquot of 1-(2-chloroethyl)pyrrolidine hydrochloride (100mg) was added, with a further 25min at 120°C in the microwave. The mixture was partitioned between water and EtOAc, the organic phase separated, washed with brine and evaporated. This material was partitioned between EtOAc and 2M HCl. The separated aqueous phase was basified to pH9, saturated with NaCl and extracted with EtOAc (x2). The extracts were evaporated and the residue (28mg) stirred in dry degassed DMF (1.5ml) with tetrakis(triphenylphosphine)palladium(0) (50mg) and morpholine (0.2ml) for 6h. The mixture was partitioned between EtOAc and 2M HCl, the aqueous phase filtered, extracted twice with EtOAc and evaporated to dryness. The residue was purified by the aminopropyl SPE procedure, followed by MDAP to yield the title compound (1.9mg).

LC/MS: m/z 462 $[MH]^+$, RT 2.46min.

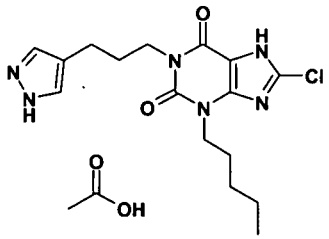
Example 266 : 8-Chloro-1-(3-{1-[(5-chloro-2-thienyl)methyl]-1*H*-pyrazol-4-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



To 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 (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 and morpholine (0.13ml) and tetrakis(triphenylphosphine)palladium(0) (35mg) added and stirring continued for 6h. Further quantities (0.2ml morpholine, 50mg $Pd(PPh_3)_4$) 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).

LC/MS: m/z 495 $[MH]^+$, RT 3.68min.

Example 267 : 8-Chloro-3-pentyl-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione acetate

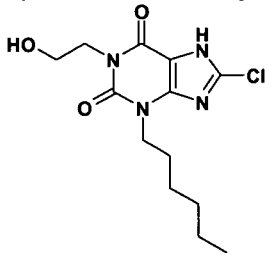


8-Chloro-3-pentyl-7-(2-propen-1-yl)-1-[3-(1*H*-pyrazol-4-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione (50mg, 0.124mmol) in dry degassed THF (1.5ml) was stirred with tetrakis(triphenylphosphine)palladium(0) (29mg, 0.025mmol) and morpholine (0.108ml) under nitrogen for 5h. The mixture was partitioned between EtOAc and 0.5M citric acid and the organic phase separated. Two further EtOAc extractions were performed and the combined organics were evaporated and the product purified by aminopropyl SPE (2g), loading and washing with THF-MeOH (1:1) then washing with MeOH and eluting with DCM-MeOH (1:1) containing 5% AcOH. Yield 28.3mg.

LC/MS: m/z 365 $[MH]^+$, RT 2.89min.

Example 268 : 8-Chloro-3-hexyl-1-(2-hydroxyethyl)-3,7-dihydro-1*H*-purine-2,6-dione

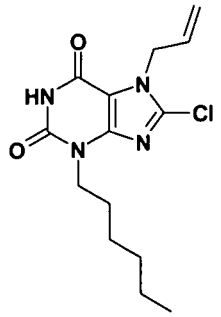
a) 8-Chloro-3-hexyl-1-(2-hydroxyethyl)-3,7-dihydro-1*H*-purine-2,6-dione



8-Chloro-3-hexyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.322mmol), cesium carbonate (126mg, 0.387mmol) and 2-chloroethanol (29.8mg, 0.37mmol) in dry DMF (3ml) were heated together under nitrogen at 55°C for 42h. The cooled mixture was degassed thoroughly and stirred with tetrakis(triphenylphosphine)palladium(0) (74mg) and morpholine (0.28ml) for 5h. The reaction was worked up by partition between EtOAc and 2M HCl, the organic phase being separated and evaporated. The residue was loaded onto an aminopropyl SPE cartridge (5g) in THF-MeOH (1:1), washed with the same solvent, then with neat MeOH, and the product eluted with DCM-MeOH (1:1) containing AcOH (2.5% rising to 5%). The product thus obtained was further purified by MDAP to afford the title compound (38mg).

LC/MS: m/z 315 $[MH]^+$, RT 2.79min.

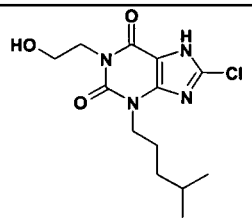
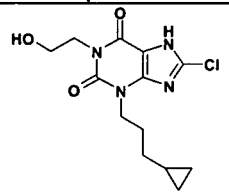
b) 8-Chloro-3-hexyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



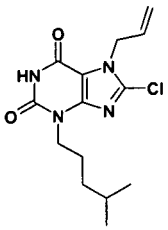
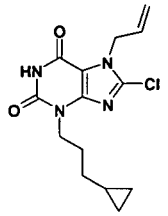
To 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (226mg, 1mmol) and sodium carbonate (117mg, 1.1mmol) in dry DMF (7ml) was added 1-iodohexane (223mg, 1.05mmol). The mixture was stirred and heated at 50°C for 2 days. After cooling, the mixture was partitioned between EtOAc and water, the organic phase washed with brine, dried over Na_2SO_4 and evaporated. The crude product was recrystallised from EtOAc-cyclohexane (1:2). Yield 146mg.
LC/MS: m/z 311 $[MH]^+$, RT 3.12min.

The following compounds (**Table 17**) were prepared by a method analogous to that for **Example 268**, except for **Example 270** the scale was reduced to 75mg (0.243mmol) of the precursor 8-chloro-3-(3-cyclopropylpropyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione.

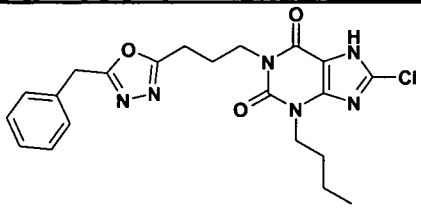
Table 17

Example	Structure	Precursor	Yield (mg)	LC/MS
269	 8-chloro-1-(2-hydroxyethyl)-3-(4-methylpentyl)-3,7-dihydro-1*H*-purine-2,6-dione	8-chloro-3-(4-methylpentyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione	37	m/z 315 $[MH]^+$ RT 2.74min
270	 8-chloro-3-(3-cyclopropylpropyl)-1-(2-hydroxyethyl)-3,7-dihydro-1*H*-purine-2,6-dione	8-chloro-3-(3-cyclopropylpropyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione	26	m/z 313 $[MH]^+$ RT 2.58min

The intermediates were prepared according to the method of **Example 268b**, except that 8-chloro-3-(3-cyclopropylpropyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione was purified by silica SPE (5g) eluting with EtOAc-cyclohexane (2:3).

Intermediate	Name	Scale (mmol)	Alkylating agent	Yield (mg)	LC/MS
	8-chloro-3-(4-methylpentyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione	1	1-bromo-4-methylpentane (173mg)	210	m/z 311[MH]$^+$ RT 3.08min
	8-chloro-3-(3-cyclopropylpropyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione	0.662	3-cyclopropylpropyl 4-methylbenzenesulfonate (170mg)	125	m/z 309 [MH]$^+$ RT 2.93min

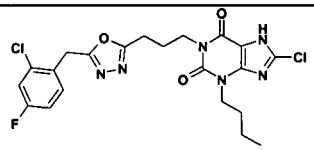
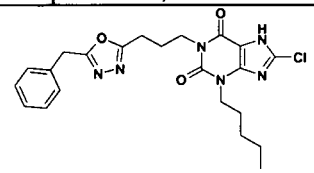
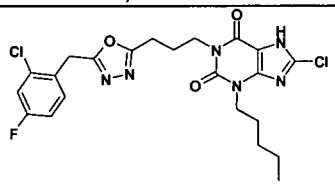
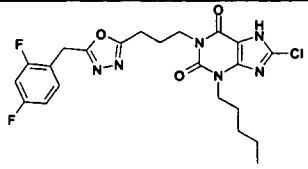
Example 271: 3-Butyl-8-chloro-1-{3-[5-(phenylmethyl)-1,3,4-oxadiazol-2-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

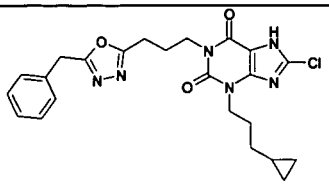
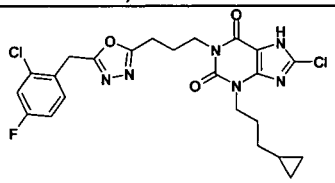
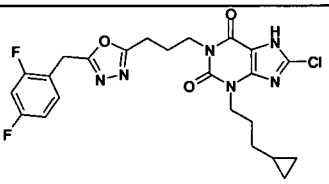


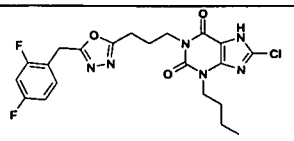
To 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (99mg, 0.35mmol) in dry DMF (2ml) was added cesium carbonate (137mg, 0.42mmol) followed by a solution in dry DMF (1ml) of 2-(3-chloropropyl)-5-(phenylmethyl)-1,3,4-oxadiazole (99mg, 0.42mmol). The mixture was stirred under nitrogen and heated at 55°C for 2.5h then stirred at room temperature overnight. The mixture was degassed by repeatedly 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 18**) were prepared by a method analogous to that for **Example 271**, with the exception that **Example 279** was further purified by HPLC.

Table 18

Example	Product structure	Xanthine precursor	Alkylating agent	Yield (mg)	LC/MS
272	 3-butyl-8-chloro-1-(3-{5-[(2-chloro-4-fluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3,7-dihydro-1*H*-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
273	 8-chloro-3-pentyl-1-{3-[5-(phenylmethyl)-1,3,4-oxadiazol-2-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (104mg)	2-(3-chloropropyl)-5-(phenylmethyl)-1,3,4-oxadiazole (99mg)	98	m/z 457 [MH]+ RT 3.35 min
274	 8-chloro-1-(3-{5-[(2-chloro-4-fluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-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
275		8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-	2-(3-chloropropyl)-5-[(2,4-difluorophenyl)	43	m/z 493 [MH]+

	8-chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	purine-2,6-dione (104mg)	methyl]-1,3,4-oxadiazole (111mg)		RT 3.40 min
276	 8-chloro-3-(3-cyclopropylpropyl)-1-{3-[5-(phenylmethyl)-1,3,4-oxadiazol-2-yl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	8-chloro-3-(3-cyclopropylpropyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (108mg)	2-(3-chloropropyl)-5-(phenylmethyl)-1,3,4-oxadiazole (99mg)	95	m/z 469 [MH]+ RT 3.34 min
277	 8-chloro-1-(3-{5-[(2-chloro-4-fluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3-(3-cyclopropylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione	8-chloro-3-(3-cyclopropylpropyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-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
278	 8-chloro-3-(3-cyclopropylpropyl)-1-(3-{5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	8-chloro-3-(3-cyclopropylpropyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (108mg)	2-(3-chloropropyl)-5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazole (111mg)	49	m/z 505 [MH]+ RT 3.40 min

279	 3-butyl-8-chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-1,3,4-oxadiazol-2-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-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

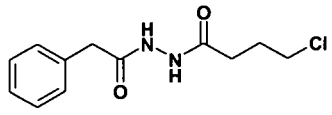
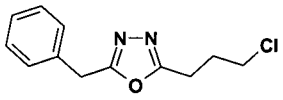
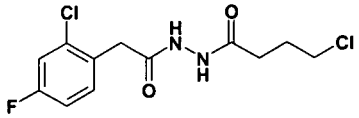
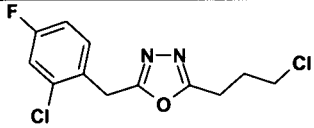
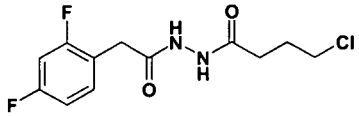
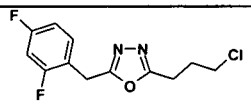
Synthesis of chloropropyl 1,3,4-oxadiazole intermediates from Table 18:

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

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

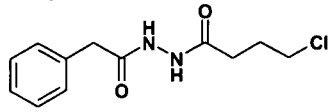
2-(3-chloropropyl)-5-(phenylmethyl)-1,3,4-oxadiazole

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 $NaHCO_3$. The organic phases were washed with brine, dried over Na_2SO_4 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-*N'*-(phenylacetyl)butanohydrazide	 2-(3-chloropropyl)-5-(phenylmethyl)-1,3,4-oxadiazole	446	m/z 237 $[MH]^+$ RT 2.94min
 4-chloro-*N'*-[(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
 4-chloro-*N'*-[(2,4-	 2-(3-chloropropyl)-5-[(2,4-	333	m/z 273 $[MH]^+$ RT 3.03min

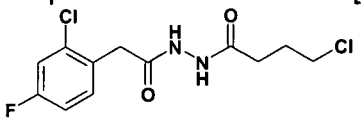
difluorophenyl)acetyl]butanohydrazide	difluorophenyl)methyl]-1,3,4-oxadiazole		

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



To 4-chlorobutyryl 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

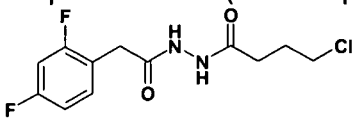


(i) A solution of 2-chloro-4-fluorophenylacetyl chloride (10mmol) in dry DCM (15ml) was added over 20min to a mixture of t-butyl carbazate (1.32g, 10mmol) and DIPEA (1.77ml, 10.2mmol) in dry DCM (20ml). After stirring for a further 2h, the mixture was washed with 1M HCl then with aqueous $NaHCO_3$. A 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 $NaHCO_3$ and the organic phase washed with brine, dried (Na_2SO_4) 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-chlorobutyryl 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



(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 $NaHCO_3$. The organic phase was evaporated to afford 1,1-dimethylethyl 2-[(2,4-difluorophenyl)acetyl]hydrazinecarboxylate as a white solid.

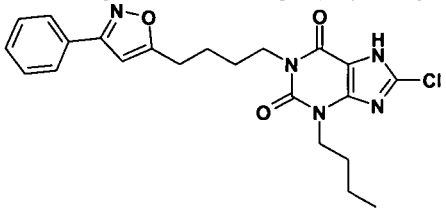
(ii) 1,1-dimethylethyl 2-[(2,4-difluorophenyl)acetyl]hydrazinecarboxylate (10mmol) in dioxan (5ml) was stirred with 4M HCl in dioxan (8ml) for 1.5h. The mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$ and the organic phase washed with brine, dried (Na_2SO_4) and evaporated. Reaction 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).

(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-chlorobutyryl 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).

LC/MS: m/z 291 $[MH]^+$, RT 2.45min.

Example 280 : 3-Butyl-8-chloro-1-[4-(3-phenyl-5-isoxazolyl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione

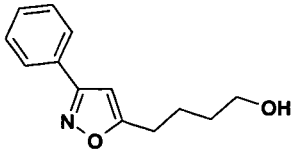
a) 3-Butyl-8-chloro-1-[4-(3-phenyl-5-isoxazolyl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione



3-Butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-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 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.

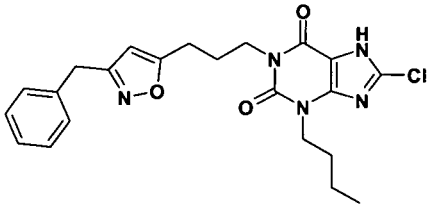
b) 4-(3-Phenyl-5-isoxazolyl)-1-butanol



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.

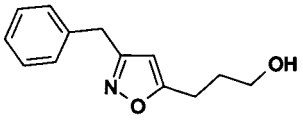
Example 281: 3-Butyl-8-chloro-1-{3-[3-(phenylmethyl)-5-isoxazolyl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

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 280) 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.

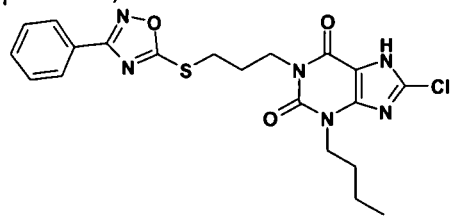
b) 3-[3-(Phenylmethyl)-5-isoxazolyl]-1-propanol



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.

Example 282: 3-Butyl-8-chloro-1-{3-[(3-phenyl-1,2,4-oxadiazol-5-yl)thio]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

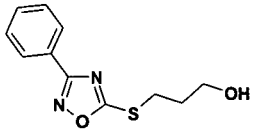
a) 3-Butyl-8-chloro-1-{3-[(3-phenyl-1,2,4-oxadiazol-5-yl)thio]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



Prepared by the method of 3-butyl-8-chloro-1-[4-(3-phenyl-5-isoxazolyl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione starting from 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.354mmol) and 3-[(3-phenyl-1,2,4-oxadiazol-5-yl)thio]-1-propanol (83.5mg, 0.354mmol) except that a 2nd aliquot of 250mg of tetrakis(triphenylphosphine)palladium(0) was added during the deprotection step. Yield 19.6mg

LC/MS: m/z 461[MH]$^+$, RT 3.75min.

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

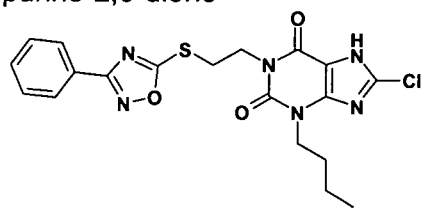


To 3-phenyl-1,2,4-oxadiazole-5(2*H*)-thione (178mg, 1mmol) in dry THF (3ml) was added DIPEA (0.174ml, 1mmol) and 3-bromo-1-propanol (139mg, 1mmol). Stirring was continued for 65h then the mixture was partitioned between EtOAc and water. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated to give title compound as an oil (235mg).

LC/MS: m/z 237 [MH]$^+$, RT 2.94min.

Example 283: 3-Butyl-8-chloro-1-{2-[(3-phenyl-1,2,4-oxadiazol-5-yl)thio]ethyl}-3,7-dihydro-1*H*-purine-2,6-dione

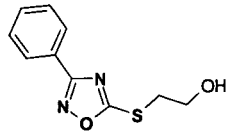
a) 3-Butyl-8-chloro-1-{2-[(3-phenyl-1,2,4-oxadiazol-5-yl)thio]ethyl}-3,7-dihydro-1*H*-purine-2,6-dione



Prepared by a method analogous to that used for Example 270 (3-Butyl-8-chloro-1-[4-(3-phenyl-5-isoxazolyl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione) starting from 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (141mg, 0.5mmol) and 2-[(3-

phenyl-1,2,4-oxadiazol-5-yl)thio]ethanol (111mg, 0.5mmol). A single portion of tetrakis(triphenylphosphine)palladium(0) (232mg) was used in the deprotection step, however, stirring being continued for 6h. Purification by aminopropyl SPE followed by MDAP afforded the title compound as a white solid (33.1mg).
LC/MS: m/z 447 $[MH]^+$, RT 3.67 min.

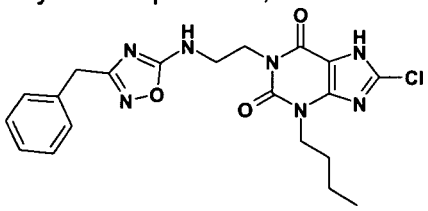
b) 2-[(3-phenyl-1,2,4-oxadiazol-5-yl)thio]ethanol



The title compound was obtained in a similar manner to 3-[(3-phenyl-1,2,4-oxadiazol-5-yl)thio]-1-propanol, from 2-bromoethanol, after a reaction time of 24h and purification by silica SPE (ethyl acetate-cyclohexane 1:1). Yield 176mg.
LC/MS: m/z 223 $[MH]^+$, RT 2.98 min.

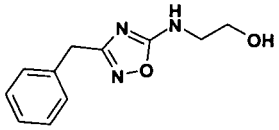
Example 284: 3-Butyl-8-chloro-1-(2-{[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]amino}ethyl)-3,7-dihydro-1*H*-purine-2,6-dione

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



3-Butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (64.4mg, 0.228mol), 2-{[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]amino}ethanol (50mg, 0.228mmol) and dibenzyl azodicarboxylate (136mg, 0.456mmol) were stirred in dry THF (3ml) at 0°C as triphenylphosphine (119mg, 0.456mmol) in dry THF (1ml) was added dropwise. The mixture was stirred at 0°C for 10min. then at room temperature for 2 overnight periods. It was thoroughly degassed and stirred with morpholine (0.2ml) and tetrakis(triphenylphosphine)palladium(0) (53mg, 0.046mmol) for 5h. A further 53mg of the catalyst was then 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 (11.8mg).
LC/MS: m/z 444 $[MH]^+$, RT 3.12min.

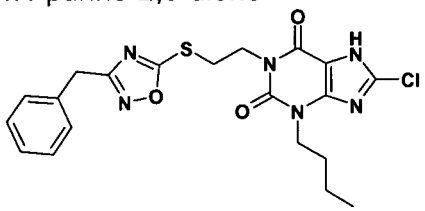
b) 2-{[3-(Phenylmethyl)-1,2,4-oxadiazol-5-yl]amino}ethanol



3-(Phenylmethyl)-5-(trichloromethyl)-1,2,4-oxadiazole (140mg, 0.505mmol) in dry DMF (2ml) was stirred with ethanolamine (0.25ml) for 1.5h. The mixture was partitioned between EtOAc and water, the organic phase washed with water, brine, dried (Na_2SO_4) and evaporated to give a white waxy solid (87mg).
LC/MS: m/z 220 $[MH]^+$, RT 2.22min.

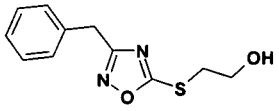
Example 285 : 3-Butyl-8-chloro-1-(2-{[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]thio}ethyl)-3,7-dihydro-1*H*-purine-2,6-dione

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



3-Butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (150mg, 0.531mmol) and 2-{[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]thio}ethanol (125mg, 0.530mmol) in dry THF (4ml) were cooled to 0°C and dibenzyl azodicarboxylate (94%, 336mg, 1.06mmol) in dry THF (2ml) was added followed by triphenylphosphine (278mg, 1.06mmol). The mixture was stirred at 0°C for 15min. then at room temperature for 2 overnight periods. Morpholine (1g) and tetrakis(triphenylphosphine)palladium(0) (250mg, 0.216mmol) were added to the degassed solution, and after 5h a further 100mg of $Pd(PPh_3)_4$ was added and stirring continued for 3 overnight periods. 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 afforded title compound (26mg).
LC/MS: m/z 461$[MH]^+$, RT 3.47min.

b) 2-{[3-(Phenylmethyl)-1,2,4-oxadiazol-5-yl]thio}ethanol

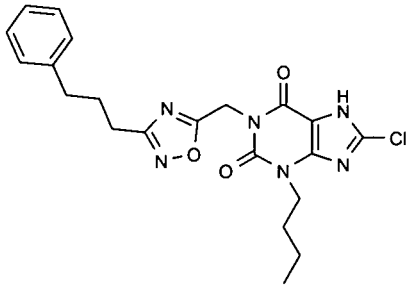


To 3-(phenylmethyl)-1,2,4-oxadiazole-5(2*H*)-thione (384mg, 2mmol) in dry THF (5ml) was added DIPEA (0.348ml, 2mmol) and 2-bromoethanol (250mg, 2mmol). The mixture was stirred at room temperature overnight and then partitioned between EtOAc and 1M HCl. The organic phase was washed with brine, dried, evaporated and purified

by silica SPE (10g) eluting with EtOAc-cyclohexane (1:2) to give title compound (315mg) as a colourless oil.
LC/MS: m/z 237 $[MH]^+$, RT 2.74min.

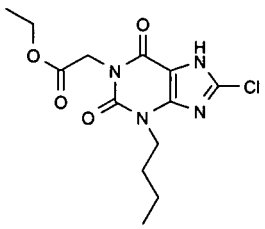
Example 286: 3-Butyl-8-chloro-1-{[3-(3-phenylpropyl)-1,2,4-oxadiazol-5-yl]methyl}-3,7-dihydro-1*H*-purine-2,6-dione

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



Ethyl (3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetate (66mg, 0.2mmol) and (1*Z*)-*N*-hydroxy-4-phenylbutanimidamide (39mg, 0.22mmol) were stirred in dry ethanol (1ml) with ethanolic sodium ethoxide (21%wt. solution, 0.111ml, 0.3mmol) and heated under microwave irradiation at 140 C for 10 min. The cooled mixture was partitioned between ethyl acetate and 2M hydrochloric acid, the organic phase separated and evaporated. The product was purified by MDAP to give the title compound as a solid (31.5mg).
LC/MS: m/z 443 $[MH]^+$, RT 3.56 min.

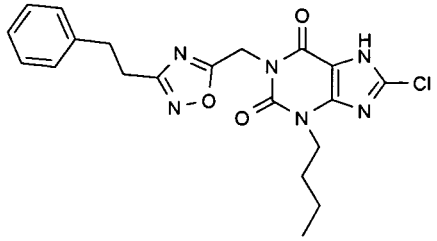
b) Ethyl (3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)acetate



3-Butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (1.5g, 5.31 mmol) and cesium carbonate (1.903g, 5.84mmol) were stirred together in dry DMF (25ml). Ethyl bromoacetate (0.648ml, 5.84mmol) was added and the mixture was stirred at 55 C overnight. The cooled mixture was degassed using nitrogen and stirred with tetrakis(triphenylphosphine)palladium(0) (1g) and morpholine (3.73ml) for 4.5h. The mixture was partitioned between ethyl acetate (80ml) and 2M HCl (50ml). The organic phase was washed with 3 x 80ml brine, filtered, dried over Na_2SO_4 and evaporated. The product was purified by aminopropyl SPE (20g), washing with THF-MeOH (1:1),

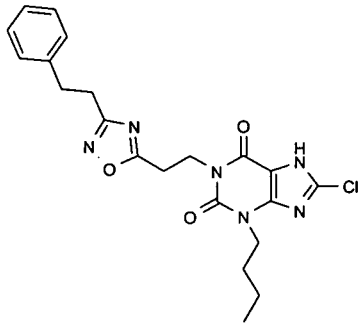
then neat MeOH and eluting the product with DCM-MeOH (1:1) containing acetic acid (2.5% rising to 5%), which gave pure title compound (1.16g).
LC/MS: m/z 329 $[MH]^+$, RT 2.87min.

Example 287: 3-Butyl-8-chloro-1-{[3-(2-phenylethyl)-1,2,4-oxadiazol-5-yl]methyl}-3,7-dihydro-1*H*-purine-2,6-dione



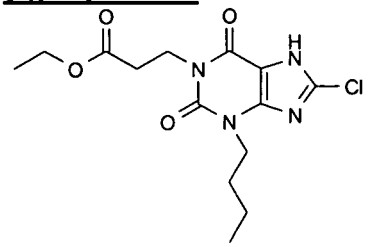
Synthesised by a method analogous to that for **Example 286**, starting from (1*Z*)-*N*-hydroxy-3-phenylpropanimidamide. Yield 22.6mg.
LC/MS: m/z 429 $[MH]^+$, RT 3.43 min.

Example 288: 3-Butyl-8-chloro-1-{2-[3-(2-phenylethyl)-1,2,4-oxadiazol-5-yl]ethyl}-3,7-dihydro-1*H*-purine-2,6-dione



Synthesised by a method analogous to that for **Example 286**, starting from (1*Z*)-*N*-hydroxy-3-phenylpropanimidamide and ethyl 3-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propanoate. Yield 23.3mg.
LC/MS: m/z 443 $[MH]^+$, RT 3.40 min.

Example 289: Ethyl 3-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propanoate

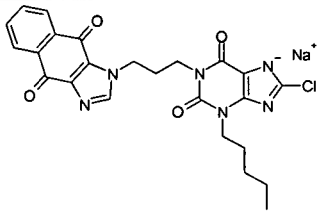
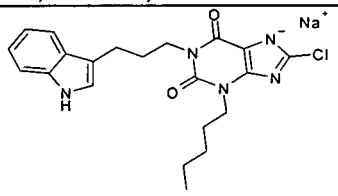
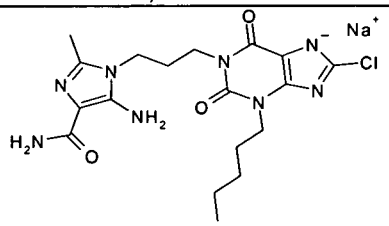


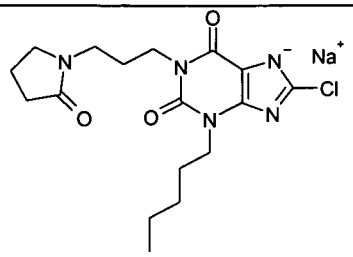
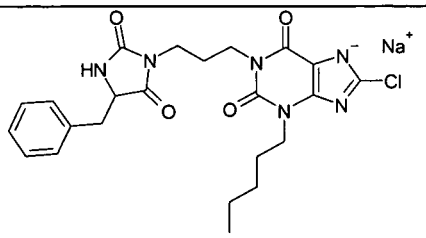
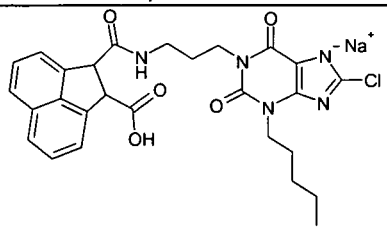
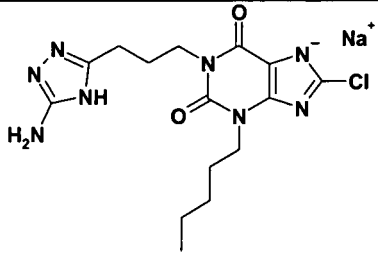
Synthesised as for ethyl (3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetate starting from ethyl 3-bromopropanoate (0.749ml, 5.84mmol), except that,

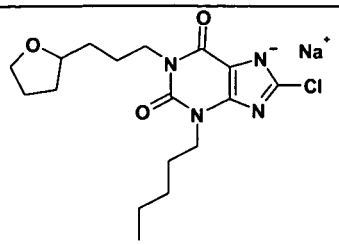
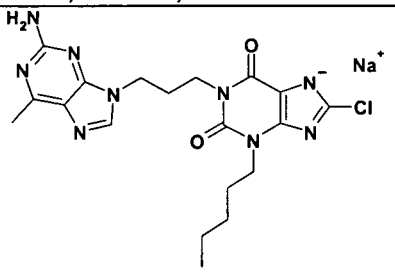
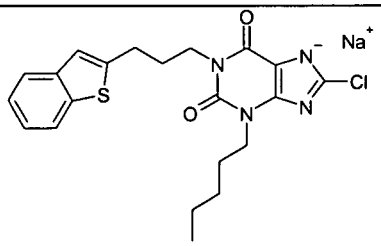
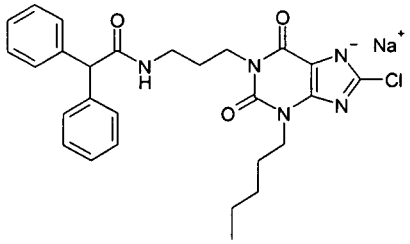
after the initial overnight heating period, further ethyl 3-bromopropanoate (1.5ml) was added, heating was resumed for a further 4h, then a further portion of cesium carbonate (1.903g), followed 2h later by a third portion of ethyl 3-bromopropanoate (1.5ml) were added. Heating at 55 C was then continued for a second overnight period before workup and deprotection as above. Yield 0.404g.
LC/MS: m/z 343 $[MH]^+$, RT 2.90min.

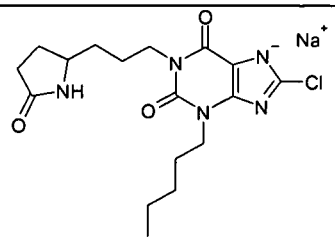
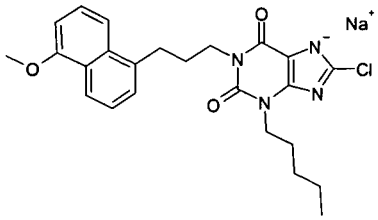
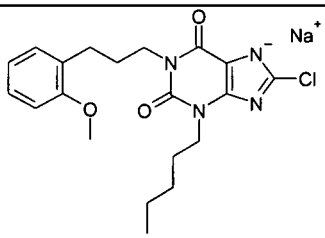
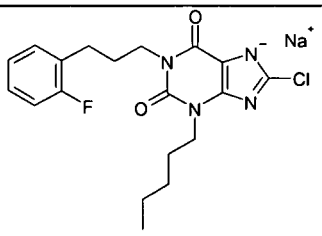
The following compounds (**Table 19**) were prepared by a method analogous to that for **Example 3**, with any modification noted in the method A-F.

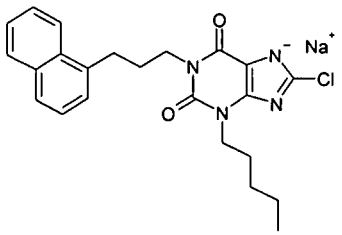
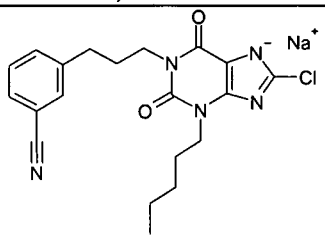
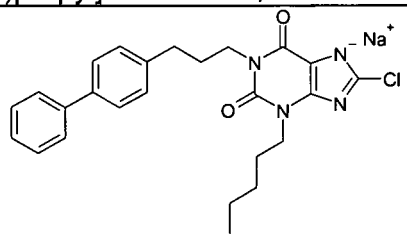
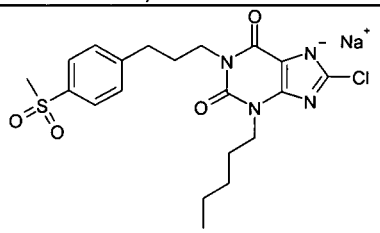
Table 19

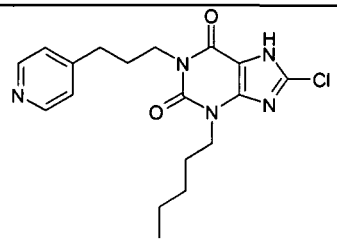
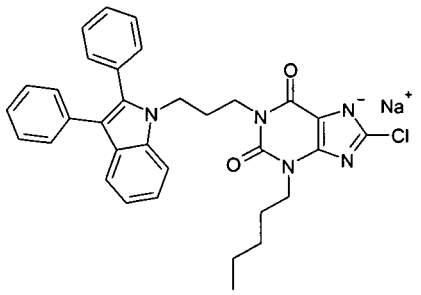
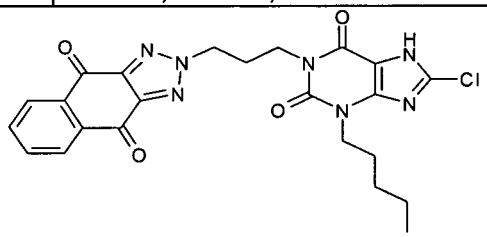
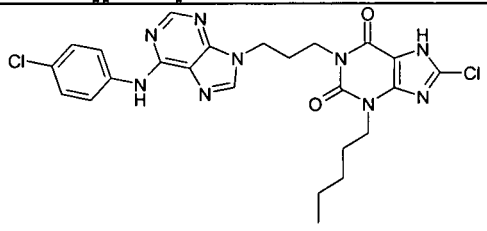
Example	Structure	Yield (mg)	LC/MS	Method
290	 1-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-1H-naphtho[2,3-d]imidazole-4,9-dione, sodium salt	10	m/z 495 $[MH]^+$ RT 3.30min	A
291	 8-chloro-1-[3-(1H-indol-3-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	24	m/z 414 $[MH]^+$ RT 3.72min	A
292	 5-amino-1-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-2-methyl-1H-imidazole-4-carboxamide, sodium salt	27	m/z 437 $[MH]^+$ RT 2.41min	A

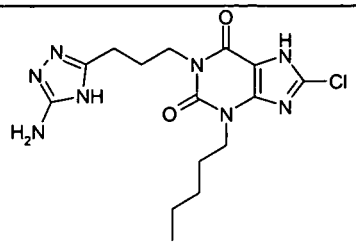
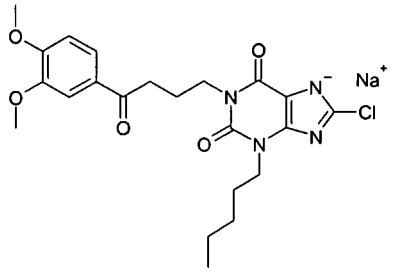
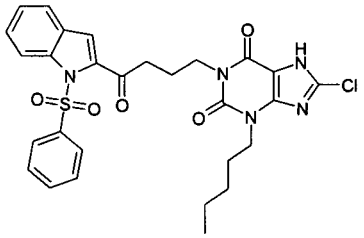
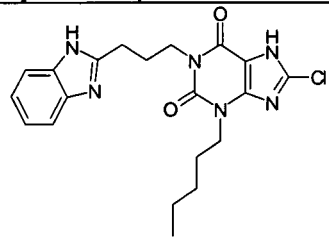
Example	Structure	Yield (mg)	LC/MS	Method
293	 8-chloro-1-[3-(2-oxo-1-pyrrolidinyl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	21	m/z 382 $[MH]^+$ RT 2.86min	A
294	 8-chloro-1-{3-[2,5-dioxo-4-(phenylmethyl)-1-imidazolidinyl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	9	m/z 487 $[MH]^+$ RT 3.15min	A
295	 2-({[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]amino}carbonyl)-1,2-dihydro-1-acenaphthylenecarboxylic acid, sodium salt	39	m/z 538 $[MH]^+$ RT 3.46min	A
296	 1-[3-(3-amino-1H-1,2,4-triazol-5-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	18	m/z 381 $[MH]^+$ RT 2.33min	A

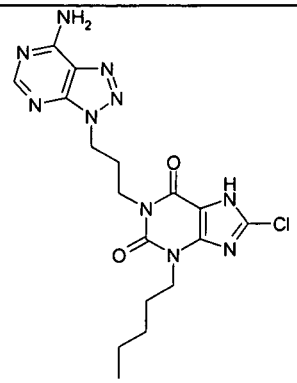
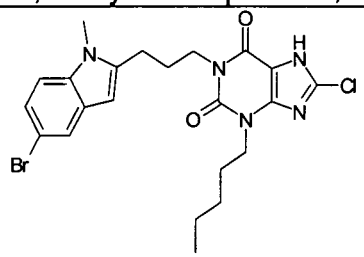
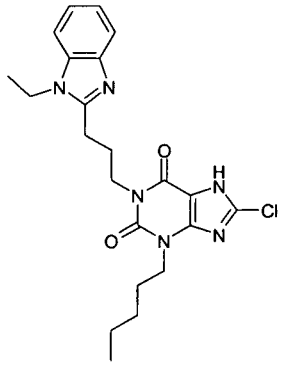
Example	Structure	Yield (mg)	LC/MS	Method
297	 8-chloro-3-pentyl-1-[3-(tetrahydro-2-furanyl)propyl]-3,7-dihydro-1H-purine-2,6-dione, sodium salt	22	m/z 369 $[MH]^+$ RT 3.2min	A
298	 1-[3-(2-amino-6-methyl-9H-purin-9-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	8	m/z 446 $[MH]^+$ RT 2.55min	A
299	 1-[3-(1-benzothien-2-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	21	m/z 431 $[MH]^+$ RT 3.9min	A
300	 N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-2,2-diphenylacetamide, sodium salt	31	m/z 508 $[MH]^+$ RT 3.56min	A

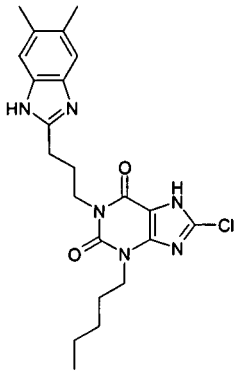
Example	Structure	Yield (mg)	LC/MS	Method
301	 8-chloro-1-[3-(5-oxo-2-pyrrolidinyl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	22	m/z 382 $[MH]^+$ RT 2.76min	A
302	 8-chloro-1-{3-[5-(methyloxy)-1-naphthalenyl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	33	m/z 455 $[MH]^+$ RT 4.01min	A
303	 8-chloro-1-{3-[2-(methyloxy)phenyl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	5	m/z 405 $[MH]^+$ RT 3.71min	A
304	 8-chloro-1-[3-(2-fluorophenyl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	15	m/z 393 $[MH]^+$ RT 3.7min	A

Example	Structure	Yield (mg)	LC/MS	Method
305	 8-chloro-1-[3-(1-naphthalenyl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	15	m/z 425 $[MH]^+$ RT 4.04min	A
306	 3-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]benzonitrile, sodium salt	13	m/z 400 $[MH]^+$ RT 3.51min	A
307	 1-[3-(4-biphenylyl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	19	m/z 451 $[MH]^+$ RT 4.06min	A
308	 8-chloro-1-{3-[4-(methylsulfonyl)phenyl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	30	m/z 453 $[MH]^+$ RT 3.2min	A

Example	Structure	Yield (mg)	LC/MS	Method
309	 8-chloro-3-pentyl-1-[3-(4-pyridinyl)propyl]-3,7-dihydro-1H-purine-2,6-dione	2	m/z 376 $[MH]^+$ RT 2.41min	A
310	 8-chloro-1-[3-(2,3-diphenyl-1H-indol-1-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	46	m/z 566 $[MH]^+$ RT 4.23min	A
311	 2-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-2H-naphtho[2,3-d][1,2,3]triazole-4,9-dione	1	m/z 513 $[MNH4]^+$ RT 3.38min	B
312	 8-chloro-1-(3-{6-[(4-chlorophenyl)amino]-9H-purin-9-yl}propyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	21	m/z 542 $[MH]^+$ RT 3.62min	B

Example	Structure	Yield (mg)	LC/MS	Method
313	 1-[3-(3-amino-1H-1,2,4-triazol-5-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	7	m/z 381 $[MH]^+$ RT 2.33min	B
314	 1-{4-[3,4-bis(methyloxy)phenyl]-4-oxobutyl}-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	17	m/z 463 $[MH]^+$ RT 3.24min	B
315	 8-chloro-1-{4-oxo-4-[1-(phenylsulfonyl)-1H-indol-2-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	2	m/z 582 $[MH]^+$ RT 3.79min	B
316	 1-[3-(1H-benzimidazol-2-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	14	m/z 415 $[MH]^+$ RT 2.45min	B

Example	Structure	Yield (mg)	LC/MS	Method
317	 1-[3-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	5	m/z 433 $[MH]^+$ RT 2.69min	C
318	 1-[3-(5-bromo-1-methyl-1H-indol-2-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	2	m/z 508 $[MH]^+$ RT 4.11min	D
319	 8-chloro-1-[3-(1-ethyl-1H-benzimidazol-2-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	17	m/z 443 $[MH]^+$ RT 2.59min	E

Example	Structure	Yield (mg)	LC/MS	Method
320	 8-chloro-1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	25	m/z 443 $[MH]^+$ RT 2.61min	F

Method A: Analogous to that for **Example 3**

Method B: Similar to Method A, except material was purified using autopreparative HPLC after purification by aminopropyl SPE.

Method C: Similar to Method A, except material was purified by washing with water after purification by aminopropyl SPE.

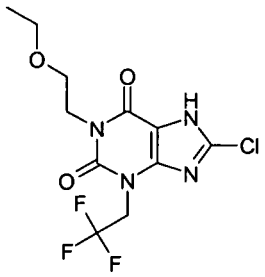
Method D: Similar to Method A, except material was purified by MDAP after purification by aminopropyl SPE.

Method E: Similar to Method A, except material was purified by SCX SPE after initial purification using aminopropyl SPE.

Method F: Similar to Method A, except material was purified using preparative HPLC using a Zorbax Phenyl column.

Example 321: 8-Chloro-1-[3-(ethyloxy)ethyl]-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-1-[3-(ethyloxy)ethyl]-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione

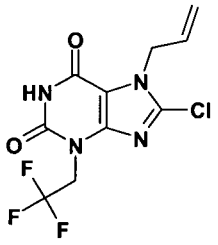


To a greenhouse tube equipped with a stirrer was added caesium carbonate (85mg, 0.26mmol), followed by a solution of 8-chloro-7-(2-propen-1-yl)-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione (69mg, 0.22mmol) in dry DMF (1ml) and then a solution of 1-bromo-3-(ethyloxy)ethane (60mg, 0.39mmol) in dry DMF (1ml). The mixture was heated to 80°C for 5h under nitrogen, then allowed to cool to room temperature for 16h. The reaction mixture was concentrated using a vacuum centrifuge. THF (2.5ml) was added to the mixture, followed by $Pd(PPh_3)_4$ (30mg, 0.026mmol) and morpholine (190uL, 2.2mmol) and the mixture stirred at rt under nitrogen for 72h. The mixture was partitioned between 2N HCl (2ml) and chloroform (4ml), the organic layer separated using a hydrophobic frit, and the aqueous layer extracted with chloroform (2x4ml). Combined organic layers were concentrated under reduced pressure then loaded in 1:1 DCM/MeOH onto an aminopropyl SPE (5g), washing with 1:1 DCM/MeOH and eluting with 20% to 80% acetic acid in 1:1 DCM/MeOH. Solvent was removed under reduced pressure to afford the title compound as a solid (70mg, 93%).

^{1}H NMR (MeOD) δ: 1.11 (t, 3H, J = 7Hz), 3.51 (q, 2H, J = 7Hz), 3.64 (t, 2H, J = 6Hz), 4.18 (t, 2H, J = 6Hz), 4.73 (q, 2H, J = 9Hz).

LC/MS: m/z 341 $[MH]^+$, RT 2.72min.

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

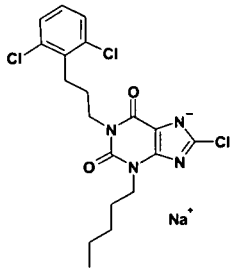


8-Chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.5g, 6.62mmol) in dry DMF (50ml) was stirred with sodium carbonate (980mg, 9.25mmol) and 1,1,1-trifluoro-2-iodoethane (1.2g, 5.71mmol) at room temperature for 18h under nitrogen. The mixture was heated at 50°C for 6h then cooled to rt and stirred for a further 10h. The mixture was heated at 120°C for 4h, further 1,1,1-trifluoro-2-iodoethane (426mg, 2.03mmol) added, and the reaction mixture heated at 120°C for a further 3h. The reaction mixture was concentrated under reduced pressure.

A further amount of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (3.8g, 16.8mmol) in dry DMF (125ml) was stirred with sodium carbonate (2.5g, 23.1mmol)

and 1,1,1-trifluoro-2-iodoethane (4.1g, 19.5mmol) and the reaction mixture heated at 120°C for 16h under nitrogen. This reaction mixture was combined with the previous crude material and concentrated under reduced pressure. The residue was triturated with DCM, the mixture filtered, and the filtrate concentrated under reduced pressure then dissolved in DCM (20ml). 10ml of this material was purified by silica chromatography using a 100g Silica column, eluting the title compound with a suitable gradient of ethyl acetate/cyclohexane. The remaining 10ml was purified using a Silica RediSep cartridge (130g) on a Companion, eluting the title compound with a suitable gradient of ethyl acetate/cyclohexane. Fractions containing the title compound from both purification modes were combined and concentrated under reduced pressure to give the title compound as a white solid (1.6g, 22% overall yield).
LC/MS: m/z 309 $[MH]^+$, RT 2.59min.

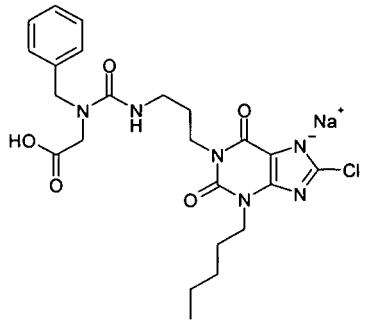
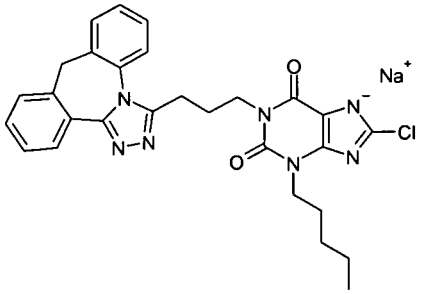
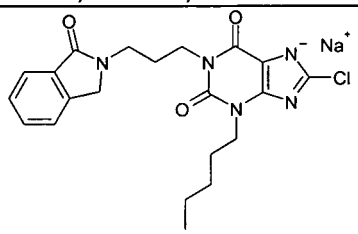
Example 322: 8-Chloro-1-[3-(2,6-dichlorophenyl)propyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione, sodium salt

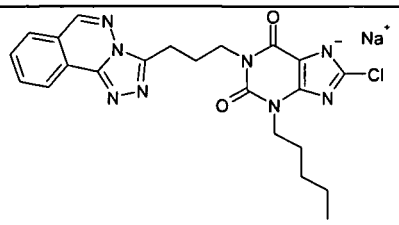
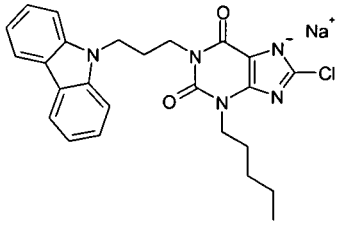
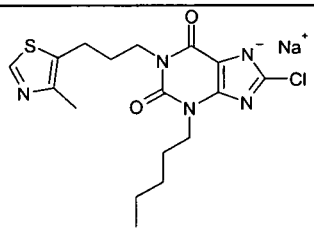
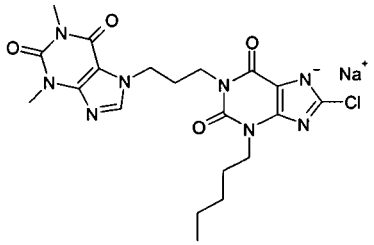


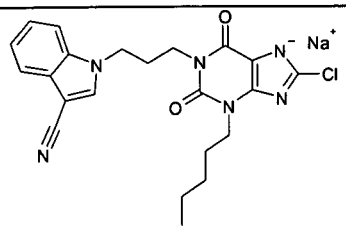
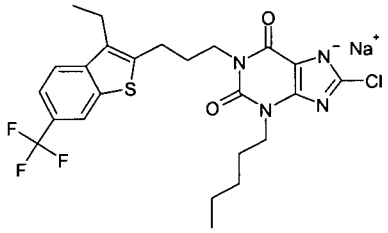
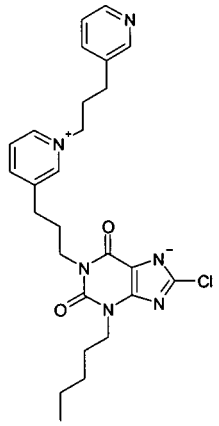
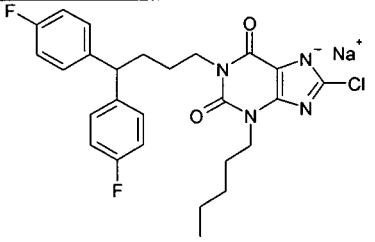
To a solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (40mg, 0.14mmol) in dry DMF (0.25ml) was added caesium carbonate (49mg, 0.15mmol) followed by a solution of 2-(3-bromopropyl)-1,3-dichlorobenzene (54mg, 0.20mmol) in dry DMF (0.25ml). The mixtures were stirred at 60°C for 16h, then $Pd(PPh_3)_4$ (16mg, 0.014mmol) added, followed by morpholine (118uL, 1.4mmol) and the mixtures stirred for a further 16h. Solvent was removed using a vacuum centrifuge and the sample dissolved in DMSO (0.25ml) then loaded onto a C18 SPE (5g). 2N NaOH (0.5ml) was added and a suitable gradient of ammonia/water/MeCN used to elute the product. The title compound was isolated as a solid (52mg, 83%).
^1H NMR (DMSO-d_6) δ: 0.84 (t, 3H, J = 7Hz), 1.18 - 1.36 (m, 4H), 1.55 - 1.69 (m, 2H), 1.69 - 1.85 (m, 2H), 2.78 - 2.89 (m, 2H), 3.85 (t, 2H, J = 7Hz), 3.95 (t, 2H, J = 7Hz), 7.23 (dd, 1H, J = 9 and 7Hz), 7.41 (d, 2H, J = 7Hz).
LC/MS: m/z 445 $[MH]^+$, RT 4.05min.

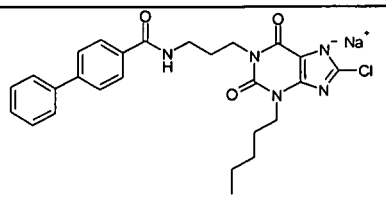
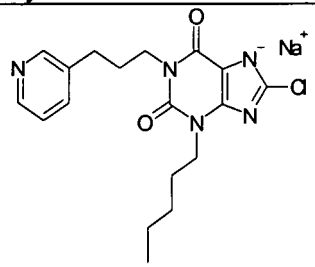
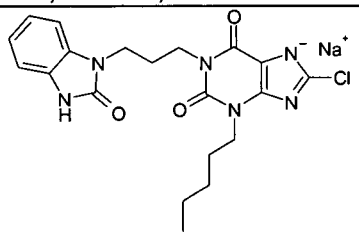
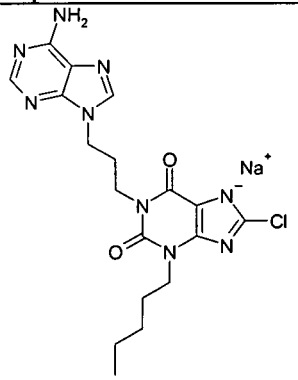
The following compounds (**Table 20**) were prepared using a method analogous to that for the **Example 322**, from the corresponding alkyl halides:

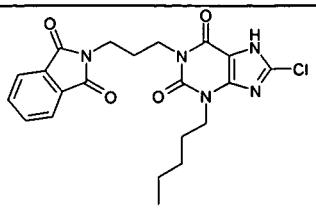
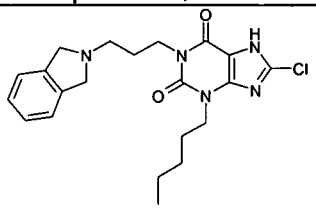
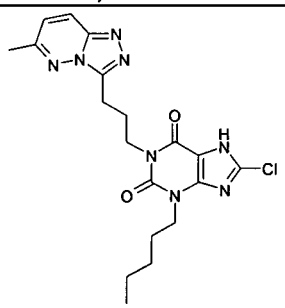
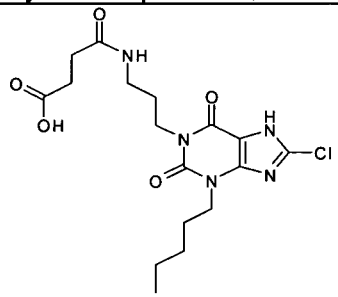
Table 20

Example	Structure	Yield (mg)	LC/MS:	Method
323	 *N*-({[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl]amino}carbonyl)-*N*-(phenylmethyl)glycine, sodium	57	m/z 505 $[MH]^+$ RT 3.14min	A
324	 8-chloro-1-[3-(9H-dibenzo[c,f][1,2,4]triazolo[4,3-a]azepin-3-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium	16	m/z 530 $[MH]^+$ RT 3.36min	A
325	 8-chloro-1-[3-(1-oxo-1,3-dihydro-2H-isoindol-2-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	18	m/z 430 $[MH]^+$ RT 3.12min	A

Example	Structure	Yield (mg)	LC/MS:	Method
326	 8-chloro-3-pentyl-1-(3-[1,2,4]triazolo[3,4-a]phthalazin-3-ylpropyl)-3,7-dihydro-1H-purine-2,6-dione, sodium salt	18	m/z 467 $[MH]^+$ RT 2.99min	A
327	 1-[3-(9H-carbazol-9-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	30	m/z 464 $[MH]^+$ RT 4.03min	A
328	 8-chloro-1-[3-(4-methyl-1,3-thiazol-5-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	42	m/z 396 $[MH]^+$ RT 3.17min	A
329	 7-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	31	m/z 477 $[MH]^+$ RT 2.83min	A

Example	Structure	Yield (mg)	LC/MS:	Method
330	 1-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-1H-indole-3-carbonitrile, sodium salt	50	m/z 439 $[MH]^+$ RT 3.56min	A
331	 8-chloro-1-{3-[3-ethyl-6-(trifluoromethyl)-1-benzothien-2-yl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium	10	m/z 527 $[MH]^+$ RT 4.3min	A
332	 3-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-1-[3-(3-pyridinyl)propyl]pyridinium	5	m/z 495 $[MH]^+$ RT 2.21min	A
333	 1-[4,4-bis(4-fluorophenyl)butyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	45	m/z 501 $[MH]^+$ RT 4.01min	A

Example	Structure	Yield (mg)	LC/MS:	Method
334	 N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-4-biphenylcarboxamide, sodium salt	33	m/z 494 $[MH]^+$ RT 3.69min	A
335	 8-chloro-3-pentyl-1-[3-(3-pyridinyl)propyl]-3,7-dihydro-1H-purine-2,6-dione, sodium salt	18	m/z 376 $[MH]^+$ RT 2.5min	A
336	 8-chloro-1-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	39	m/z 431 $[MH]^+$ RT 3.13min	A
337	 1-[3-(6-amino-9H-purin-9-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione, sodium salt	4	m/z432 $[MH]^+$ RT 2.53min	B

Example	Structure	Yield (mg)	LC/MS:	Method
338	 8-chloro-1-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	1	m/z 444 $[MH]^+$ RT 3.39min	C
339	 8-chloro-1-[3-(1,3-dihydro-2H-isoindol-2-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	3	m/z 416 $[MH]^+$ RT 2.87min	C
340	 8-chloro-1-[3-(6-methyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	8	m/z 431 $[MH]^+$ RT 2.83min	D
341	 8-chloro-1-[3-(6-methyl[1,2,4]triazolo[4,3-b]pyridazin-3-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	3	m/z 414 $[MH]^+$ RT 2.64min	E

Method A: Analogous to that for **Example 3**

Method B: Similar to Method A, except after concentration by vacuum centrifuge, material was partitioned between 2M HCl and DCM, the aqueous layer isolated then purified using C18 SPE in the manner described in Method A.

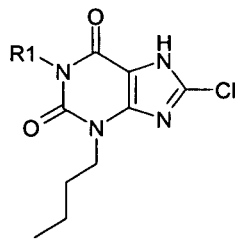
Method C: Similar to Method A, except after concentration by vacuum centrifuge, material was partitioned between 2M HCl and DCM, and the product was isolated from the organic layer after autopreparative HPLC.

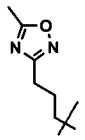
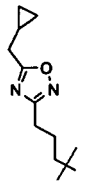
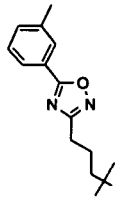
Method D: Similar to Method A, except product was isolated using aminopropyl SPE.

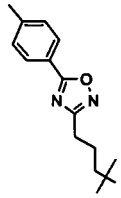
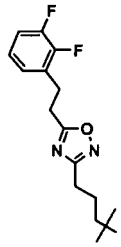
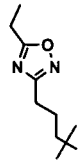
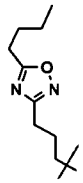
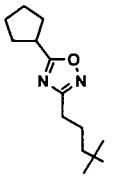
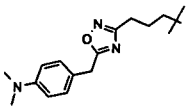
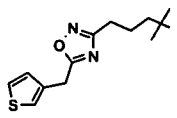
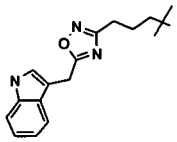
Method E: Similar to Method A, except material was further purified on a phenyl HPLC using a suitable gradient of water/MeOH/MeCN/TFA, then autopreparative HPLC, using a suitable gradient of water/acetonitrile.

The following compounds (**Table 21**) were prepared using a method analogous to that for **Example 142**, 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.

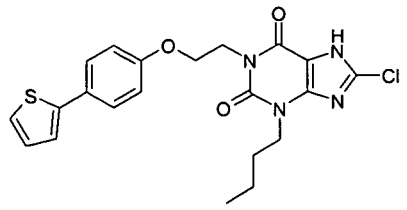
Table 21



Example	Name	Compound: R1 =	LC/MS
342	3-butyl-8-chloro-1-[3-(5-methyl-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione		m/z 367 $[MH]^+$ RT 2.7min
343	3-butyl-8-chloro-1-{3-[5-(cyclopropylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione		m/z 407 $[MH]^+$ RT 3.11min
344	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

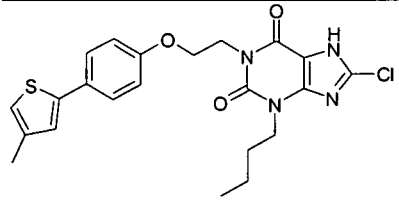
Example	Name	Compound: R1 =	LC/MS
345	3-butyl-8-chloro-1-{3-[5-(4-methylphenyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione		m/z 443 $[MH]^+$ RT 3.34min
346	3-butyl-8-chloro-1-(3-{5-[2-(2,3-difluorophenyl)ethyl]-1,2,4-oxadiazol-3-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione		m/z 493 $[MH]^+$ RT 3.47min
347	3-butyl-8-chloro-1-[3-(5-ethyl-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione		m/z 381 $[MH]^+$ RT 2.9min
348	3-butyl-1-[3-(5-butyl-1,2,4-oxadiazol-3-yl)propyl]-8-chloro-3,7-dihydro-1H-purine-2,6-dione		m/z 409 $[MH]^+$ RT 3.27min
349	3-butyl-8-chloro-1-[3-(5-cyclopentyl-1,2,4-oxadiazol-3-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione		m/z 421 $[MH]^+$ RT 3.29min
350	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
351	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
352	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 353: 3-Butyl-8-chloro-1-(2-{[4-(2-thienyl)phenyl]oxy}ethyl)-3,7-dihydro-1*H*-purine-2,6-dione



A microwave vial containing a magnetic stirrer bar was charged with 2-thienylboronic acid (16mg, 0.125mmol), 1-{2-[(4-bromophenyl)oxy]ethyl}-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione (50mg, 0.113mmol), aqueous sodium carbonate (1ml, 1M solution) and dimethoxyethane (1ml). This mixture was degassed with nitrogen and then $Pd(PPh_3)_2Cl_2$ (4mg, 5.6x10-6mol) was added. The reaction mixture was capped and heated at 140°C in a microwave for 15min (pressure reached 7bar). The crude reaction mixture was acidified with HCl (2M, 1.5ml), washed with chloroform (2x1ml) and the phases separated. The combined organics were evaporated and the crude product purified by MDAP to afford the title compound (10mg).
LC/MS: m/z 445 $[MH]^+$, RT 3.76min

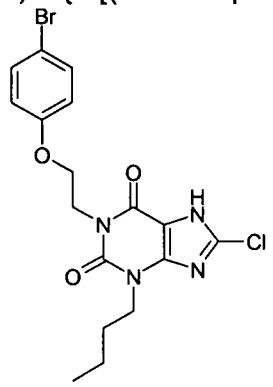
Example 354: 3-Butyl-8-chloro-1-(2-{[4-(4-methyl-2-thienyl)phenyl]oxy}ethyl)-3,7-dihydro-1*H*-purine-2,6-dione



A microwave vial containing a magnetic stirrer bar was charged with (4-methyl-2-thienyl)boronic acid (18mg, 0.125mmol), 1-{2-[(4-bromophenyl)oxy]ethyl}-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione (50mg, 0.113mmol), aqueous sodium carbonate (1ml, 1M solution) and dimethoxyethane (1ml). This mixture was degassed with nitrogen and then $Pd(PPh_3)_2Cl_2$ (4mg, 0.0056mmol) was added. The reaction mixture was capped and heated at 140°C in a microwave for 15min (pressure reached 7bar). The crude reaction mixture was acidified with HCl (2M, 1.5ml), washed with chloroform (2x1ml) and the phases separated. The combined organics were evaporated and the crude product purified by MDAP to afford the title compound (17mg).
LC/MS: m/z 459 $[MH]^+$, RT 3.9min

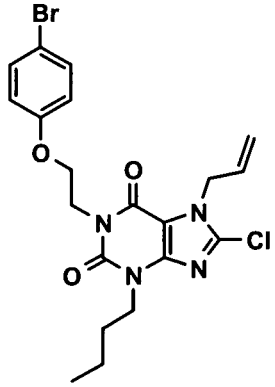
Example 355: 1-{2-[(4-Bromophenyl)oxy]ethyl}-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione

a) 1-{2-[(4-Bromophenyl)oxy]ethyl}-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione



1-{2-[(4-Bromophenyl)oxy]ethyl}-3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2.3g, 4.8mmol) was stirred in a mixture of nitrogen degassed DCM (40ml) and AcOH (4ml). Tetrakis(triphenylphosphine)palladium (1.1g, 0.896mmol) and phenylsilane (5.9ml, 48mmol) were added and the mixture stirred at rt for 2h. This was then evaporated and the residue triturated with a mixture of diethylether:cyclohexane (1:2) to afford the title compound (1.02g, 49%) as a white solid.
LC/MS: m/z 441/443 $[MH]^+$, RT 3.6min

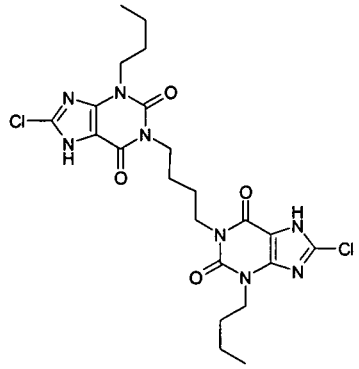
b) 1-{2-[(4-bromophenyl)oxy]ethyl}-3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



3-Butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2.8g, 9.8mmol) in dry DMF (50ml) was added Cs_2CO_3 (6.4g, 19.6mmol) followed by 2-bromoethyl 4-bromophenyl ether (3.6g, 13mmol). The mixture was heated at 80°C for 17h 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 ($MgSO_4$) and evaporated to give the crude product. This was purified by silica SPE (50g), eluting with cyclohexane:ethylacetate (10:1 to 1:1) to afford the title compound as a cream coloured solid (2.9g, 62%).
LC/MS: m/z 381/483 $[MH]^+$, RT 3.87min.

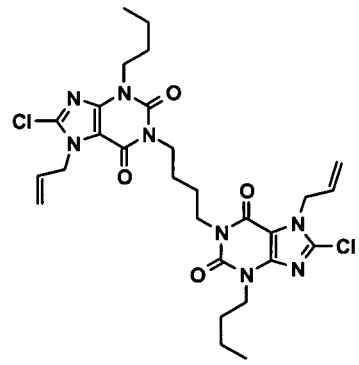
Example 356: 1,1'-(1,4-Butanediyl)bis(3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione)

a) 1,1'-(1,4-Butanediyl)bis(3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione)



1,1'-(1,4-Butanediyl)bis[3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione] (24mg, 0.039mmol) was stirred in a mixture of nitrogen degassed DCM (2ml) and AcOH (0.2ml). Tetrakis(triphenylphosphine)palladium (38mg, 0.033mmol) and phenylsilane (42uL, 0.39mmol) were added and the mixture stirred at rt for 2h. This was then evaporated and the crude product purified by reverse phase chromatography (5-95% gradient, H_2O: CH_3CN) to afford the title compound (2mg).
LC/MS: m/z 539 $[MH]^+$, RT 3.33min

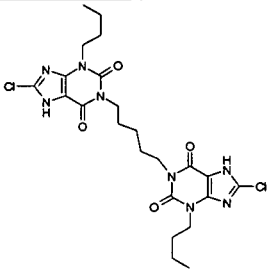
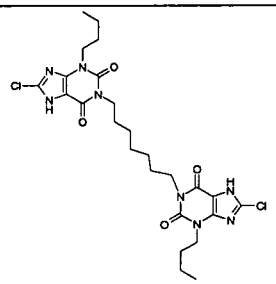
b) 1,1'-(1,4-Butanediyl)bis[3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione]



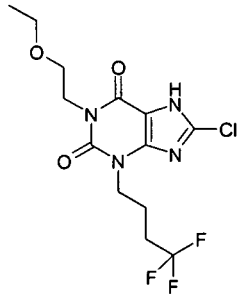
3-Butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (60mg, 0.212mmol) in dry DMF (1ml) was added Cs_2CO_3 (207mg, 0.636mol) followed by 1,4-diiodobutane (16uL, 0.106mmol). The mixture was heated at 80°C for 17h and then allowed to cool. The reaction mixture was partitioned between DCM and HCl (2M). The organic phase was separated and washed with brine, dried ($MgSO_4$) and evaporated to give the crude product. This was purified by MDAP to afford the title compound as a cream coloured solid (24mg).
LC/MS: m/z 619 $[MH]^+$, RT 3.95min.

The following compounds (**Table 22**) were prepared using a method analogous to that for **Example 356**.

Table 22

Example	Name	Structure	Yield	LC/MS:
357	3-butyl-1-[5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,9-tetrahydro-1*H*-purin-1-yl)pentyl]-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione		2.4mg	m/z 553 $[MH]^+$ RT 3.43min
358	3-butyl-1-[7-(3-butyl-8-chloro-2,6-dioxo-2,3,6,9-tetrahydro-1*H*-purin-1-yl)heptyl]-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione		3.6mg	m/z 581 $[MH]^+$ RT 3.72min

Example 359: 8-Chloro-1-[2-(ethyloxy)ethyl]-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione



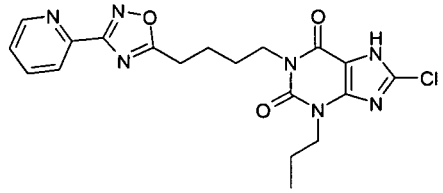
A solution of 8-chloro-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1H-purine-2,6-dione (84mg, 0.25mmol) in DMF (1ml) was treated with caesium carbonate (163mg, 0.5mmol) and 1-bromo-2-(ethyloxy)ethane (42mg, 0.275mmol). The mixture was heated at 80°C for 4h and then cooled.

The reaction mixture was degassed with nitrogen and then treated with morpholine (220uL) and tetrakis(triphenylphosphine)palladium (29mg, 0.025mmol) and stirred for 4h. The reaction mixture was partitioned between chloroform and HCl (2M). The organic phase was separated and evaporated. The crude product was loaded on to an aminopropyl SPE. The non acidic impurities were eluted with a mixture of DCM and MeOH and the desired product eluted with 10%AcOH in DCM. Evaporation afforded the title compound (77mg).

LC/MS: m/z 369 $[MH]^+$, RT 1.96min.

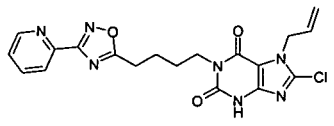
Example 360: 8-Chloro-3-propyl-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione

a) 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



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-1*H*-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. 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 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.

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

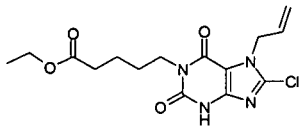


A suspension of *N*-hydroxy-2-pyridinecarboximidamide (1.15g, 8.4mmol) in anhydrous THF (20ml) was treated with sodium methoxide (0.38g, 7.0mmol) and the mixture stirred for 5min. The mixture was treated with ethyl 5-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]pentanoate (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.
LC/MS: m/z 428 $[MH]^+$, RT 2.70min.

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.

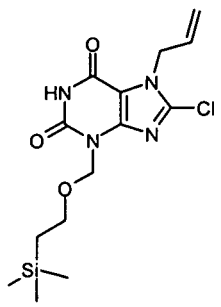
c) Ethyl 5-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]pentanoate



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-1*H*-purin-1-yl]pentanoate as a white solid.
LC/MS: m/z 355 $[MH]^+$, RT 2.75min.

Similarly prepared was 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 341 $[MH]^+$, RT 2.61min.

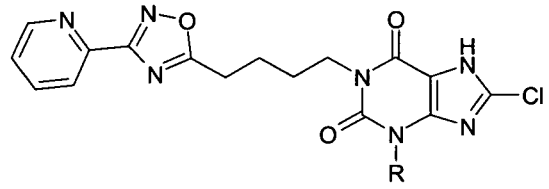
d) 8-Chloro-7-(2-propen-1-yl)-3-({[2-(trimethylsilyl)ethyl]oxy}methyl)-3,7-dihydro-1H-purine-2,6-dione



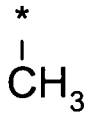
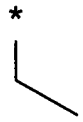
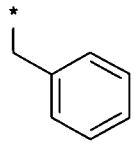
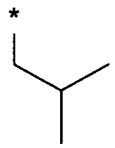
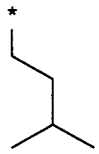
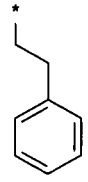
To a solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (5g, 22.1mmol) in DMF (80ml) was added 2-2-(trimethylsilyl)ethoxymethyl chloride (4.3ml, 24.2mmol) and sodium carbonate (2.6g, 24.2mmol). After stirring at room temperature overnight further 2-2-(trimethylsilyl)ethoxymethyl chloride (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 Biotage™ chromatogratphy using a silica cartridge eluting 1:4-1:2 ethyl acetate/cyclohexane afforded the title compound (3.14g, 40%).
m/z 374 [MNH_4^+]

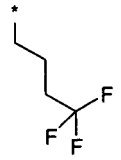
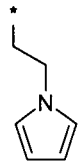
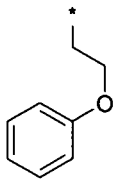
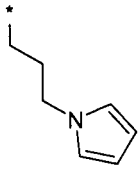
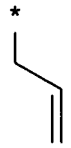
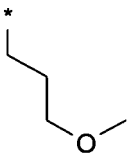
The following compounds (**Table 23**) were prepared by a method analogous to that for **Example 360**, from 8-chloro-7-(2-propen-1-yl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione and the appropriate alkylating agent.

Table 23



Example	R =	Name	Yield (mg)	m/z	RT (min)
361		8-chloro-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	2.5	388	2.37

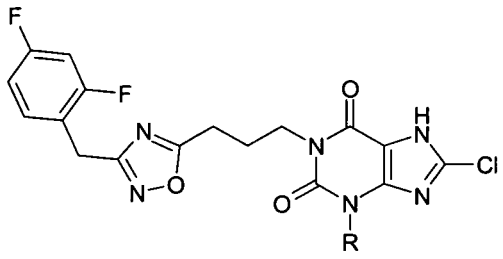
Example	R =	Name	Yield (mg)	m/z	RT (min)
362		8-chloro-3-methyl-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	1.7	402	2.53
363		8-chloro-3-ethyl-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	1.4	416	2.66
364		8-chloro-3-(phenylmethyl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	1.3	478	3.09
365		8-chloro-3-(2-methylpropyl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	2.0	444	2.99
366		8-chloro-3-(3-methylbutyl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	1.6	458	3.21
367		8-chloro-3-(2-phenylethyl)-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	2.1	492	3.18

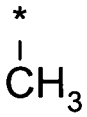
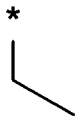
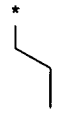
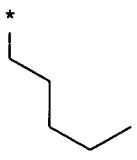
Example	R =	Name	Yield (mg)	m/z	RT (min)
368		8-chloro-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione	2.1	498	3.07
369		8-chloro-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3-[2-(1*H*-pyrrol-1-yl)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione	2.7	481	2.89
370		8-chloro-3-[2-(phenyloxy)ethyl]-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	1.7	508	3.11
371		8-chloro-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3-[3-(1*H*-pyrrol-1-yl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	2.1	495	3.01
372		8-chloro-3-(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	1.3	428	2.73
373		8-chloro-3-[3-(methyloxy)propyl]-1-{4-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	1.0	460	2.65

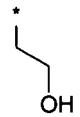
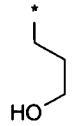
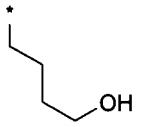
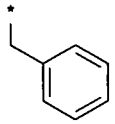
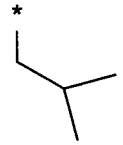
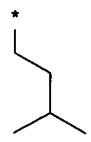
The following compounds (Table 24) were prepared by a method analogous to that for **Example 360**, from 8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-

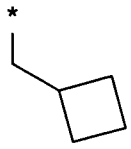
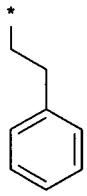
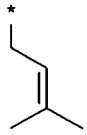
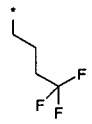
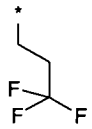
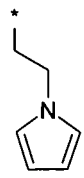
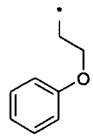
yl}propyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione and the appropriate alkylating agent.

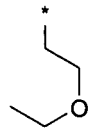
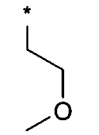
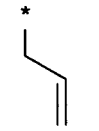
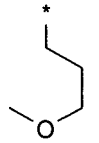
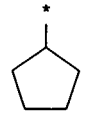
Table 24



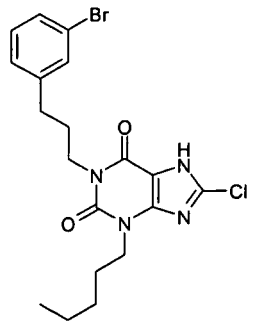
Example	R =	Name	Yield (mg)	m/z	RT (min)
374		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	2.5	423	2.71
375		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-methyl-3,7-dihydro-1*H*-purine-2,6-dione	1.7	437	2.92
376		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione	1.4	451	3.06
377		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione	2.2	465	3.22
378		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	2.6	493	3.54

Example	R =	Name	Yield (mg)	m/z	RT (min)
379		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(2-hydroxyethyl)-3,7-dihydro-1*H*-purine-2,6-dione	2.7	467	2.72
380		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(3-hydroxypropyl)-3,7-dihydro-1*H*-purine-2,6-dione	2.0	481	2.77
381		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(4-hydroxybutyl)-3,7-dihydro-1*H*-purine-2,6-dione	1.4	495	2.80
382		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(phenylmethyl)-3,7-dihydro-1*H*-purine-2,6-dione	1.6	513	3.43
383		8-chloro-3-(cyclopropylmethyl)-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	1.8	477	3.30
384		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(2-methylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione	3.5	479	3.36
385		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(3-methylbutyl)-3,7-dihydro-1*H*-purine-2,6-dione	3.1	493	3.53

Example	R =	Name	Yield (mg)	m/z	RT (min)
386		8-chloro-3-(cyclobutylmethyl)-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	2.2	491	3.45
387		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(2-phenylethyl)-3,7-dihydro-1*H*-purine-2,6-dione	2.4	527	3.50
388		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(3-methyl-2-buten-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione	3.1	491	3.46
389		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*H*-purine-2,6-dione	3.0	533	3.39
390		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*H*-purine-2,6-dione	2.7	519	3.34
391		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(1*H*-pyrrol-1-yl)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione	2.0	516	3.27
392		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(phenyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione	1.6	543	3.44

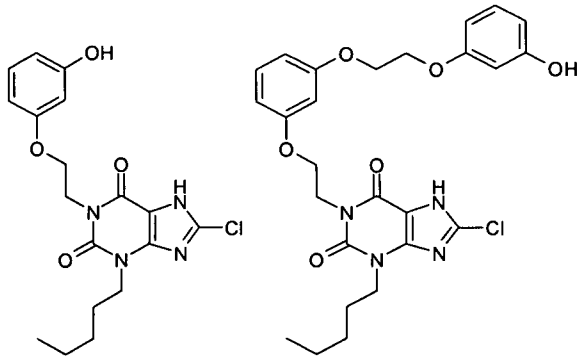
Example	R =	Name	Yield (mg)	m/z	RT (min)
393		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(ethyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione	2.8	495	3.11
394		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[2-(methyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione	2.6	481	2.98
395		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione	3.1	463	3.17
396		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[3-(methyloxy)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	2.1	495	3.04
397		8-chloro-3-cyclopentyl-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	2.5	491	3.52

Example 398: 1-[3-(3-Bromophenyl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 3-(3-bromophenyl)-propan-1-ol (1.627g, 7.56mmol) in THF (65ml) was treated with 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2.04g, 6.87mmol) under nitrogen. PPh_3 (2.164g, 8.25mmol) was added to the stirred mixture after 2min and after a further 6min DBAD (1.9g, 8.25mmol) was added in one portion. The mixture was stirred for 2.5h and then left to react for 16h. The mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (794mg, 0.69mmol) was added and the mixture degassed once more. Morpholine (6ml, 68.8mmol) was added and the mixture was stirred under nitrogen for 6h. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was taken up into MeOH and purified by passing down an aminopropyl SPE, the product eluted with 2-5% AcOH/MeOH. The title compound was obtained as an off-white solid (2.48g, 79%). LC/MS: m/z 455, 453 $[MH]^+$, RT 3.85min.

Example 399: 8-Chloro-1-{2-[(3-hydroxyphenyl)oxy]ethyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione and Example 400: 8-chloro-1-(2-{[3-({2-[(3-hydroxyphenyl)oxy]ethyl}oxy)phenyl]oxy}ethyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



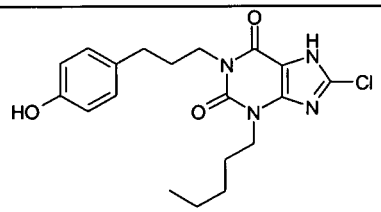
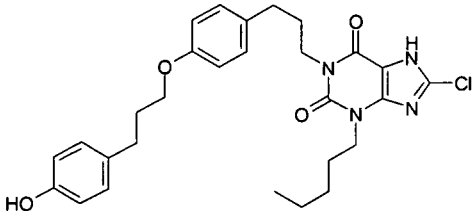
A solution of 2-(2-hydroxyethyl)-resorcinol (1.156g, 7.5mmol) in THF (60ml) was treated with 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2.016g, 6.79mmol) under nitrogen. PPh_3 (2.138g, 8.15mmol) was added to the stirred mixture after 4min and after a further 8min DBAD (1.88g, 8.16mmol) was added in one portion. The mixture was stirred for 1h 50min and then left to react for 16h. The mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (785mg, 0.68mmol) was added and the mixture degassed once more. Morpholine (5.9ml, 67.7mmol) was added and the mixture was stirred under nitrogen for 4.5h. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was taken up into MeOH and purified by passing it down an aminopropyl SPE, the product gradient elution with 2-5% AcOH/MeOH. The fractions containing product were evaporated to give a pale yellow foam (2.39g) and a pale yellow gum (213mg). The foam was dissolved in dichloromethane (50ml) and passed through a hydrophobic frit. The solution was evaporated and dried in vacuo to give 8-chloro-1-{2-[(3-

hydroxyphenyl)oxy]ethyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione as a white solid (1.919g, containing 15% 8-chloro-1-(2-{[3-({2-[(3-hydroxyphenyl)oxy]ethyl}oxy)phenyl]oxy}ethyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione).

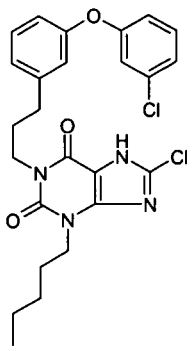
The gum was purified by MDAP to give 8-chloro-1-{2-[(3-hydroxyphenyl)oxy]ethyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione as a white solid (126mg).
LC/MS: m/z 393 $[MH]^+$, RT 3.23min
as well as
8-chloro-1-(2-{[3-({2-[(3-hydroxyphenyl)oxy]ethyl}oxy)phenyl]oxy}ethyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione as a pale yellow solid (38mg).
LC/MS: m/z 529 $[MH]^+$, RT 3.62min.

The following compounds (**Table 25**) were prepared using a method analogous to that for 8-chloro-1-{2-[(3-hydroxyphenyl)oxy]ethyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione above, from the corresponding alcohol.

Table 25

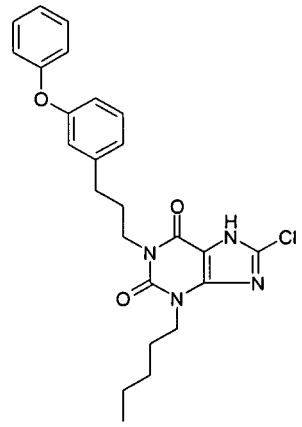
Example	Structure	Yield (mg)	LC/M:
401	 8-chloro-1-[3-(4-hydroxyphenyl)propyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	58	m/z 391 $[MH]^+$ RT 3.38min
402	 8-chloro-1-[3-(4-{[3-(4-hydroxyphenyl)propyl]oxy}phenyl)propyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	12	m/z 525 $[MH]^+$ RT 4.07min

Example 403: 8-Chloro-1-(3-{3-[(3-chlorophenyl)oxy]phenyl}propyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



1-[3-(3-Bromophenyl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.22mmol) was dissolved in dioxan (0.75ml). Copper (1) iodide (9mg, 0.05mmol), N,N-dimethylglycine hydrochloride (9mg, 0.06mmol), cesium carbonate (215mg, 0.66mmol) and 3-chlorophenol (52mg, 0.4mmol) were added to the solution. The mixture was heated under microwave irradiation at 200°C for 10min, followed by another 10min at 200°C after which the cooled mixture was filtered and the residue washed with EtOAc and MeOH. The filtrate and washings were combined and evaporated under reduced pressure to leave a red/brown solid. The solid was partitioned between DCM and water. The phases were separated by hydrophobic frit and the organic evaporated under reduced pressure to leave a solid. The solid was purified by MDAP to give the title compound as a yellow solid/ gum (27mg, 24%).
LC/MS: m/z 501 $[MH]^+$, RT 4.25min.

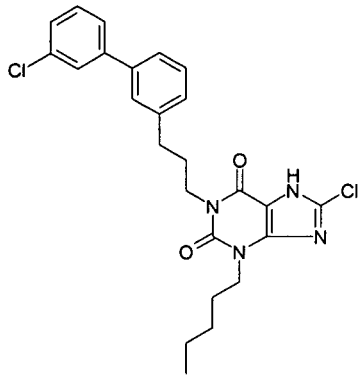
Example 404: 8-Chloro-3-pentyl-1-{3-[3-(phenyloxy)phenyl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione



1-[3-(3-Bromophenyl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.22mmol), copper (1) iodide (4mg, 0.02mmol), N,N-dimethylglycine hydrochloride (9mg, 0.06mmol) cesium carbonate (144mg, 0.44mmol) and phenol (31mg, 0.33mmol) were placed in dioxan (0.44ml). Then the mixture was heated in the microwave at 150°C for 3.3min, then further quantities of cesium carbonate (72mg, 0.22mmol), copper (1) iodide (6mg, 0.03mmol) and dioxan (0.44ml) were added to the mixture and heated in the microwave at 170°C for 10min, followed by another 10min at 200°C. The cooled mixture was filtered and the residue washed with EtOAc. The filtrate

and washings were combined and evaporated under reduced pressure to leave a dark brown gum. The gum was purified by MDAP to give the title compound as a pale cream solid (44mg, 42%).
LC/MS: m/z 467 $[MH]^+$, RT 4.14min.

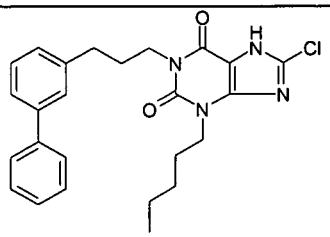
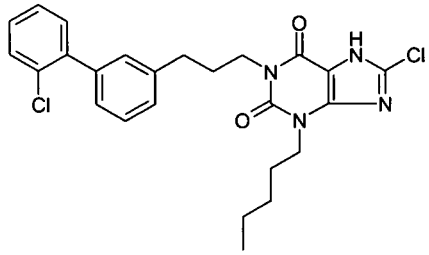
Example 405: 8-Chloro-1-[3-(3'-chloro-3-biphenylyl)propyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



A mixture of 1-[3-(3-bromophenyl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.22mmol) and 3-chlorophenyl boronic acid (35mg, 0.22mmol) was stirred in isopropanol (0.35ml). A solution of sodium carbonate (70mg, 0.66mmol) in water (0.35ml) was added to the mixture followed by 10% palladium on carbon (6mg, Degussa type E101 NE/W). The mixture was heated in the microwave at 160°C for 10min, then filtered (glass fibre filter) and the residues washed with IPA. The filtrate and washings were combined and evaporated under reduced pressure to leave a gum. The gum was partitioned between DCM and water. The organic phase was separated and the aqueous phase extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated to leave a foam. The foam was purified by MDAP to give the title compound as a colourless gum (40mg, 37%).
LC/MS: m/z 485 $[MH]^+$, RT 4.27min.

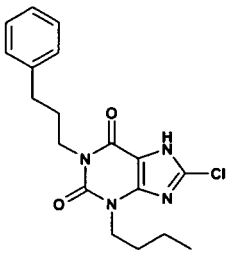
The following compounds (**Table 26**) were prepared using a method analogous to that for 8-chloro-1-[3-(3'-chloro-3-biphenylyl)propyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (Example 405) above, from the corresponding boronic acid, except that the 2-chorophenyl analogue was heated in the microwave at 160°C for 10min twice while in the work up 1M hydrochloric acid was used instead of water. Also the EtOAc extraction was omitted.

Table 26

Example	Structure	Yield (mg)	LC/MS:
406	 1-[3-(3-biphenylyl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	51	m/z 451 $[MH]^+$ RT 4.02min
407	 8-chloro-1-[3-(2'-chloro-3-biphenylyl)propyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	56	m/z 485 $[MH]^+$ RT 4.15min

Example 408: 3-Butyl-8-chloro-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione

a) 3-Butyl-8-chloro-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione

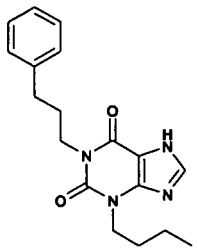


3-Butyl-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.31mmol) and NCS (41mg, 0.31mmol) were suspended in MeCN (5ml) and heated at 120°C under microwave irradiation for 10min. The reaction mixture was concentrated under reduced pressure and the title compound isolated using HPLC.

^{1}H NMR ($CDCl_3$) δ: 0.96 (3H, t), 1.37-1.43 (2H, m), 1.70-1.78 (2H, m), 2.00-2.09 (2H, m), 2.73 (2H, t), 4.08 (2H, t), 4.14 (2H, t), 7.13-7.26 (5H, m), 12.6 (1H, br.s).

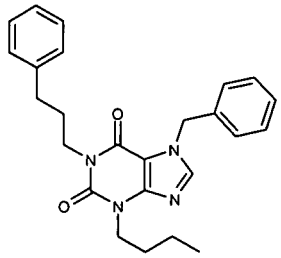
LC/MS: m/z 361 $[MH]^+$.

b) 3-Butyl-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione



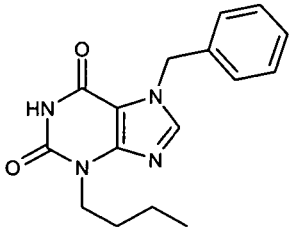
3-Butyl-7-(phenylmethyl)-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione (0.6g, 1.44mmol) was dissolved in acetic acid (35ml), 20% palladium hydroxide on carbon (0.366g) was added, and the mixture was shaken under hydrogen (at 50psi) overnight. The catalyst was removed by filtration through Celite® and washed with acetic acid. The filtrate was concentrated under reduced pressure and the title compound isolated using HPLC (0.385g, 82%).
LC/MS: m/z 327 $[MH]^+$.

c) 3-Butyl-7-(phenylmethyl)-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione



7-Benzyl-3-butyl-3,7-dihydro-1*H*-purine-2,6-dione (0.5g, 1.68mmol) and potassium carbonate (0.347g, 2.5mmol) were suspended in DMF (20ml), (3-bromopropyl)benzene (390mg, 1.96mmol) was added. The reaction mixture was stirred at ambient temperature overnight. The reaction mixture was evaporated to dryness and the residue was partitioned between water and ethyl acetate. The organic layer was washed with water, followed by brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to yield the title compound.
^{1}H NMR ($CDCl_3$) δ: 0.95 (3H, t), 1.34-1.43 (2H, m), 1.68-1.76 (2H, m), 1.98-2.07 (2H, m), 2.71 (2H, t), 4.05-4.10 (4H, m), 5.49 (2H, s), 7.19-7.24 (5H, m), 7.33-7.38 (5H, m), 7.52 (1H, s).
LC/MS: m/z 417 $[MH]^+$.

d) 7-Benzyl-3-butyl-3,7-dihydro-1*H*-purine-2,6-dione

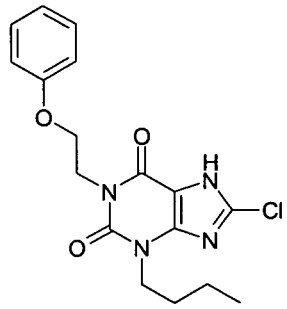


7-Benzyl-3,7-dihydro-1H-purine-2,6-dione (17.14g, 70.8mmol) **[Synthetic Communications, 20(16), *2459-2467*, 1990]** and potassium carbonate (11.43g, 82.8mmol) were suspended in DMF (400ml) at 40°C. After stirring for thirty minutes, butyl iodide (8.76ml, 77.0mmol) was added, and the mixture was stirred at 40°C overnight. 50% Aqueous acetic acid (60ml) was added, and the solution was concentrated under reduced pressure. The residue was suspended in water (500ml), and the products were extracted into chloroform. The organics were collected, concentrated, and product was isolated using flash chromatography eluting with 1% methanol in dichloromethane (9.49g, 45%).

^{1}H NMR ($CDCl_3$) δ: 0.95 (3H, t), 1.34-1.41 (2H, m), 1.70-1.78 (2H, m), 4.05 (2H, t), 5.46 (2H, s), 7.31-7.40 (5H, m), 7.56 (1H, s), 8.21 (1H, br.s).
LC/MS: m/z 299 $[MH]^+$.

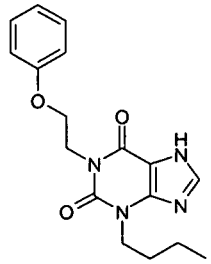
Example 409: 3-Butyl-8-chloro-1-[2-(phenyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione

a) 3-Butyl-8-chloro-1-[2-(phenyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione



The title compound was prepared using the procedure for 3-butyl-8-chloro-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione, from 3-butyl-1-[2-(phenyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione and NCS.
^{1}H NMR ($CDCl_3$) δ: 0.95 (3H, t), 1.36-1.45 (2H, m), 1.71-1.79 (2H, m), 4.11 (2H, t), 4.29 (2H, t), 4.54 (2H, t), 6.87-6.94 (3H, m), 7.21-7.27 (2H, m), 13.10 (1H, br.s).
LC/MS: m/z 363 $[MH]^+$.

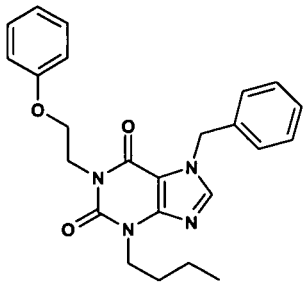
b) 3-Butyl-1-[2-(phenyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione



The title compound was prepared using the procedure outlined for 3-butyl-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione, from 3-butyl-7-(phenylmethyl)-1-[2-(phenyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione.

LC/MS: m/z 329 $[MH]^+$.

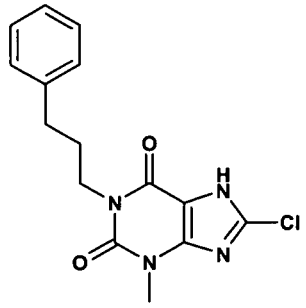
c) 3-Butyl-7-(phenylmethyl)-1-[2-(phenyloxy)ethyl]-3,7-dihydro-1*H*-purine-2,6-dione



The title compound was prepared using the procedure outlined for 3-butyl-7-(phenylmethyl)-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione, from 7-benzyl-3-butyl-3,7-dihydro-1*H*-purine-2,6-dione and 2-bromoethyl phenyl ether.
^{1}H NMR ($CDCl_3$) δ: 0.95 (3H, t), 1.35-1.44 (2H, m), 1.69-1.78 (2H, m), 4.07-4.11 (2H, m), 4.26 (2H, t), 4.434 (2H, t), 5.49 (2H, s), 6.87-7.38 (10H, m), 7.55 (1H, s).
LC/MS: m/z 419 $[MH]^+$.

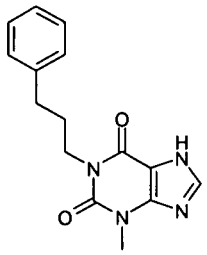
Example 410: 8-Chloro-3-methyl-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-3-methyl-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione



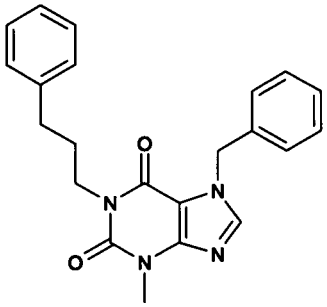
The title compound was prepared using the procedure outlined for 3-butyl-8-chloro-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione, from 3-methyl-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione and NCS.
^{1}H NMR ($CDCl_3$) δ: 2.01-2.12 (2H, m), 2.74 (2H, t), 3.57 (3H, s), 4.14 (2H, t), 6.99-7.24 (5H, m), 12.5 (1H, br.s).
LC/MS: m/z 319 $[MH]^+$.

b) 3-Methyl-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione



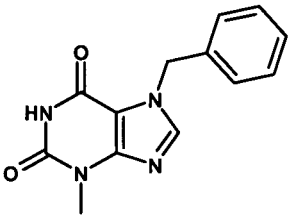
The title compound was prepared using the procedure outlined for 3-butyl-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione, from 3-methyl-7-(phenylmethyl)-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione.
LC/MS: m/z 285 $[MH]^+$.

c) 3-Methyl-7-(phenylmethyl)-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione



The title compound was prepared using the procedure outlined for 3-butyl-7-(phenylmethyl)-1-(3-phenylpropyl)-3,7-dihydro-1*H*-purine-2,6-dione, from 3-methyl-7-(phenylmethyl)-3,7-dihydro-1*H*-purine-2,6-dione and (3-bromopropyl)benzene.
LC/MS: m/z 375 $[MH]^+$.

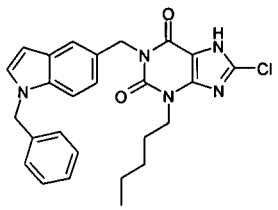
d) 3-Methyl-7-(phenylmethyl)-3,7-dihydro-1*H*-purine-2,6-dione



The title compound was prepared using the procedure described for 7-benzyl-3-butyl-3,7-dihydro-1*H*-purine-2,6-dione using methyl iodide (0.28ml, 4.46mmol). Purification was achieved by trituration. The product was isolated as a solid, insoluble in chloroform and water (0.334g, 57%).
^{1}H NMR (DMSO-d_6) δ: 3.34 (3H, s), 5.44 (2H, s), 7.26-7.37 (5H, m), 8.21 (1H, s), 11.13 (1H, s).
LC/MS: m/z 257 $[MH]^+$.

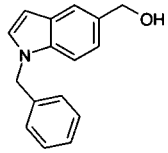
Example 411: 8-Chloro-3-pentyl-1-{[1-(phenylmethyl)-1*H*-indol-5-yl]methyl}-3,7-dihydro-1*H*-purine-2,6-dione

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



8-Chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (156mg, 0.5mmol) was dissolved in anhydrous THF (5ml) under nitrogen and [1-(phenylmethyl)-1*H*-indol-5-yl]methanol (138mg, 0.58mmol) was added. After several minutes triphenylphosphine (168mg, 0.63mmol) was added followed 5-10min later by DBAD (155mg, 0.67mmol) and the solution stirred for 18h. The mixture was degassed by applying a vacuum and then nitrogen was introduced. $Pd(PPh_3)_4$ (63mg, 0.054mmol) was added and the mixture degassed once more. Morpholine (0.461ml, 5.3mmol) was added and the mixture was stirred under nitrogen for 24h. A further quantity of $Pd(PPh_3)_4$ (58mg, 0.05mmol) was added and the mixture was stirred under nitrogen for 96h. The mixture was diluted with EtOAc and washed with 2M HCl (5ml) then brine (15ml), dried ($MgSO_4$) and concentrated. The crude material was purified by an aminopropyl SPE (eluent MeOH to wash through the impurities, then with 3-4% AcOH/MeOH). The product fractions were combined and concentrated to give the title compound as a white solid (43mg, 17%).
LC/MS: m/z 476 $[MH]^+$, RT 3.78min.

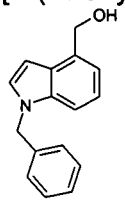
b) [1-(Phenylmethyl)-1*H*-indol-5-yl]methanol



Methyl 1-(phenylmethyl)-1*H*-indole-5-carboxylate (1.17g, 4.4mmol) was dissolved in anhydrous THF under nitrogen and cooled to -5°C. 1M Lithium aluminiumhydride in diethylether (4.0ml) was added slowly. The cooling bath was removed and the reaction mixture was left overnight at room temperature. The reaction was quenched by the sequential addition of water (0.15ml), 15% NaOH (0.15ml) followed by water (0.45ml) then ethyl acetate and sodium sulphate were added and the mixture stirred for 0.5h. The insoluble material was filtered and washed well with ethyl acetate. The filtrate was concentrated *in vacuo* to give the title compound as a cream solid which darkened on standing (1.04g, 100%).
LC/MS: m/z 238 $[MH]^+$, RT 3.03min.

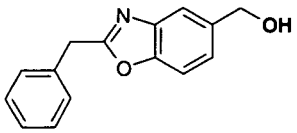
The following alcohols were prepared by reduction of the corresponding methyl ester in a similar manner:

[1-(Phenylmethyl)-1*H*-indol-4-yl]methanol



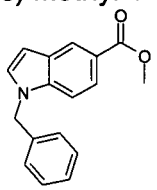
LC/MS: m/z 238 $[MH]^+$, RT 3.03min.

[2-(Phenylmethyl)-1,3-benzoxazol-4-yl]methanol



LC/MS: m/z 240 $[MH]^+$, RT 2.02min.

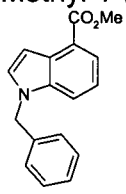
c) Methyl 1-(phenylmethyl)-1*H*-indole-5-carboxylate



Methyl 1*H*-indole-5-carboxylate (1.0g, 5.7mmol) was dissolved in anhydrous DMF under nitrogen and cooled to 2°C. Sodium hydride (0.25g, 6.3mmol, 60% in paraffin) was added. After 0.5h benzyl bromide (0.75ml, 6.0mmol) was added and the reaction mixture stirred for 4hr at room temperature, then left overnight. The reaction mixture was poured into water (50ml) and ethyl acetate (10ml). The aqueous phase was extracted further with ethyl acetate (50ml). The combined organic phases were washed with dil. ammonia then brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified on a 50g Si SPE (gradient elution cyclohexane/ethyl acetate 8% to 16%). The relevant fractions were concentrated *in vacuo* to give the title compound as a white solid (1.17g, 77%)

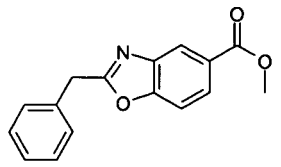
LC/MS: m/z 266 $[MH]^+$, RT 3.60min.

Methyl 1-(phenylmethyl)-1*H*-indole-4-carboxylate was prepared in a similar manner



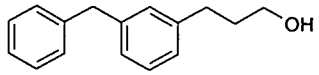
LC/MS: m/z 266 $[MH]^+$, RT 3.58min.

Methyl 2-(phenylmethyl)-1,3-benzoxazole-5-carboxylate



Trimethylbenzylorthoformate (1.34g, 6.8mmol) was dissolved in methanol (2ml) and methyl-3-amino-hydoxybenzoate (0.56g, 3.35mmol) was added followed by conc. hydrochloric acid (9.1ml). The mixture was stirred at reflux for 4.75h, allowed to cool and evaporated *in vacuo*. The residue was partitioned between diethyl ether (10ml) and 2M NaOH solution (5ml). The organic phase was washed with water (5ml) and the combined aqueous phases were back extracted with ether (10ml). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to leave an orange oil (1.37g). The crude product was purified on silica (40g SPE, gradient elution cyclohexane/ethyl acetate 0-100%) to give the title compound as a white solid (0.72g, 80%).
LC/MS: m/z 268 $[MH]^+$, RT 3.27min.

3-[3-(Phenylmethyl)phenyl]-1-propanol

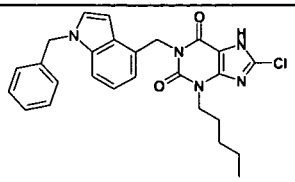
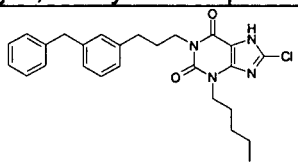
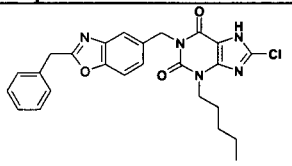


3-[3-(phenylcarbonyl)phenyl]propanoic acid (491mg, 1.96mmol) was dissolved in anhydrous THF under nitrogen and cooled to 0°C. 1M $LiAlH_4$ in ether (2.13ml) was added slowly and the reaction mixture was stirred at room temperature for 20h. The reaction was cooled in ice and tetrahydrofuran (5ml) and 1M $LiAlH_4$ in ether solution (2.2ml) added. The reaction mixture was heated at reflux for 7hr then left at room temperature for 3 days. The reaction was quenched with sequentially, water (0.16ml), 15% NaOH (0.16ml) and water (0.47ml) then diluted with ethyl acetate and dried with sodium sulphate. The insoluble material was filtered and thoroughly washed with ethyl acetate. The filtrate was concentrated *in vacuo* to give 3-{3-[hydroxy(phenyl)methyl]phenyl}-1-propanol as a white opaque oil (0.42g, 90%)
LC/MS: m/z 243 $[MH]^+$, RT 2.71min.

The above material (200mg, 0.82mmol) was dissolved in anhydrous dichloromethane (5ml) and triethylsilane (0.53ml, 3.2mmol) followed by trifluoroacetic acid (0.36ml, 4.1mmol) were added. The reaction mixture was stirred for 1h then washed with saturated sodium hydrogen carbonate solution. The organic phase was filtered through a hydrophobic frit and concentrated *in vacuo*. The crude product was purified over silica (4g SPE, gradient elution cyclohexane/ethyl acetate 0-30%) to give the title compound as a colourless oil (68mg, 37%).
LC/MS: m/z 227 $[MH]^+$, RT 3.25min.

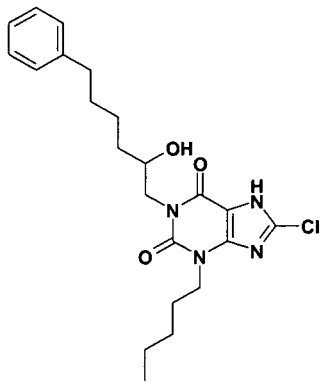
The following compounds (**Table 27**) were prepared using a method analogous to that for 8-chloro-3-pentyl-1-{[1-(phenylmethyl)-1*H*-indol-5-yl]methyl}-3,7-dihydro-1*H*-purine-2,6-dione from the corresponding alcohols as described above.

Table 27

Example	Structure	Yield (mg)	LC/MS:
412	 8-chloro-3-pentyl-1-{[1-(phenylmethyl)-1*H*-indol-4-yl]methyl}-3,7-dihydro-1*H*-purine-2,6-dione	49	m/z 476 $[MH]^+$ RT 3.82min
413	 8-chloro-3-pentyl-1-{3-[3-(phenylmethyl)phenyl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione	70	m/z 465 $[MH]^+$ RT 4.01min
414	 8-chloro-3-pentyl-1-{[2-(phenylmethyl)-1,3-benzoxazol-5-yl]methyl}-3,7-dihydro-1*H*-purine-2,6-dione	174	m/z 478 $[MH]^+$ RT 3.70min

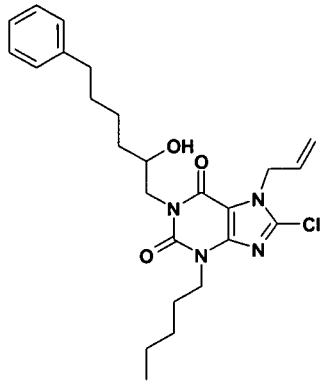
Example 415: 8-Chloro-1-(2-hydroxy-6-phenylhexyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

a) 8-Chloro-1-(2-hydroxy-6-phenylhexyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



A solution of 8-chloro-1-(2-hydroxy-6-phenylhexyl)-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.084g, 0.18mmol) and $Pd(PPh_3)_4$ (0.042g, 0.035mmol) in THF (5ml) was degassed (sequential evacuation followed by addition of nitrogen x 3) then morpholine (0.25ml, 2.8mmol) added and the mixture stirred overnight. The solution was loaded onto an aminopropyl SPE (5g) and eluted with MeOH to remove by-products then with 5%AcOH/MeOH to isolate the title compound, after concentration, as an oil (0.022g, 29%).
LC/MS: m/z 433 $[MH]^+$

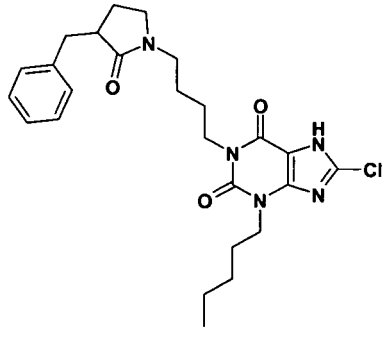
b) 8-Chloro-1-(2-hydroxy-6-phenylhexyl)-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



To a solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.107g, 0.36mmol) and 1-chloro-6-phenyl-2-hexanol (0.107g, 0.5mmol) in DMF (5ml) was added cesium carbonate (0.24g, 0.74mmol) and the mixture heated at 60°C for 3h, whereupon a further 80mg of cesium carbonate was added and heating continued at 100°C for 18h. The solution was allowed to cool, concentrated and the residues purified by chromatography over silica (20g SPE, eluting with first with DCM then DCM/10%ether) to yield the title compound as a yellow oil (0.085mg, 53%).
LC/MS: m/z 473 $[MH]^+$

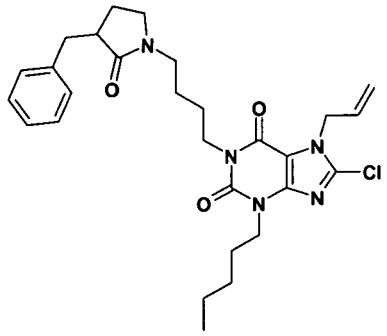
Example 416: 8-Chloro-1-{4-[2-oxo-3-(phenylmethyl)-1-pyrrolidinyl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

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



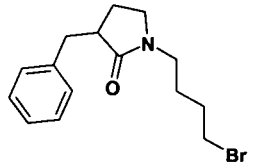
A solution of 8-chloro-1-{4-[2-oxo-3-(phenylmethyl)-1-pyrrolidinyl]butyl}-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.35g, 0.67mmol), $Pd(PPh_3)_4$ (0.082g, 0.07mmol) and morpholine (0.6ml, 6.7mmol) in THF (10ml) was degassed (sequential evacuation followed by addition of nitrogen 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-1*H*-purine-2,6-dione



Prepared as with 8-chloro-1-(2-hydroxy-6-phenylhexyl)-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-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 $[MH]^+$

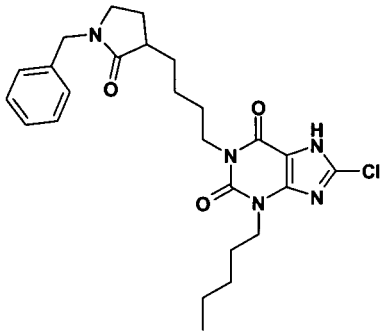
c) 1-(4-bromobutyl)-3-(phenylmethyl)-2-pyrrolidinone



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 417: 8-Chloro-1-{4-[2-oxo-1-(phenylmethyl)-3-pyrrolidinyl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

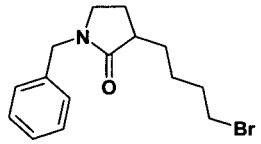
a) 8-Chloro-1-{4-[2-oxo-1-(phenylmethyl)-3-pyrrolidinyl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



To a solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-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 $Pd(PPh_3)_4$ (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 $[MH]^+$

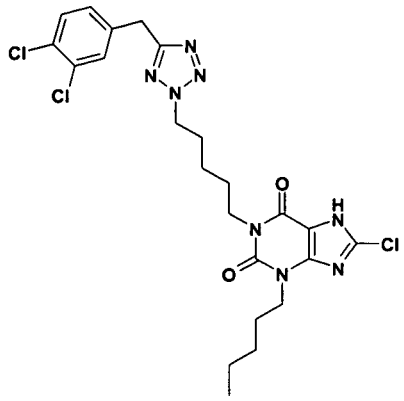
b) 3-(4-Bromobutyl)-1-(phenylmethyl)-2-pyrrolidinone



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 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 used in the next step without further purification.

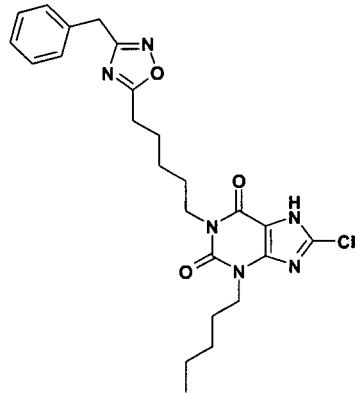
LC/MS: m/z 310, 312 $[MH]^+$

Example 418: 8-Chloro-1-(5-{5-[(3,4-dichlorophenyl)methyl]-2*H*-tetrazol-2-yl}pentyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



To a solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.18g, 0.61mmol) in THF (5ml) was added 5-{5-[(3,4-dichlorophenyl)methyl]-2*H*-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 $Pd(PPh_3)_4$ (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 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 $[MH]^+$

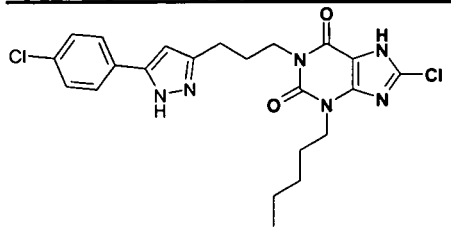
Example 419: 8-Chloro-3-pentyl-1-{5-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]pentyl}-3,7-dihydro-1*H*-purine-2,6-dione



To a solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.093g, 0.3mmol) in THF (5ml) was added 5-[3-(phenylmethyl)-1,2,4-oxadiazol-5-yl]-1-pentanol (0.077g, 0.3mmol; prepared in similar fashion to **Example 87b**), triphenylphosphine (0.17g, 0.6mmol) and finally dibenzylazodicarboxylate (0.20g, 0.6mmol). The solution was stirred for 18h, degassed, after which $Pd(PPh_3)_4$ (0.08g, 0.07mmol) followed by morpholine (0.35ml, 3.9mmol) was added and the solution stirred at ambient temperature for 6h. The solution was loaded onto an aminopropyl

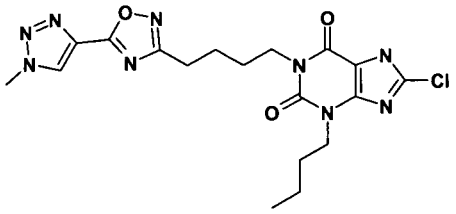
SPE (5g) and eluted with MeOH then 5%AcOH/MeOH to yield the title compound as a cream solid (0.051g, 34%).
LC/MS: m/z 485 $[MH]^+$

Example 420: 8-Chloro-1-{3-[5-(4-chlorophenyl)-1*H*-pyrazol-3-yl]propyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



Prepared as with 8-chloro-1-(5-{5-[(3,4-dichlorophenyl)methyl]-2*H*-tetrazol-2-yl}pentyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione using 3-[5-(4-chlorophenyl)-1*H*-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 $[MH]^+$

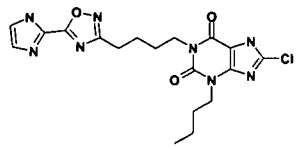
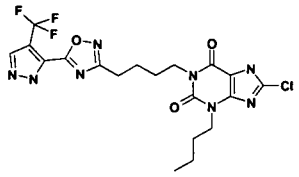
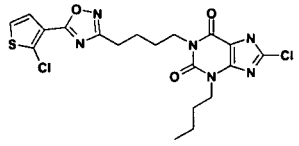
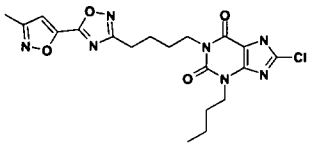
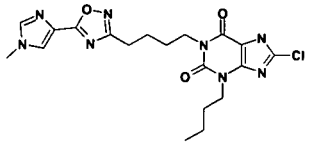
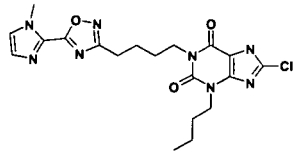
Example 421: 3-Butyl-8-chloro-1-{4-[5-(1-methyl-1*H*-1,2,3-triazol-4-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione

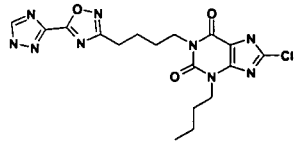
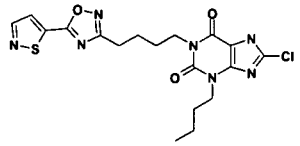
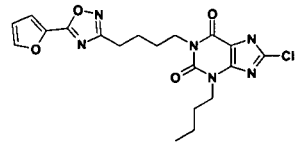
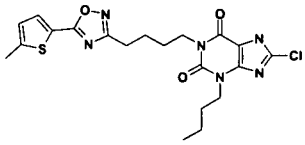
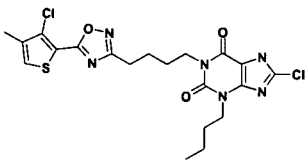
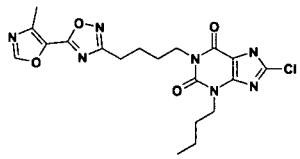
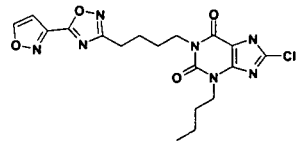


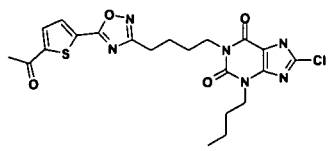
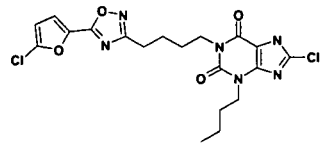
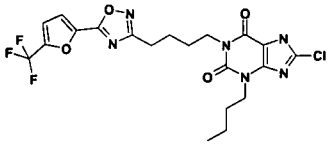
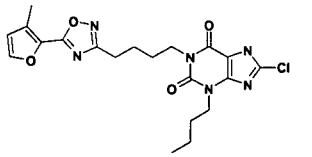
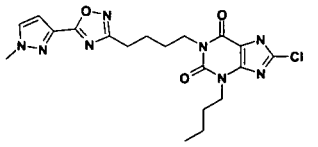
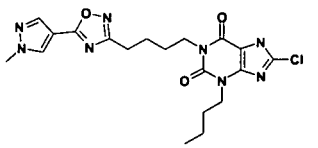
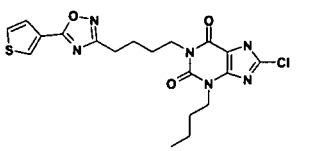
A solution of the 1-methyl-1*H*-1,2,3-triazole-4-carboxylic acid (18mg, 0.14mmol) in DMF (0.5ml) was treated with CDI (23mg, 0.14mmol) at rt for 1h. A solution of (1Z)-5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-N-hydroxypentanimidamide (50mg, 0.14mmol) in DMSO (0.4ml) was added 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.

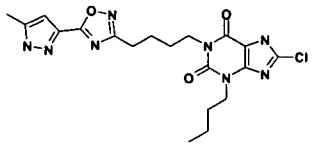
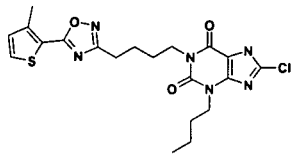
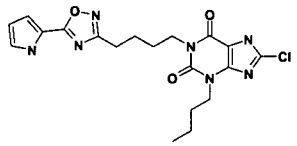
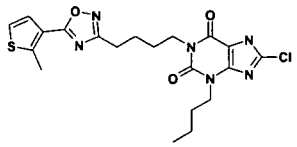
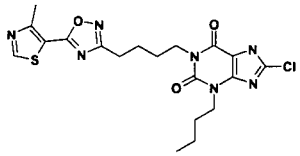
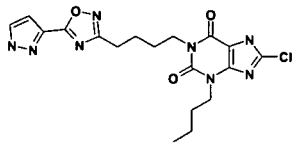
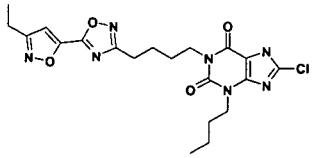
The following compounds (**Table 28**) were prepared using a method analogous to that for **Example 421**, using the appropriate carboxylic acid.

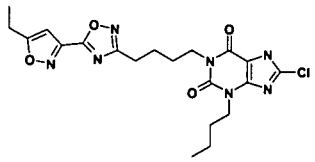
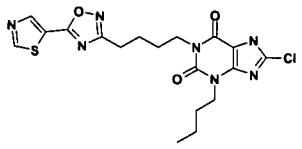
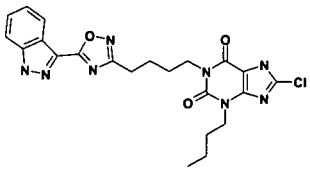
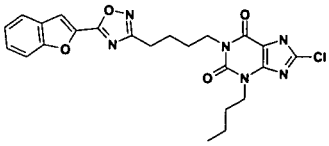
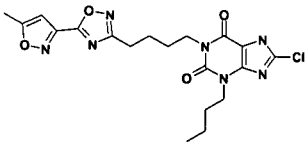
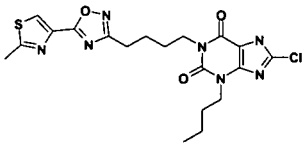
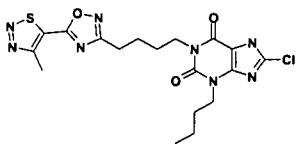
Table 28

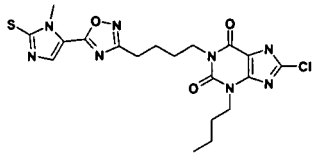
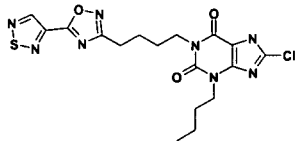
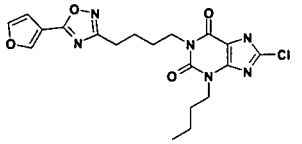
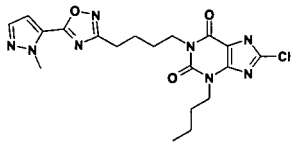
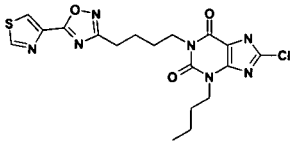
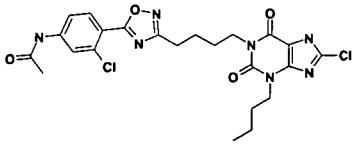
Example	Structure	Name	Yield (mg)	LC/MS
422		3-butyl-8-chloro-1-{4-[5-(1*H*-imidazol-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	16	m/z 433 $[MH]^+$ RT 2.79min
423		3-butyl-8-chloro-1-(4-{5-[4-(trifluoromethyl)-1*H*-pyrazol-5-yl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1*H*-purine-2,6-dione	19	m/z 501 $[MH]^+$ RT 3.28min
424		3-butyl-8-chloro-1-{4-[5-(2-chloro-3-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	26	m/z 483 $[MH]^+$ RT 3.59min
425		3-butyl-8-chloro-1-{4-[5-(3-methyl-5-isoxazolyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	25	m/z 448 $[MH]^+$ RT 3.21min
426		3-butyl-8-chloro-1-{4-[5-(1-methyl-1*H*-imidazol-4-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	16	m/z 447 $[MH]^+$ RT 2.74min
427		3-butyl-8-chloro-1-{4-[5-(1-methyl-1*H*-imidazol-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	9	m/z 447 $[MH]^+$ RT 2.91min

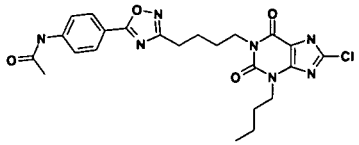
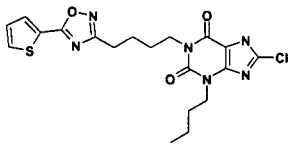
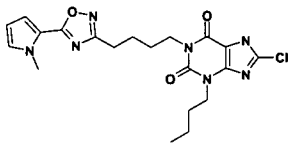
428		3-butyl-8-chloro-1-{4-[5-(1*H*-1,2,4-triazol-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	10	m/z 434 $[MH]^+$ RT 2.73min
429		3-butyl-8-chloro-1-{4-[5-(5-isothiazolyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	17	m/z 450 $[MH]^+$ RT 3.34min
430		3-butyl-8-chloro-1-{4-[5-(2-furanyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	26	m/z 433 $[MH]^+$ RT 3.27min
431		3-butyl-8-chloro-1-{4-[5-(5-methyl-2-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	29	m/z 463 $[MH]^+$ RT 3.61min
432		3-butyl-8-chloro-1-{4-[5-(3-chloro-4-methyl-2-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	30	m/z 497 $[MH]^+$ RT 3.76min
433		3-butyl-8-chloro-1-{4-[5-(4-methyl-1,3-oxazol-5-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	25	m/z 448 $[MH]^+$ RT 3.13min
434		3-butyl-8-chloro-1-{4-[5-(3-isoxazolyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	23	m/z 434 $[MH]^+$ RT 3.20min

435		1-{4-[5-(5-acetyl-2-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione	28	m/z 491 $[MH]^+$ RT 3.43min
436		3-butyl-8-chloro-1-{4-[5-(5-chloro-2-furanyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	27	m/z 467 $[MH]^+$ RT 3.51min
437		3-butyl-8-chloro-1-(4-{5-[5-(trifluoromethyl)-2-furanyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1*H*-purine-2,6-dione	27	m/z 501 $[MH]^+$ RT 3.61min
438		3-butyl-8-chloro-1-{4-[5-(3-methyl-2-furanyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	27	m/z 447 $[MH]^+$ RT 3.43min
439		3-butyl-8-chloro-1-{4-[5-(1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	25	m/z 447 $[MH]^+$ RT 3.02min
440		3-butyl-8-chloro-1-{4-[5-(1-methyl-1*H*-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	8	m/z 447 $[MH]^+$ RT 2.99min
441		3-butyl-8-chloro-1-{4-[5-(3-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	19	m/z 449 $[MH]^+$ RT 3.43min

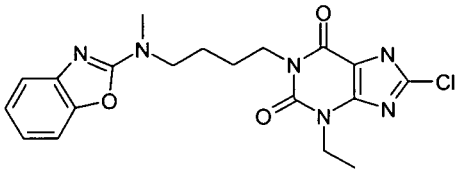
442		3-butyl-8-chloro-1-{4-[5-(5-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	26	m/z 447 $[MH]^+$ RT 3.03min
443		3-butyl-8-chloro-1-{4-[5-(3-methyl-2-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	27	m/z 463 $[MH]^+$ RT 3.62min
444		3-butyl-8-chloro-1-{4-[5-(1*H*-pyrrol-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	13	m/z 432 $[MH]^+$ RT 3.26min
445		3-butyl-8-chloro-1-{4-[5-(2-methyl-3-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	18	m/z 463 $[MH]^+$ RT 3.64min
446		3-butyl-8-chloro-1-{4-[5-(4-methyl-1,3-thiazol-5-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	24	m/z 464 $[MH]^+$ RT 3.26min
447		3-butyl-8-chloro-1-{4-[5-(1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	20	m/z 433 $[MH]^+$ RT 3.00min
448		3-butyl-8-chloro-1-{4-[5-(3-ethyl-5-isoxazolyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	20	m/z 462 $[MH]^+$ RT 3.43min

449		3-butyl-8-chloro-1-{4-[5-(5-ethyl-3-isoxazolyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	23	m/z 462 $[MH]^+$ RT 3.46min
450		3-butyl-8-chloro-1-{4-[5-(1,3-thiazol-5-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	20	m/z 450 $[MH]^+$ RT 3.13min
451		3-butyl-8-chloro-1-{4-[5-(1*H*-indazol-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	24	m/z 483 $[MH]^+$ RT 3.50min
452		1-{4-[5-(1-benzofuran-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione	6	m/z 483 $[MH]^+$ RT 3.72min
453		3-butyl-8-chloro-1-{4-[5-(5-methyl-3-isoxazolyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	13	m/z 448 $[MH]^+$ RT 3.30min
454		3-butyl-8-chloro-1-{4-[5-(2-methyl-1,3-thiazol-4-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	20	m/z 464 $[MH]^+$ RT 3.14min
455		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-1*H*-purine-	14	m/z 465 $[MH]^+$ RT 3.40min

		2,6-dione		
456		3-butyl-8-chloro-1-{4-[5-(3-methyl-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	16	m/z 479 $[MH]^+$ RT 3.08min
457		3-butyl-8-chloro-1-{4-[5-(1,2,5-thiadiazol-3-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	24	m/z 451 $[MH]^+$ RT 3.27min
458		3-butyl-8-chloro-1-{4-[5-(3-furanyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	21	m/z 433 $[MH]^+$ RT 3.29min
459		3-butyl-8-chloro-1-{4-[5-(1-methyl-1*H*-pyrazol-5-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	23	m/z 447 $[MH]^+$ RT 3.22min
460		3-butyl-8-chloro-1-{4-[5-(1,3-thiazol-4-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	20	m/z 450 $[MH]^+$ RT 3.06min
461		*N*-(4-{3-[4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butyl]-1,2,4-oxadiazol-5-yl}-3-chlorophenyl)acetamide	23	m/z 534 $[MH]^+$ RT 3.44min

462		*N*-(4-{3-[4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butyl]-1,2,4-oxadiazol-5-yl}phenyl)acetamide	16	m/z 500 $[MH]^+$ RT 3.23min
463		3-butyl-8-chloro-1-{4-[5-(2-thienyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	27	m/z 449 $[MH]^+$ RT 3.45min
464		3-butyl-8-chloro-1-{4-[5-(1-methyl-1*H*-pyrrol-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	15	m/z 446 $[MH]^+$ RT 3.45min

Example 465 : 1-{4-[1,3-Benzoxazol-2-yl(methyl)amino]butyl}-8-chloro-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione



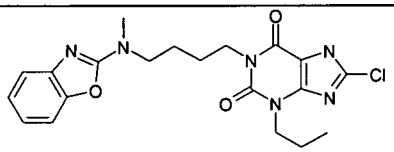
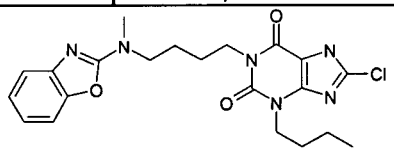
A solution of 2-chloro-1,3-benzoxazole (0.46g, 3mmol) in THF (20ml) was treated with 1-methylpyrrolidine (0.26g, 3mmol) and the reaction mixture heated at reflux for 6h, then cooled and evaporated to dryness. Purification by flash chromatography [Isco Companion, 12g Redisep cartridge, gradient elution from cyclohexane to cyclohexane/diethyl ether (3:2)] revealed 0.52g (73% yield) of *N*-(4-chlorobutyl)-*N*-methyl-1,3-benzoxazol-2-amine as a colourless oil. LC/MS: m/z 239 $[MH]^+$, RT 3.12min.

A solution of 8-chloro-3-ethyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.112g, 0.44mmol) in DMF (10ml) was treated with potassium carbonate (0.08g, 0.6mmol) and *N*-(4-chlorobutyl)-*N*-methyl-1,3-benzoxazol-2-amine (0.12g, 0.5mmol). The reaction mixture was heated at 75°C for 18h and then cooled to ambient temperature. The mixture was degassed by the repeated application of vacuum followed by backfilling with nitrogen gas and then treated with tetrakis(triphenylphosphine)palladium(0) (0.03g, 0.026mmol) and morpholine (0.5ml, 5.7mmol). Stirred for 4h under a nitrogen atmosphere at ambient temperature after which time the mixture was evaporated to dryness and the residue partitioned between

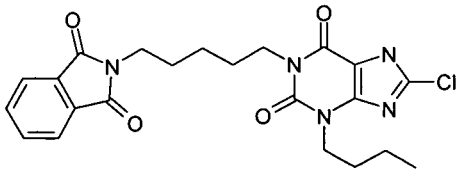
chloroform (40ml) and saturated aqueous ammonium chloride (40ml). The organic phase was evaporated to dryness and the residue dissolved in methanol (5ml) and added to a 5g aminopropyl SPE cartridge which was subsequently washed with methanol and the product eluted with a 5% solution of acetic acid in methanol. Combined product-containing fractions were evaporated to dryness and the product purified by MDAP to give the title compound as a white solid (0.043g, 23%).
LC/MS: m/z 417 $[MH]^+$, RT 2.91min.

The following compounds (**Table 29**) were prepared by a method analogous to that for **Example 465**.

Table 29

Example	Structure	Precursor	Yield (mg)	LC/MS
466	 1-{4-[1,3-benzoxazol-2-yl(methyl)amino]butyl}-8-chloro-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione	8-chloro-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione	47	m/z 431 $[MH]^+$ RT 3.09min
467	 1-{4-[1,3-benzoxazol-2-yl(methyl)amino]butyl}-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione	3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione	61	m/z 445 $[MH]^+$ RT 3.28min

Example 468 : 3-Butyl-8-chloro-1-[5-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)pentyl]-3,7-dihydro-1*H*-purine-2,6-dione



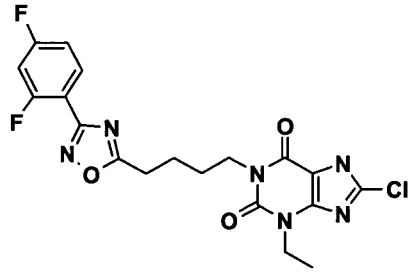
A solution of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (0.5g, 1.8mmol) in DMF (20ml) was treated with potassium carbonate (0.3g, 2.1mmol) and 1,5-dibromopentane (1.2ml, 8.9mmol) and then heated at 50°C for 2h. The mixture was cooled and evaporated to dryness. The residue was partitioned between ethyl acetate

(30ml) and saturated aqueous sodium bicarbonate (30ml). The aqueous phase was extracted with a further ethyl acetate (30ml) and the combined organics dried over magnesium sulfate, filtered and evaporated to dryness. The product was purified by flash chromatography [Isco Companion, 40g Redisep carteidge, gradient elution from cyclohehane to cyclohexane/ethyl acetate (1:1)] to reveal 0.663g (87%) of 1-(5-bromopentyl)-3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione as a colourless oil. LC/MS: m/z 431/433 $[MH]^+$, RT 3.76min.

To a solution of 1-(5-bromopentyl)-3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.642g, 1.5mmol) in DMF (10ml) was added potassium phthalimide (0.303g, 1.6mmol) and the mixture heated at 50°C for 2h 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) (0.173g, 0.15mmol) and morpholine (1.3ml, 15mmol). The mixture was allowed to stand at ambient temperature under a blanket of nitrogen for 18h after which time the mixture was evaporated and the residue partitioned between chloroform (30ml) and saturated aqueous ammonium chloride (30ml). The aqueous phase was extracted with a further chloroform (30ml) and the combined organics dried over magnesium sulfate, filtered and evaporated. The residue was dissolved in methanol (5ml) and added to a 10g aminopropyl SPE cartridge which was subsequently washed with methanol and the product eluted with a 5% solution of acetic acid in methanol. Product-containing fractions were evaporated and then purification by MDAP to give N-[5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentyl]-2-(4-morpholinylcarbonyl)benzamide as a white solid (0.137g,LC/MS: m/z 545 $[MH]^+$, RT 2.77min) and the title compound as a white solid (0.239g, 35%).
LC/MS: m/z 458 $[MH]^+$, RT 3.33min.

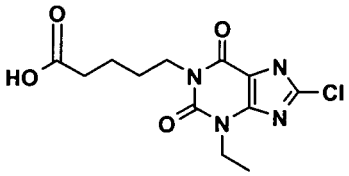
Example 469 : 8-Chloro-1-{4-[3-(2,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione

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



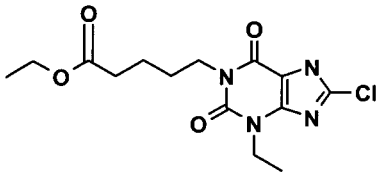
A solution of 5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid (0.05g, 0.16mmol) in DMSO (1ml) was treated with CDI (0.029g, 0.18mmol) and the mixture stirred at room temperature for 1h. Subsequently, the mixture was treated with 2,4-difluorobenzamidoxime (0.03g, 0.18mmol) 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



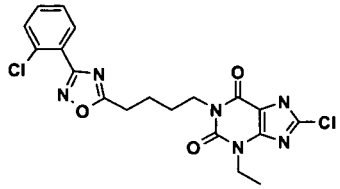
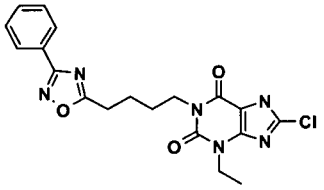
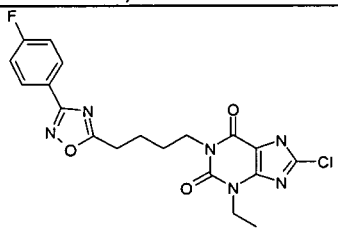
A solution of 8-chloro-7-(2-propen-1-yl)-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione (3g, 11.8mmol) in DMF (40ml) was treated with potassium carbonate (1.9g, 14.1mmol) and ethyl 5-bromopentanoate (2.24ml, 14.1mmol) and the mixture heated in a nitrogen atmosphere at 70°C for 5h and then cooled. The mixture 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

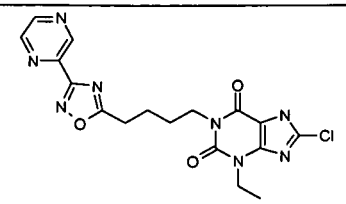
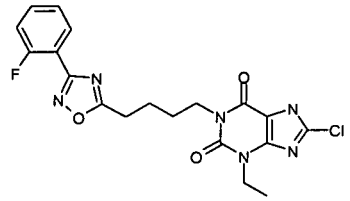
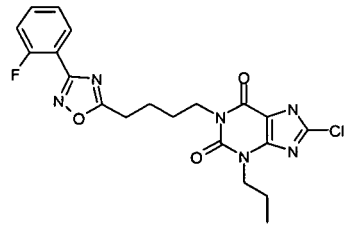
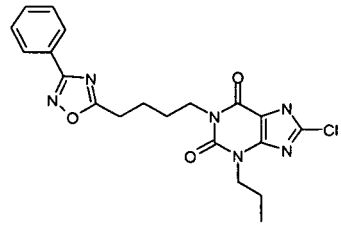
and the combined organics dried over magnesium sulfate, filtered and evaporated. The residue was triturated in diethyl ether, filtered and dried to reveal ethyl 5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoate compound as a white solid (2.3g, 57%).

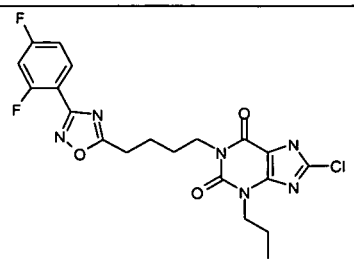
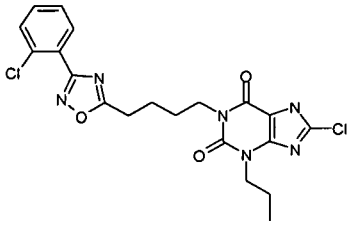
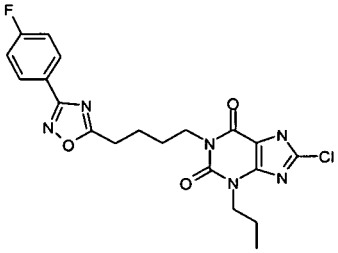
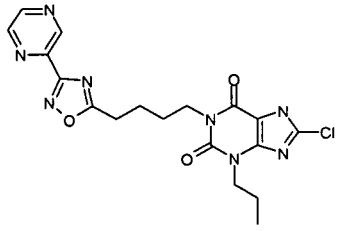
LC/MS: m/z 343 $[MH]^+$, RT 2.73min.

The following compounds (**Table 30**) were prepared by a method analogous to that for **Example 469**.

Table 30

Example	Structure	Precursor	Yield (mg)	LC/MS
470	 8-chloro-1-{4-[3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione	5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	33	m/z 449 $[MH]^+$ RT 3.27min
471	 8-chloro-1-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione	5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	32	m/z 415 $[MH]^+$ RT 3.22min
472	 8-chloro-3-ethyl-1-{4-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	31	m/z 433 $[MH]^+$ RT 3.26min

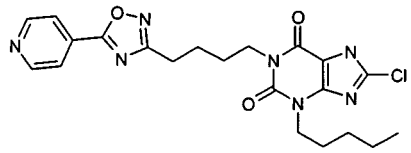
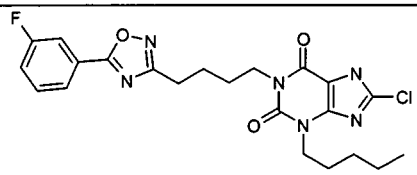
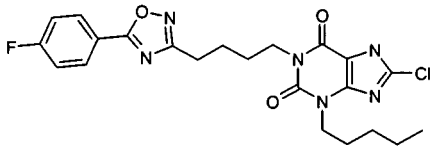
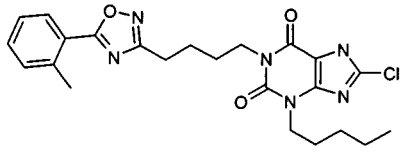
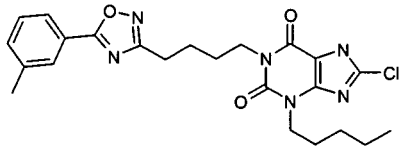
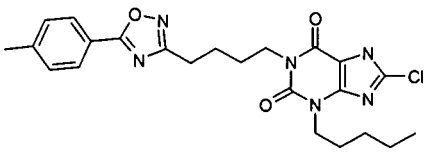
473	 8-chloro-3-ethyl-1-{4-[3-(2-pyrazinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	2	m/z 417 $[MH]^+$ RT 2.54min
474	 8-chloro-3-ethyl-1-{4-[3-(2-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	5-(8-chloro-3-ethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	38	m/z 433 $[MH]^+$ RT 3.12min
475	 8-chloro-1-{4-[3-(2-fluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione	5-(8-chloro-3-propyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	29	m/z 447 $[MH]^+$ RT 3.28min
476	 8-chloro-1-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione	5-(8-chloro-3-propyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	11	m/z 429 $[MH]^+$ RT 3.35min

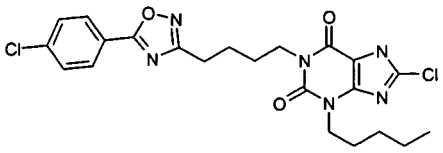
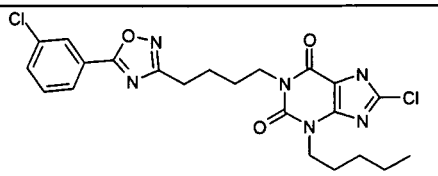
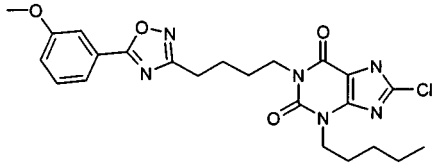
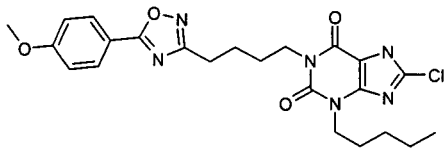
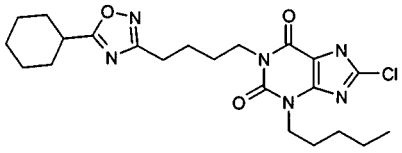
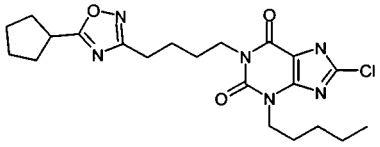
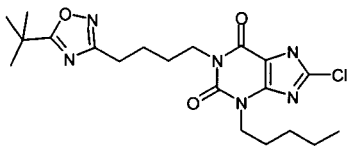
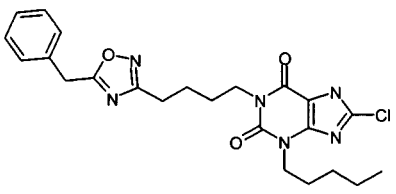
477	 8-chloro-1-{4-[3-(2,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione	5-(8-chloro-3-propyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	32	m/z 465 $[MH]^+$ RT 3.40min
478	 8-chloro-1-{4-[3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione	5-(8-chloro-3-propyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	25	m/z 463 $[MH]^+$ RT 3.40min
479	 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-1*H*-purin-1-yl)pentanoic acid	26	m/z 447 $[MH]^+$ RT 3.44min
480	 8-chloro-3-propyl-1-{4-[3-(2-pyrazinyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-	5-(8-chloro-3-propyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	25	m/z 431 $[MH]^+$ RT 3.09min

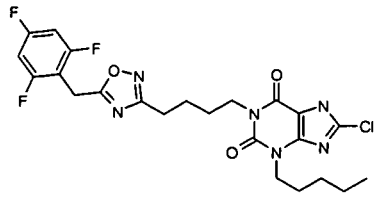
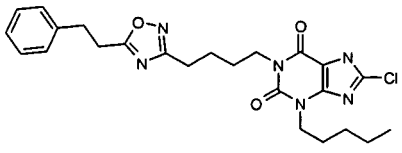
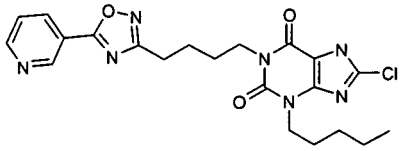
	purine-2,6-dione			

The following compounds (**Table 31**) were prepared using a method analogous to that for **Example 158**, using the appropriate acid.

Table 31

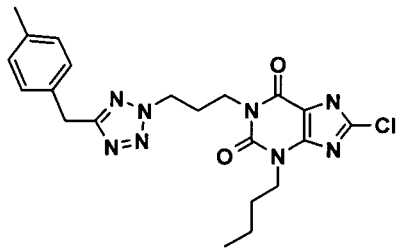
Example	Structure	Name	Yield (mg)	LC/MS
481		8-chloro-3-pentyl-1-{4-[5-(4-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	8.0	m/z 458 $[MH]^+$ RT 3.25min
482		8-chloro-1-{4-[5-(3-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	9.1	m/z 475 $[MH]^+$ RT 3.73min
483		8-chloro-1-{4-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	16.1	m/z 475 $[MH]^+$ RT 3.69min
484		8-chloro-1-{4-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	22.9	m/z 471 $[MH]^+$ RT 3.82min
485		8-chloro-1-{4-[5-(3-methylphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	18.0	m/z 471 $[MH]^+$ RT 3.81min
486		8-chloro-1-{4-[5-(4-methylphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	25.0	m/z 471 $[MH]^+$ RT 3.80min

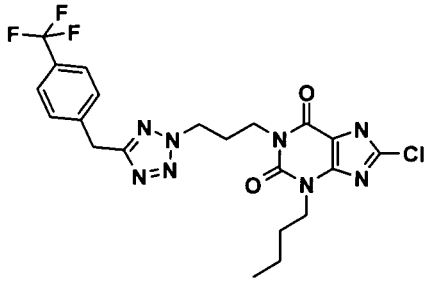
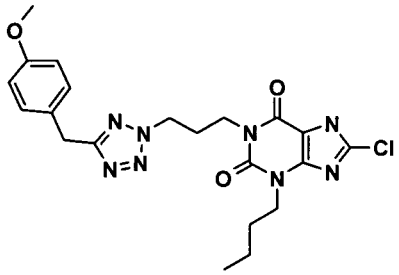
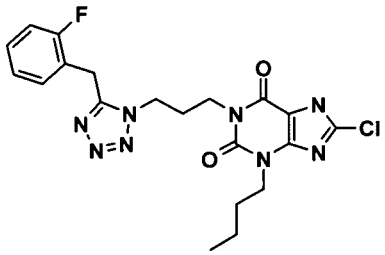
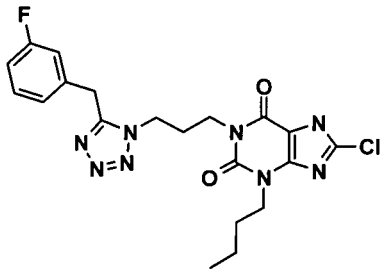
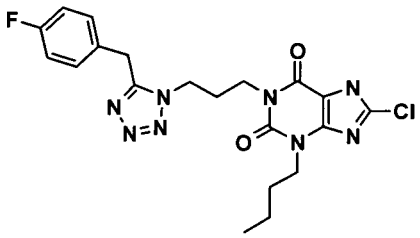
487		8-chloro-1-{4-[5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	16.6	m/z 491 $[MH]^+$ RT 3.89min
488		8-chloro-1-{4-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	12.8	m/z 491 $[MH]^+$ RT 3.91min
489		8-chloro-1-(4-{5-[3-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}butyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	23.0	m/z 487 $[MH]^+$ RT 3.71min
490		8-chloro-1-(4-{5-[4-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}butyl)-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	15.8	m/z 487 $[MH]^+$ RT 3.67min
491		8-chloro-1-[4-(5-cyclohexyl-1,2,4-oxadiazol-3-yl)butyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	16.1	m/z 463 $[MH]^+$ RT 3.73min
492		8-chloro-1-[4-(5-cyclopentyl-1,2,4-oxadiazol-3-yl)butyl]-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	11.7	m/z 449 $[MH]^+$ RT 3.59min
493		8-chloro-1-{4-[5-(1,1-dimethylethyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione	19.8	m/z 437 $[MH]^+$ RT 3.52min
494		8-chloro-3-pentyl-1-{4-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-	21.0	m/z 471 $[MH]^+$ RT 3.55min

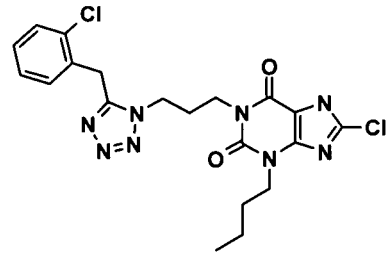
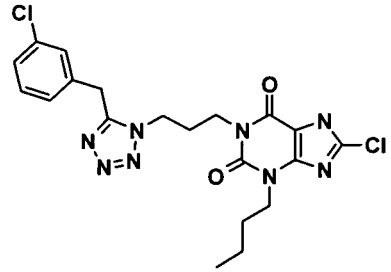
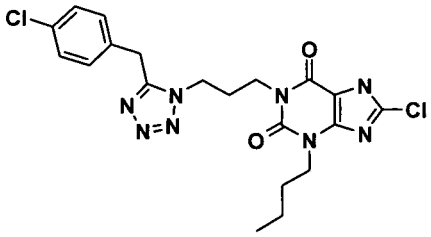
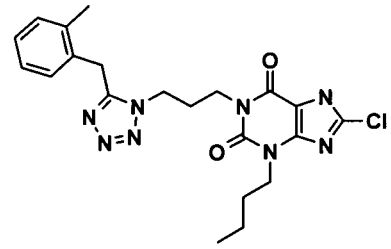
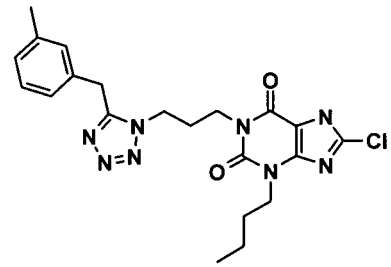
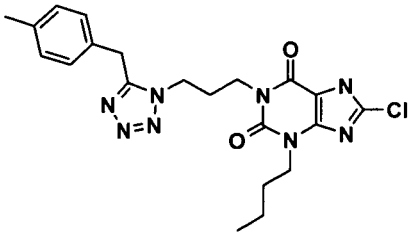
		1*H*-purine-2,6-dione		
495		8-chloro-3-pentyl-1-(4-{5-[(2,4,6-trifluorophenyl)methyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1*H*-purine-2,6-dione	29.3	m/z 525 $[MH]^+$ RT 3.62min
496		8-chloro-3-pentyl-1-{4-[5-(2-phenylethyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	18.4	m/z 485 $[MH]^+$ RT 3.64min
497		8-chloro-3-pentyl-1-{4-[5-(3-pyridinyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	8.2	m/z 458 $[MH]^+$ RT 3.23min

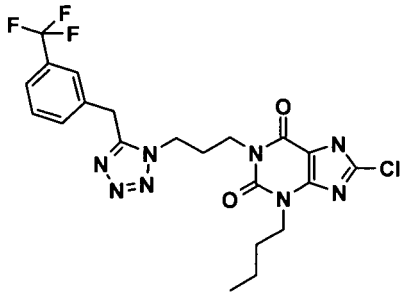
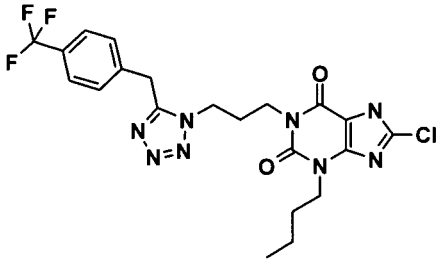
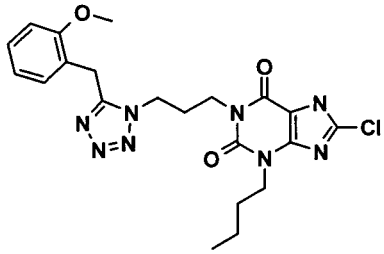
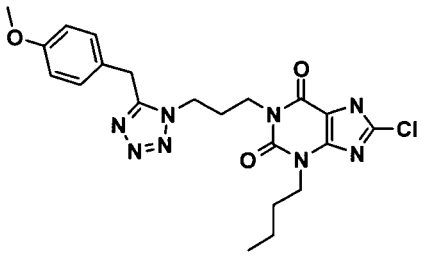
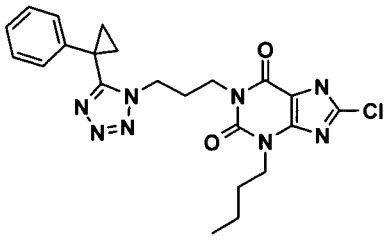
The following compounds (**Table 32**) were prepared using a method analogous to that for **Example 36**, using the appropriate tetrazole and 3-[3-alkyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]propyl methanesulfonate. MDAP was employed to further purify those compounds insufficiently pure following normal phase chromatography.

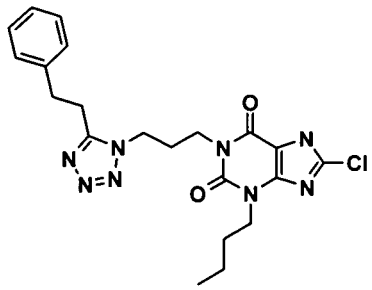
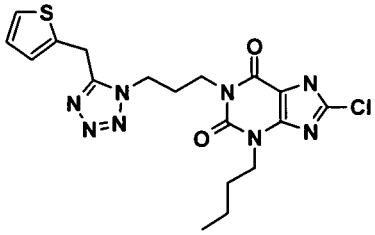
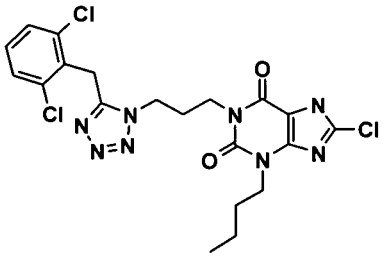
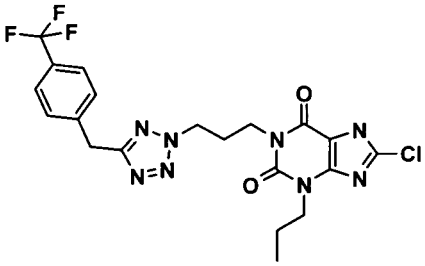
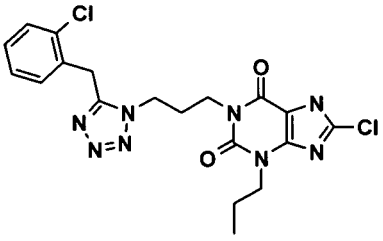
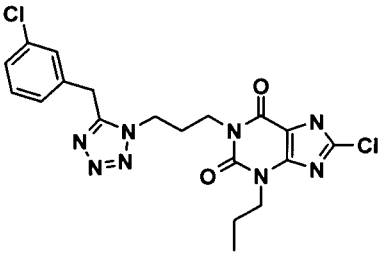
Table 32

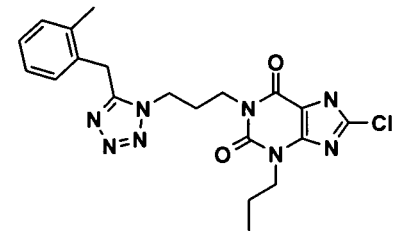
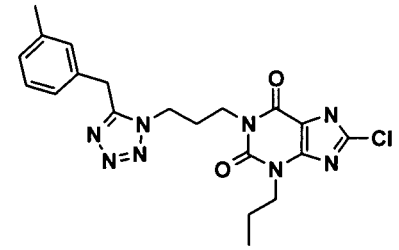
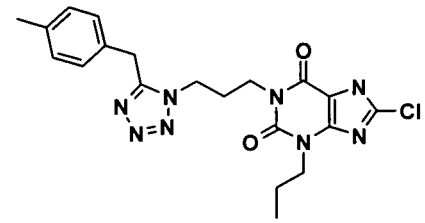
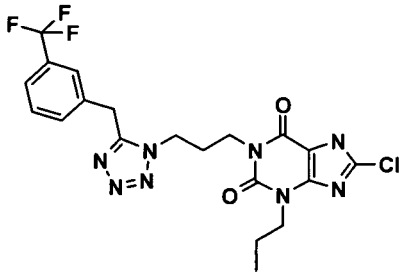
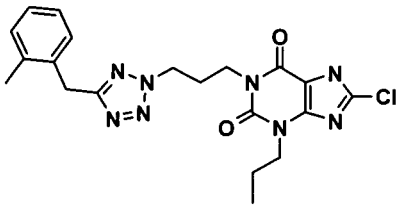
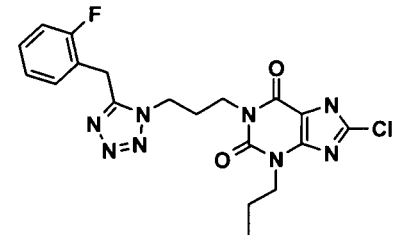
Example	Structure	Name	Yield (mg)	LC/MS
498		3-butyl-8-chloro-1-(3-{5-[(4-methylphenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	35.1	m/z 457 $[MH]^+$ RT 3.40min

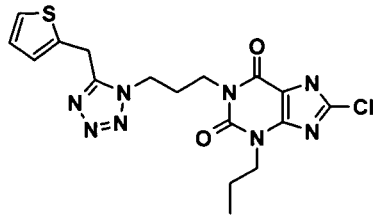
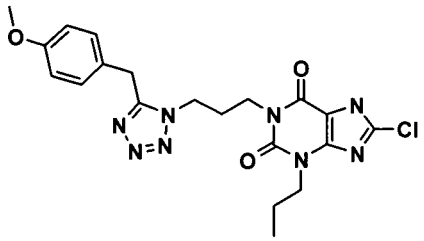
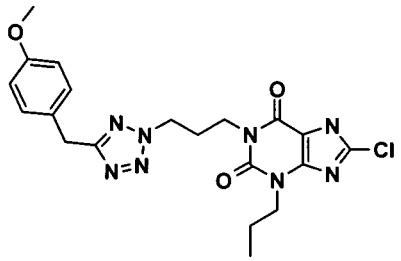
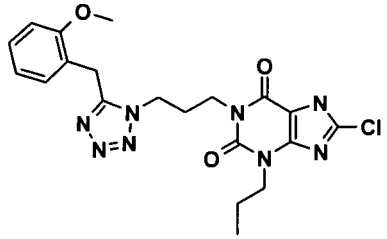
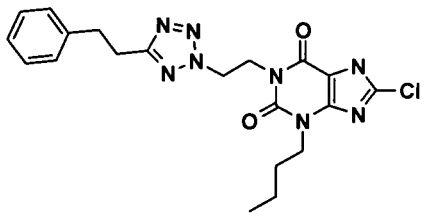
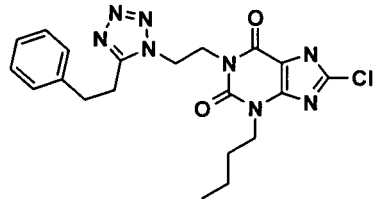
499		3-butyl-8-chloro-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	43.6	m/z 511 $[MH]^+$ RT 3.52min
500		3-butyl-8-chloro-1-[3-(5-{[4-(methyloxy)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	38.2	m/z 473 $[MH]^+$ RT 3.24min
501		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 3.07min
502		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 3.10min
503		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 3.10min

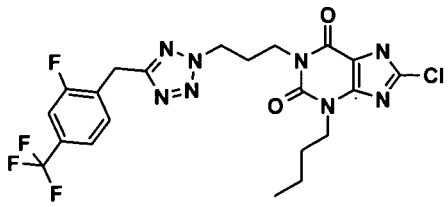
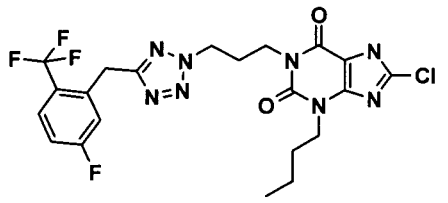
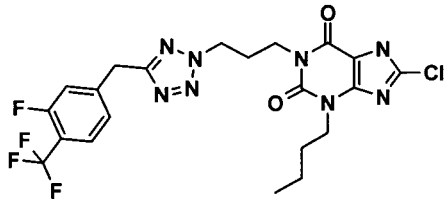
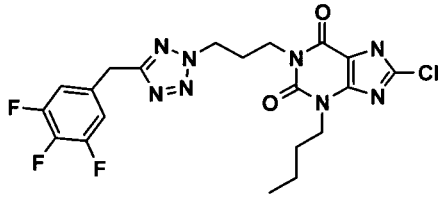
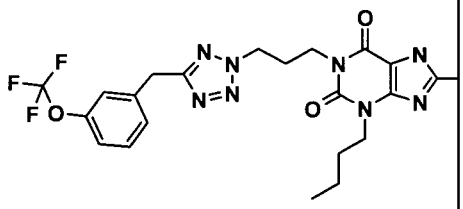
504		3-butyl-8-chloro-1-(3-{5-[(2-chlorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	8.4	m/z 477 $[MH]^+$ RT 3.17min
505		3-butyl-8-chloro-1-(3-{5-[(3-chlorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	16.4	m/z 477 $[MH]^+$ RT 3.23min
506		3-butyl-8-chloro-1-(3-{5-[(4-chlorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	17.0	m/z 477 $[MH]^+$ RT 3.24min
507		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 3.15min
508		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 3.18min
509		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 3.19min

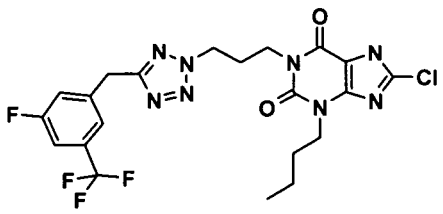
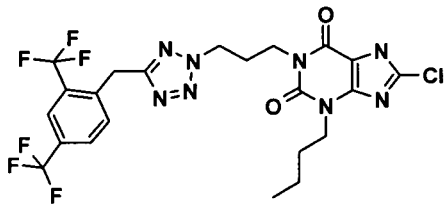
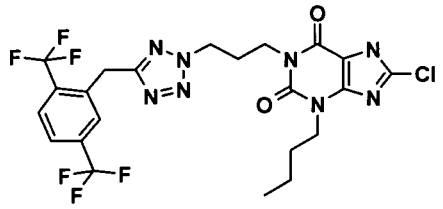
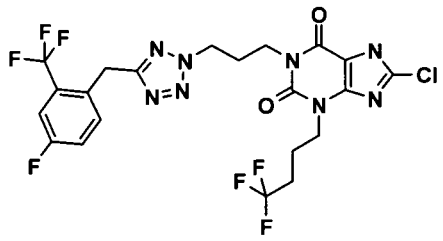
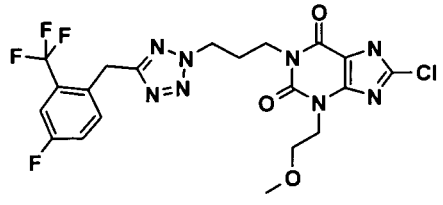
510		3-butyl-8-chloro-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-1H-tetrazol-1-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	17.7	m/z 511 $[MH]^+$ RT 3.31min
511		3-butyl-8-chloro-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-1H-tetrazol-1-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	21.6	m/z 511 $[MH]^+$ RT 3.33min
512		3-butyl-8-chloro-1-[3-(5-{[2-(methyloxy)phenyl]methyl}-1H-tetrazol-1-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	16.3	m/z 473 $[MH]^+$ RT 3.10min
513		3-butyl-8-chloro-1-[3-(5-{[4-(methyloxy)phenyl]methyl}-1H-tetrazol-1-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	20.8	m/z 473 $[MH]^+$ RT 3.05min
514		3-butyl-8-chloro-1-{3-[5-(1-phenylcyclopropyl)-1H-tetrazol-1-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	14.1	m/z 468 $[MH]^+$ RT 3.16min

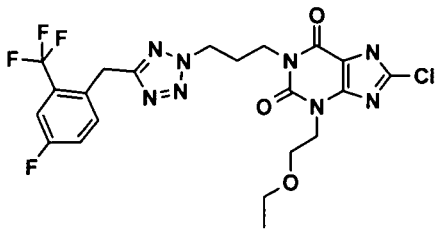
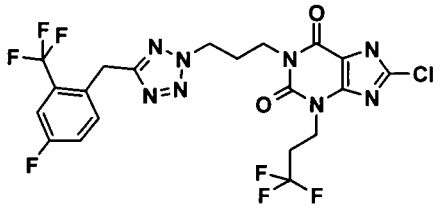
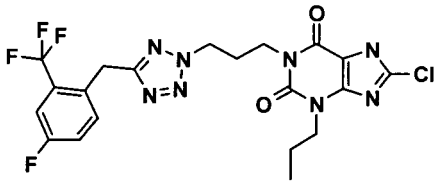
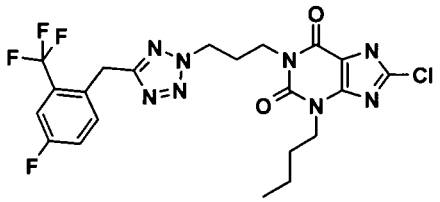
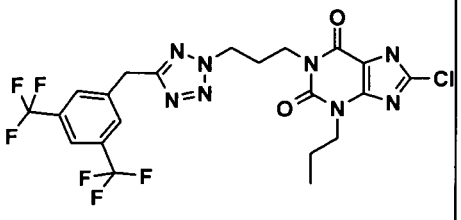
515		3-butyl-8-chloro-1-{3-[5-(2-phenylethyl)-1H-tetrazol-1-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	21.0	m/z 457 $[MH]^+$ RT 3.15min
516		3-butyl-8-chloro-1-{3-[5-(2-thienylmethyl)-1H-tetrazol-1-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	11.8	m/z 448 $[MH]^+$ RT 3.02min
517		3-butyl-8-chloro-1-(3-{5-[(2,6-dichlorophenyl)methyl]-1H-tetrazol-1-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	12.4	m/z 512 $[MH]^+$ RT 3.27min
518		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 3.38min
519		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 3.00min
520		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 3.06min

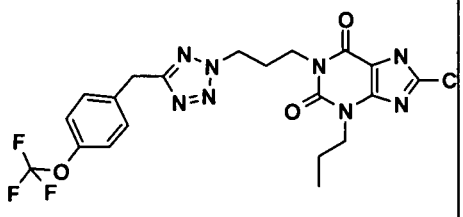
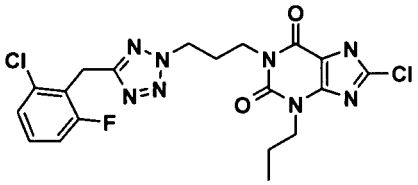
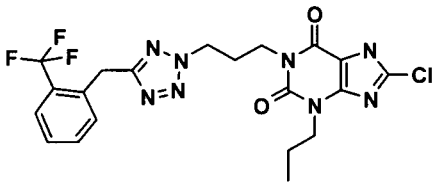
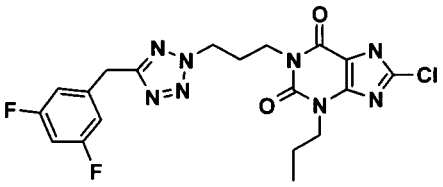
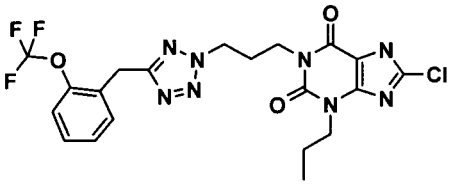
521		8-chloro-1-(3-{5-[(2-methylphenyl)methyl]-1H-tetrazol-1-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	7.2	m/z 443 $[MH]^+$ RT 2.97min
522		8-chloro-1-(3-{5-[(3-methylphenyl)methyl]-1H-tetrazol-1-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	5.7	m/z 443 $[MH]^+$ RT 3.01min
523		8-chloro-1-(3-{5-[(4-methylphenyl)methyl]-1H-tetrazol-1-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	5.5	m/z 443 $[MH]^+$ RT 3.01min
524		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 3.16min
525		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 3.20min
526		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 2.89min

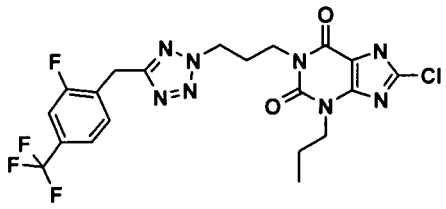
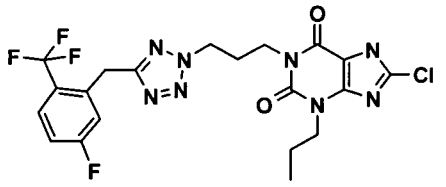
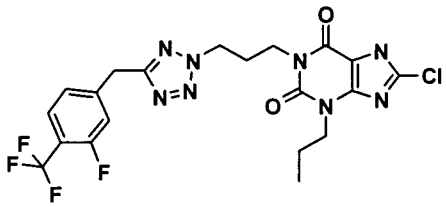
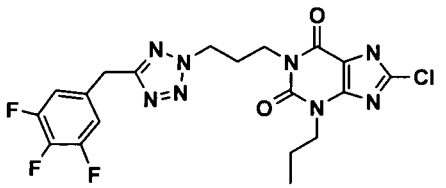
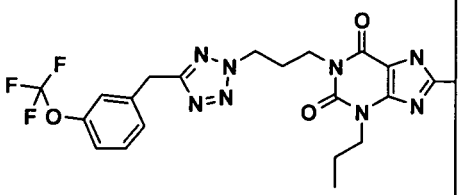
527		8-chloro-3-propyl-1-{3-[5-(2-thienylmethyl)-1H-tetrazol-1-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	5.2	m/z 435 $[MH]^+$ RT 2.83min
528		8-chloro-1-[3-(5-{[4-(methyloxy)phenyl]methyl}-1H-tetrazol-1-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	1.2	m/z 459 $[MH]^+$ RT 2.87min
529		8-chloro-1-[3-(5-{[4-(methyloxy)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	19.7	m/z 459 $[MH]^+$ RT 3.07min
530		8-chloro-1-[3-(5-{[2-(methyloxy)phenyl]methyl}-1H-tetrazol-1-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	1.9	m/z 459 $[MH]^+$ RT 2.92min
531		3-butyl-8-chloro-1-{2-[5-(2-phenylethyl)-2H-tetrazol-2-yl]ethyl}-3,7-dihydro-1H-purine-2,6-dione	44.0	m/z 443 $[MH]^+$ RT 3.31min
532		3-butyl-8-chloro-1-{2-[5-(2-phenylethyl)-1H-tetrazol-1-yl]ethyl}-3,7-dihydro-1H-purine-2,6-dione	10.4	m/z 443 $[MH]^+$ RT 3.12min

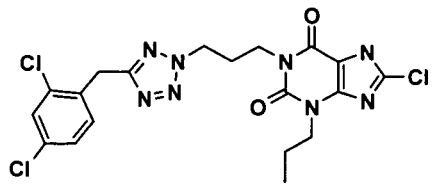
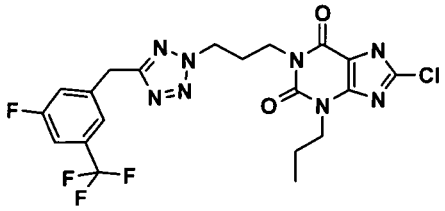
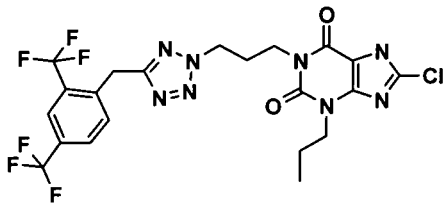
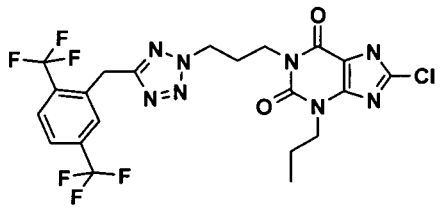
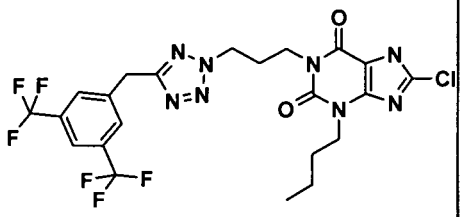
533		3-butyl-8-chloro-1-[3-(5-{[2-fluoro-4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	24.5	m/z 529 $[MH]^+$ RT 3.22min
534		3-butyl-8-chloro-1-[3-(5-{[5-fluoro-2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	25.3	m/z 529 $[MH]^+$ RT 3.51min
535		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 3.56min
536		3-butyl-8-chloro-1-(3-{5-[(3,4,5-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	19.4	m/z 497 $[MH]^+$ RT 3.45min
537		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 3.55min

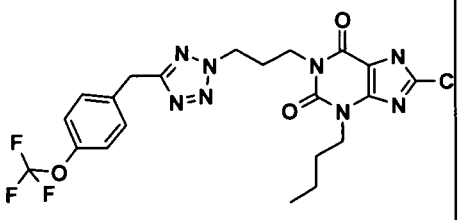
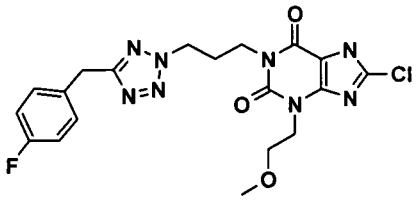
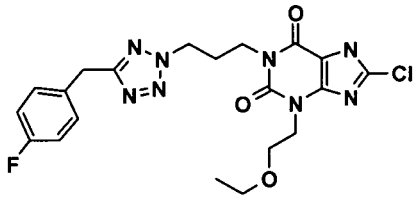
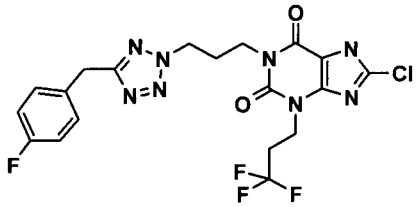
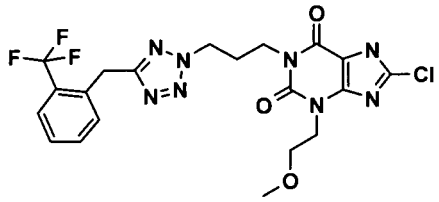
538		3-butyl-8-chloro-1-[3-(5-{[3-fluoro-5-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	19.8	m/z 529 $[MH]^+$ RT 3.56min
539		1-[3-(5-{[2,4-bis(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione	36.6	m/z 579 $[MH]^+$ RT 3.72min
540		1-[3-(5-{[2,5-bis(trifluoromethyl)phenyl]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 3.65min
541		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 3.50min
542		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 3.16min

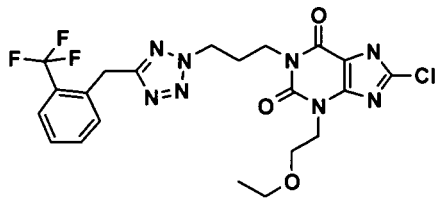
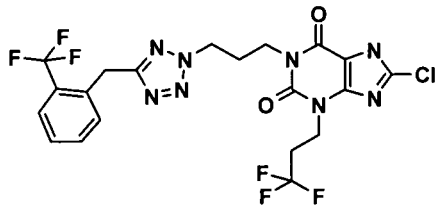
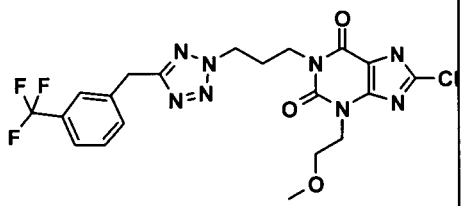
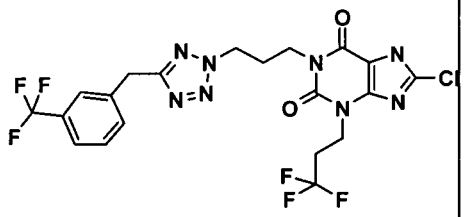
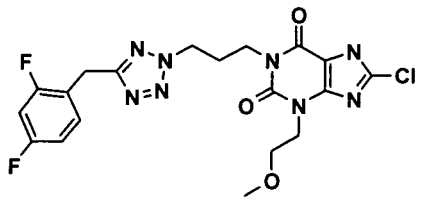
543		8-chloro-3-[2-(ethyloxy)ethyl]-1-[3-(5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	13.1	m/z 545 $[MH]^+$ RT 3.30min
544		8-chloro-1-[3-(5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	36.3	m/z 569 $[MH]^+$ RT 3.46min
545		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 3.37min
546		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 3.53min
547		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 3.54min

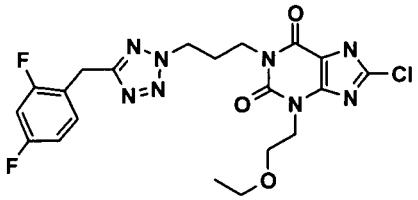
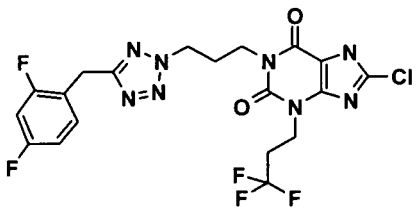
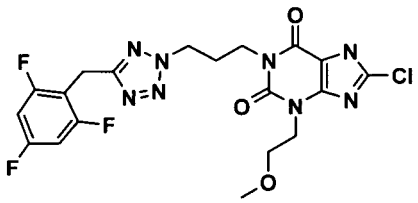
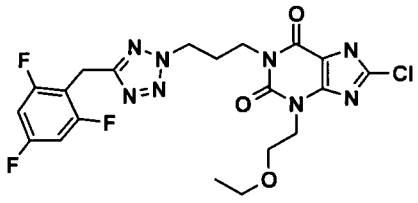
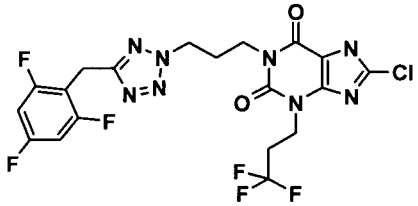
548		8-chloro-3-propyl-1-{3-[5-({4-[(trifluoromethyl)oxy]phenyl}methyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	21.6	m/z 513 $[MH]^+$ RT 3.42min
549		8-chloro-1-(3-{5-[(2-chloro-6-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	12.4	m/z 481 $[MH]^+$ RT 3.20min
550		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 3.26min
551		8-chloro-1-(3-{5-[(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 3.16min
552		8-chloro-3-propyl-1-{3-[5-({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 3.27min

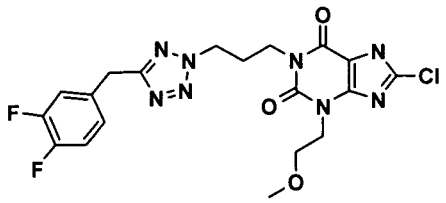
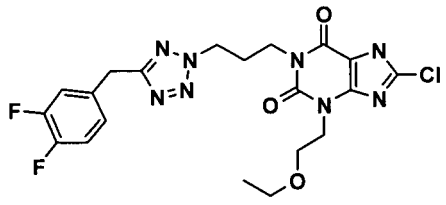
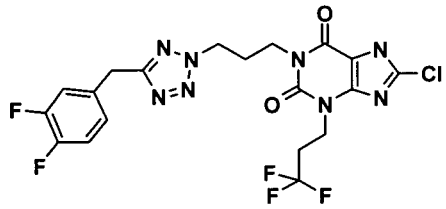
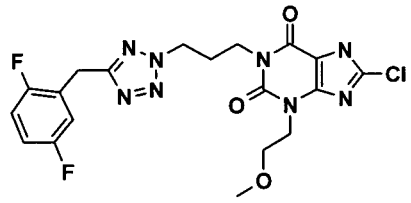
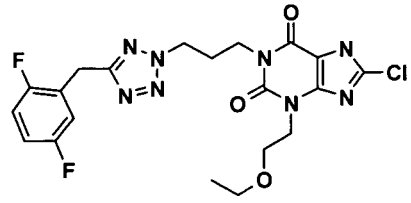
553		8-chloro-1-[3-(5-{[2-fluoro-4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	9.7	m/z 515 $[MH]^+$ RT 3.40min
554		8-chloro-1-[3-(5-{[5-fluoro-2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	26.8	m/z 515 $[MH]^+$ RT 3.26min
555		8-chloro-1-[3-(5-{[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 3.31min
556		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 3.23min
557		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 3.35min

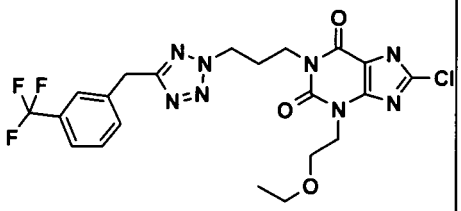
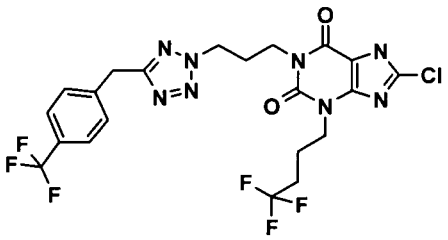
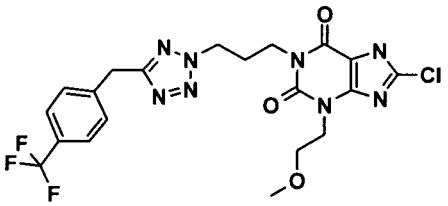
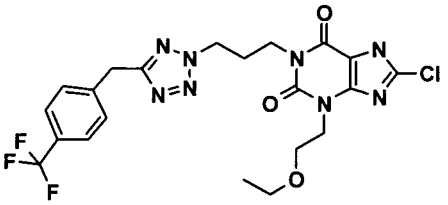
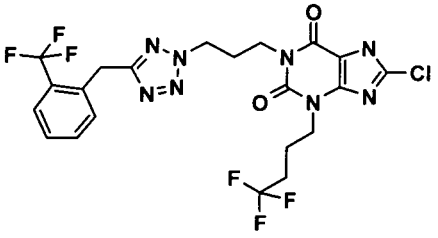
558		8-chloro-1-(3-{5-[(2,4-dichlorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-propyl-3,7-dihydro-1H-purine-2,6-dione	27.6	m/z 497 $[MH]^+$ RT 3.40min
559		8-chloro-1-[3-(5-{[3-fluoro-5-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-propyl-3,7-dihydro-1H-purine-2,6-dione	17.6	m/z 515 $[MH]^+$ RT 3.23min
560		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 3.40min
561		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 3.50min
562		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 3.68min

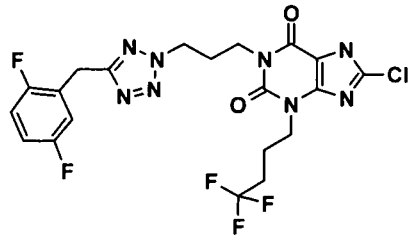
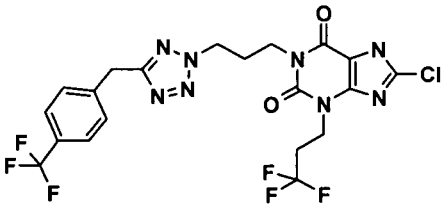
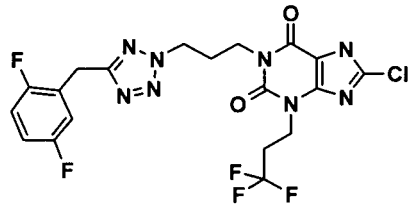
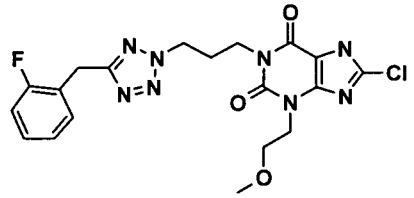
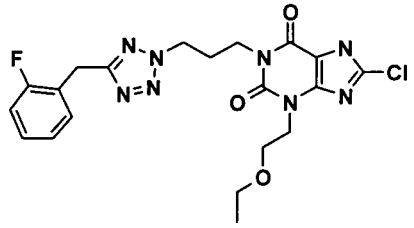
563		3-butyl-8-chloro-1-{3-[5-({4-[(trifluoromethyl)oxy]phenyl}methyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	32.1	m/z 527 $[MH]^+$ RT 3.57min
564		8-chloro-1-(3-{5-[(4-fluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(methyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	15.0	m/z 463 $[MH]^+$ RT 2.89min
565		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 3.03min
566		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 3.21min
567		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 3.10min

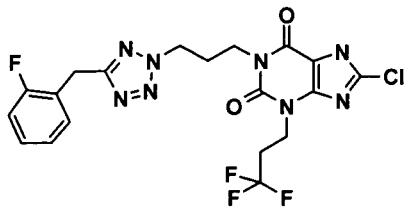
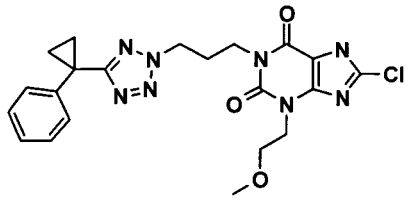
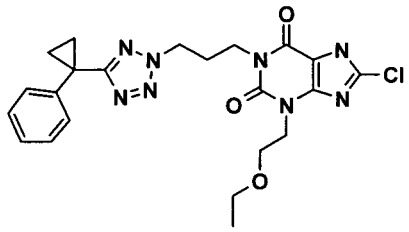
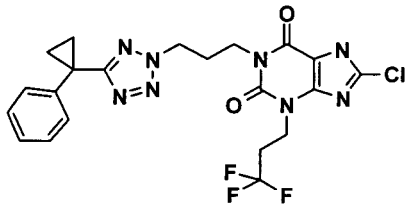
568		8-chloro-3-[2-(ethyloxy)ethyl]-1-[3-(5-{[2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	20.8	m/z 527 $[MH]^+$ RT 3.18min
569		8-chloro-1-[3-(5-{[2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	35.8	m/z 551 $[MH]^+$ RT 3.35min
570		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 3.14min
571		8-chloro-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	29.4	m/z 551 $[MH]^+$ RT 3.42min
572		8-chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(methyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	17.8	m/z 481 $[MH]^+$ RT 2.96min

573		8-chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(ethyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	14.4	m/z 495 $[MH]^+$ RT 2.86min
574		8-chloro-1-(3-{5-[(2,4-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	29.9	m/z 519 $[MH]^+$ RT 3.19min
575		8-chloro-3-[2-(methyloxy)ethyl]-1-(3-{5-[(2,4,6-trifluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3,7-dihydro-1H-purine-2,6-dione	21.3	m/z 499 $[MH]^+$ RT 2.93min
576		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 2.93min
577		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 3.29min

578		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 2.97min
579		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 3.06min
580		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 3.27min
581		8-chloro-1-(3-{5-[(2,5-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(methyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	17.1	m/z 481 $[MH]^+$ RT 2.89min
582		8-chloro-1-(3-{5-[(2,5-difluorophenyl)methyl]-2H-tetrazol-2-yl}propyl)-3-[2-(ethyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	13.5	m/z 495 $[MH]^+$ RT 3.05min

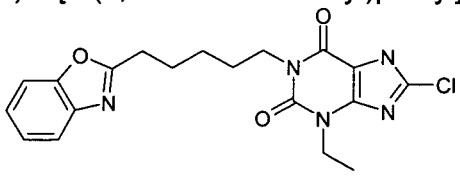
583		8-chloro-3-[2-(ethyloxy)ethyl]-1-[3-(5-{[3-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	14.6	m/z 527 $[MH]^+$ RT 3.26min
584		8-chloro-3-(4,4,4-trifluorobutyl)-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	12.1	m/z 565 $[MH]^+$ RT 3.51min
585		8-chloro-3-[2-(methyloxy)ethyl]-1-[3-(5-{[4-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	17.3	m/z 513 $[MH]^+$ RT 3.17min
586		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 3.30min
587		8-chloro-3-(4,4,4-trifluorobutyl)-1-[3-(5-{[2-(trifluoromethyl)phenyl]methyl}-2H-tetrazol-2-	5.8	m/z 565 $[MH]^+$ RT 3.46min

		yl)propyl]-3,7-dihydro-1H-purine-2,6-dione		
588		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 3.34min
589		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 3.46min
590		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 3.29min
591		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 2.84min
592		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 2.85min

593		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 3.25min
594		8-chloro-3-[2-(methyloxy)ethyl]-1-{3-[5-(1-phenylcyclopropyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	10.2	m/z 471 $[MH]^+$ RT 2.93min
595		8-chloro-3-[2-(ethyloxy)ethyl]-1-{3-[5-(1-phenylcyclopropyl)-2H-tetrazol-2-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	15.2	m/z 485 $[MH]^+$ RT 2.96min
596		8-chloro-1-{3-[5-(1-phenylcyclopropyl)-2H-tetrazol-2-yl]propyl}-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1H-purine-2,6-dione	4.6	m/z 509 $[MH]^+$ RT 3.00min

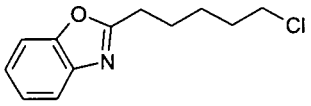
Example 597 : 1-[5-(1,3-Benzoxazol-2-yl)pentyl]-8-chloro-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione

a) 1-[5-(1,3-Benzoxazol-2-yl)pentyl]-8-chloro-3-ethyl-3,7-dihydro-1*H*-purine-2,6-dione



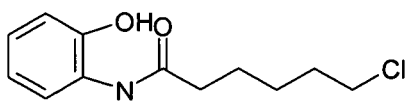
a) A solution of 3-ethyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (0.095g, 0.37mmol) in DMF (10ml) was treated with potassium carbonate (0.0615g, 0.45mmol) and 2-(5-chloropentyl)-1,3-benzoxazole (0.091g, 0.41mmol) and the mixture heated at 70°C for 4.5h. The mixture was cooled and degassed by the repeated application of vacuum to the reaction mixture and subsequent backfilling with nitrogen gas and then treated with tetrakis(triphenylphosphine)palladium(0) (0.043g, 0.037mmol) and morpholine (0.32ml, 3.7mmol) and the mixture stirred for 4h in a nitrogen atmosphere. The mixture was evaporated to dryness and the residue partitioned between 25ml of ethyl acetate and 25ml of brine. The aqueous phase was re-extracted with 25ml of ethyl acetate and the combined organics dried over magnesium sulfate, filtered and evaporated. The residue was dissolved in 5ml of methanol and added to a 5g aminopropyl SPE which was subsequently washed with methanol and the product eluted with a 5% solution of acetic acid in methanol. Product-containing fractions were pooled and evaporated to reveal a colourless gum which was triturated with diethyl ether and dried to give the title compound as a white solid (0.0538g, 36%).
LC/MS: m/z 402 $[MH]^+$, RT 3.06min

b) 2-(5-Chloropentyl)-1,3-benzoxazole



6-Chloro-*N*-(2-hydroxyphenyl)hexanamide (0.95g, 3.9mmol) was treated with toluene (20ml) and 4-toluenesulfonic acid monohydrate (0.05g, 0.26mmol) and the mixture heated in the microwave at 160°C for 1h then cooled and evaporated. The residue was partition between 25ml of ethyl acetate and 25ml of saturates aqueous sodium bicarbonate. The aqueous phase was extracted twice more with 25ml ethyl acetate and the combined organics dried over magnesium sulfate, filtered and evaporated to dryness. The product was then purified by flash chromatography (gradient elution: cyclohexane to cyclohexane/ethyl acetate 1:1) to give 2-(5-chloropentyl)-1,3-benzoxazole as a colourless oil which solidified upon standing (0.47g, 53%).
LC/MS: m/z 224 $[MH]^+$, RT 3.32min

c) 6-chloro-*N*-(2-hydroxyphenyl)hexanamide

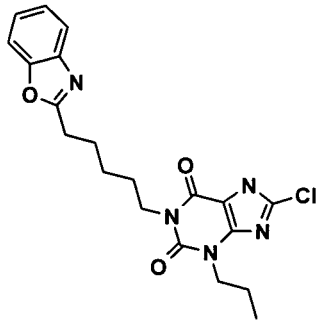
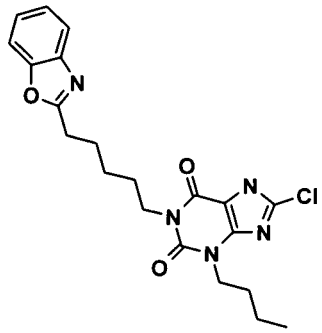
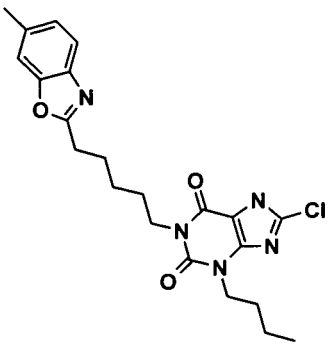


2-Aminophenol (0.5g, 4.6mmol) was stirred in ethyl acetate (15ml) and treated dropwise with 6-chlorohexanoyl chloride (0.664ml, 5.5mmol) and then dropwise with triethylamine (0.95ml, 6.9mmol). After 1h the mixture was washed with 2 x 25ml of

saturated aqueous sodium bicarbonate and the organic phase dried over magnesium sulfate, filterd and evaporated to dryness to give 6-chloro-*N*-(2-hydroxyphenyl)hexanamide as a pale brown solid (0.05g, 86%).
LC/MS: m/z 242 $[MH]^+$, RT 2.95min.

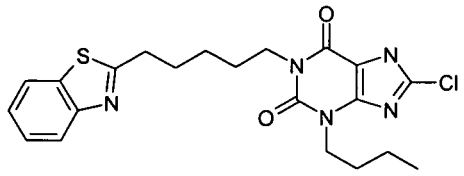
The following compounds (**Table 33**) were prepared using a method analogous to that for **Example 597**.

Table 33

Example	Structure	Name	Yield (mg)	LC/MS
598		1-[5-(1,3-benzoxazol-2-yl)pentyl]-8-chloro-3-propyl-3,7-dihydro-1H-purine-2,6-dione	60.5	m/z 416 $[MH]^+$ RT 3.23mins
599		1-[5-(1,3-benzoxazol-2-yl)pentyl]-3-butyl-8-chloro-3,7-dihydro-1H-purine-2,6-dione	55.1	m/z 428 $[MH]^+$ RT 3.42mins
600		3-butyl-8-chloro-1-[5-(6-methyl-1,3-benzoxazol-2-yl)pentyl]-3,7-dihydro-1H-purine-2,6-dione	68.9	m/z 444 $[MH]^+$ RT 3.56mins

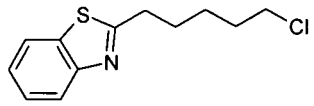
Example 601 : 1-[5-(1,3-Benzothiazol-2-yl)pentyl]-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione

a) 1-[5-(1,3-Benzothiazol-2-yl)pentyl]-3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione



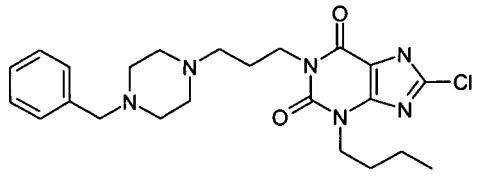
A solution of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1H-purine-2,6-dione (0.053g, 0.19mmol) in DMF (5ml) was treated with potassium carbonate (0.026g, 0.19mmol) and 2-(5-chloropentyl)-1,3-benzothiazole (0.0498g, 0.21mmol) and the mixture heated at 60°C for 3 days. The mixture was cooled and degassed by the repeated application of vacuum to the reaction mixture and subsequent backfilling with nitrogen gas and then treated with tetrakis(triphenylphosphine)palladium(0) (0.0294g, 0.025mmol) and morpholine (0.164ml, 1.9mmol) and the mixture stirred for 18 hours in a nitrogen atmosphere. The mixture was evaporated to dryness and the residue partitioned between 25ml of ethyl acetate and 25ml of saturated aqueous sodium bicarbonate. The organic phase was dried over magnesium sulfate, filtered and evaporated. The residue was dissolved in 5ml of methanol and added to a 5g aminopropyl SPE which was subsequently washed with methanol and the product eluted with a 5% solution of acetic acid in methanol. Product-containing fractions were pooled and evaporated and the residue subjected to purification by MDAP to give the title compound as a white solid (0.0101g, 12%).
LC/MS: m/z 446 $[MH]^+$, RT 3.55min.

b) 2-(5-Chloropentyl)-1,3-benzothiazole



An ice-cooled solution of 2-aminothiophenol (0.376ml, 3.54mmol) in anhydrous THF (5ml) was treated with diisopropylethylamine (0.62ml, 3.54mmol) followed by 6-chlorohexanoyl chloride (0.36ml, 2.95mmol). The mixture was stirred at ambient temperature for 2h then heated at reflux for 19h and then cooled and diluted with DCM (10ml). The solution was washed with 10ml of 2M aqueous hydrochloric acid, 10ml of 2M aqueous sodium hydroxide and 10ml of brine; dried over magnesium sulfate, filtered and evaporated to reveal 0.4122g of a pale yellow oil. The product was purified by flash chromatography using a gradient elution from cyclohexane to cylcohexane/ethyl acetate (7:3) to give 2-(5-chloropentyl)-1,3-benzothiazole as a colourless oil (0.0541g, 6%).
LC/MS: m/z 240 $[MH]^+$, RT 3.48min.

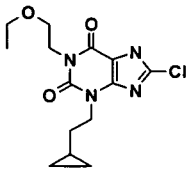
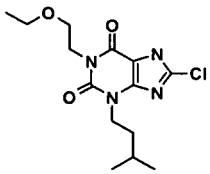
Example 602 : 3-Butyl-8-chloro-1-{3-[4-(phenylmethyl)-1-piperazinyl]propyl}-3,7-dihydro-1*H*-purine-2,6-dione

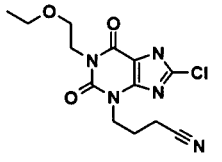
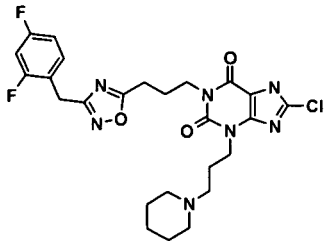
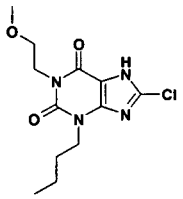
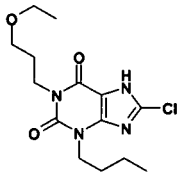
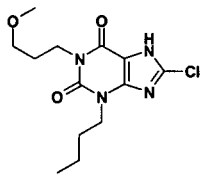
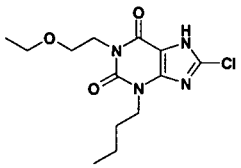
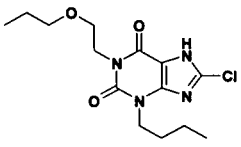


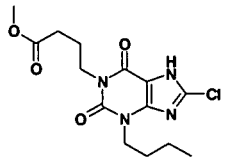
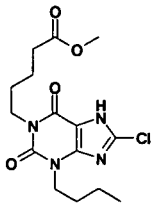
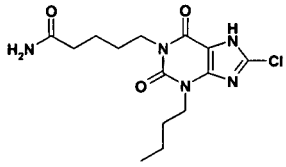
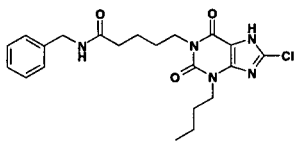
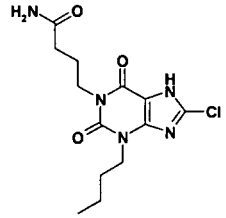
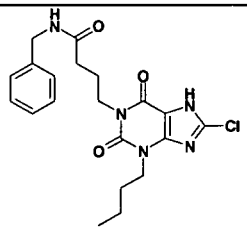
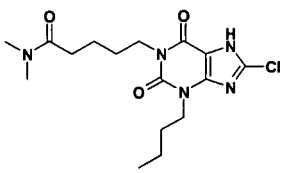
A solution of 3-[3-butyl-8-chloro-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purin-1-yl]propyl methanesulfonate (0.08g, 0.19mmol) in DMF (5ml) was treated with potassium carbonate (0.08g, 0.6mmol) and 1-benzylpiperazine (0.04g, 0.23mmol) and then heated at 70°C for 2h. The mixture was cooled, 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 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.

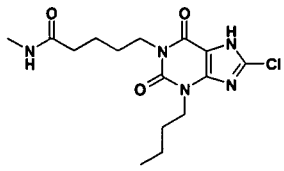
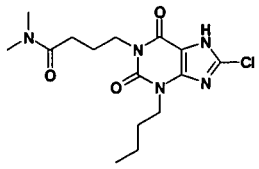
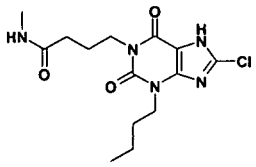
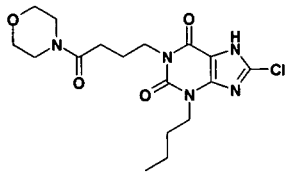
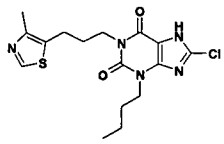
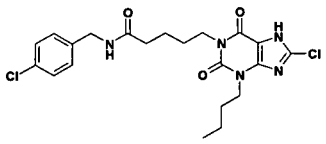
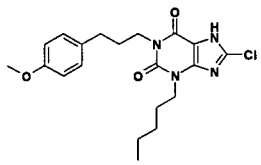
The following compounds (**Table 34**) were prepared by the appropriate general methodology described above.

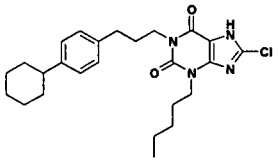
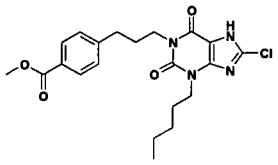
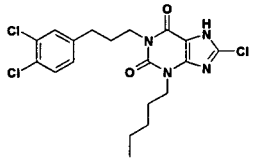
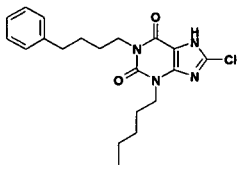
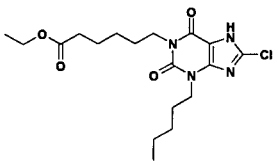
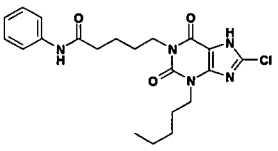
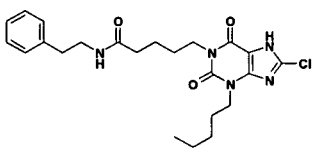
Table 34

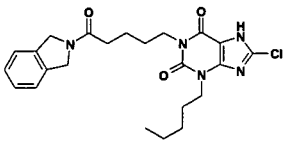
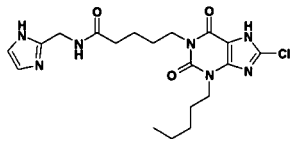
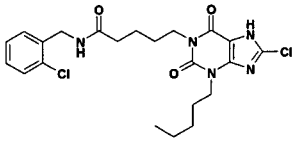
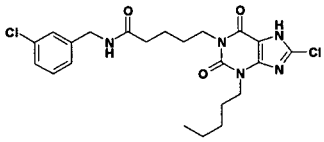
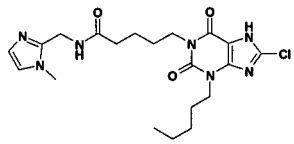
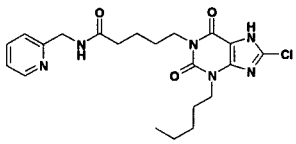
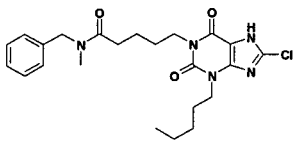
Example	Structure	Name	LC/MS
603		8-chloro-3-(2-cyclopropylethyl)-1-[2-(ethyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 327 $[MH]^+$ RT 2.80min
604		8-chloro-1-[2-(ethyloxy)ethyl]-3-(3-methylbutyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 329 $[MH]^+$ RT 3.02min

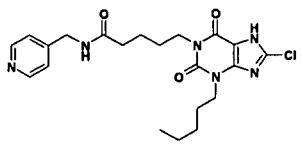
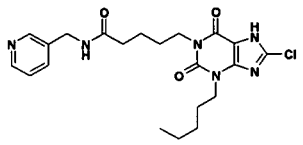
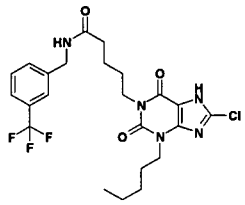
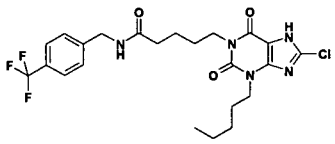
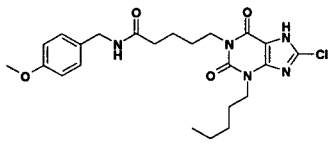
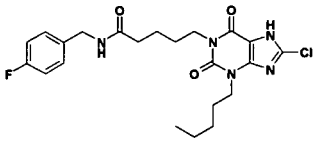
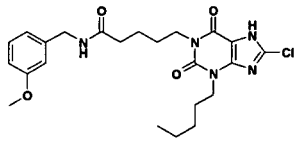
605		4-{8-chloro-1-[2-(ethyloxy)ethyl]-2,6-dioxo-1,2,6,7-tetrahydro-3H-purin-3-yl}butanenitrile	m/z 326 $[MH]^+$ RT 2.33min
606		8-chloro-1-(3-{3-[(2,4-difluorophenyl)methyl]-1,2,4-oxadiazol-5-yl}propyl)-3-[3-(1-piperidinyl)propyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 548 $[MH]^+$ RT 2.44min
607		3-butyl-8-chloro-1-[2-(methyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 301 $[MH]^+$ RT 2.31min
608		3-butyl-8-chloro-1-[3-(ethyloxy)propyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 329 $[MH]^+$ RT 2.95min
609		3-butyl-8-chloro-1-[3-(methyloxy)propyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 315 $[MH]^+$ RT 2.36min
610		3-butyl-8-chloro-1-[2-(ethyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 315 $[MH]^+$ RT 2.34min
611		3-butyl-8-chloro-1-[2-(propyloxy)ethyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 329 $[MH]^+$ RT 2.71min

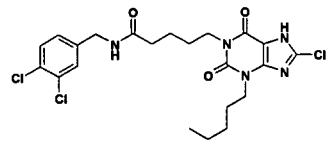
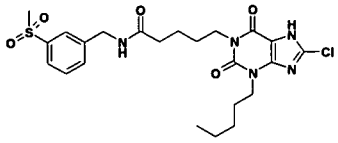
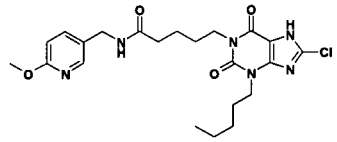
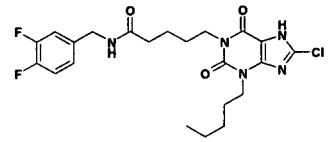
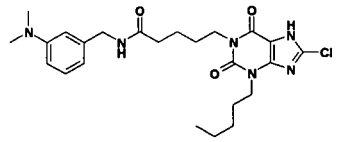
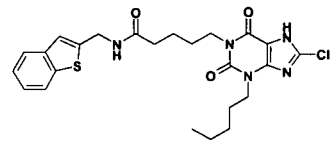
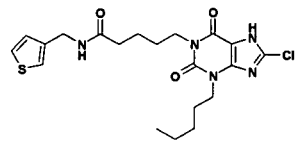
612		methyl 4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butanoate	m/z 343 $[MH]^+$ RT 2.56min
613		methyl 5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoate	m/z 357 $[MH]^+$ RT 2.66min
614		5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanamide	m/z 342 $[MH]^+$ RT 2.41min
615		5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(phenylmethyl)pentanamide	m/z 432 $[MH]^+$ RT 2.97min
616		4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butanamide	m/z 328 $[MH]^+$ RT 2.34min
617		4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(phenylmethyl)butanamide	m/z 418 $[MH]^+$ RT 2.93min
618		5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N,N-dimethylpentanamide	m/z 370 $[MH]^+$ RT 2.26min

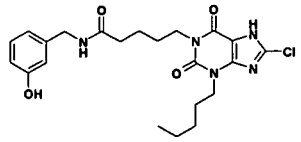
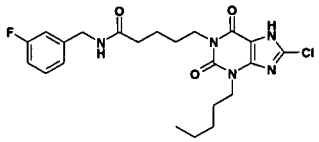
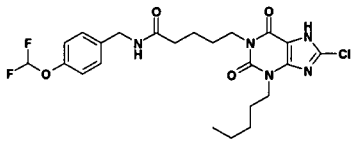
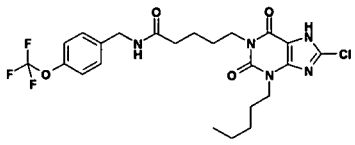
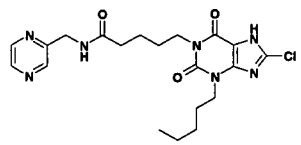
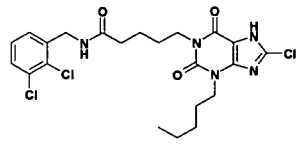
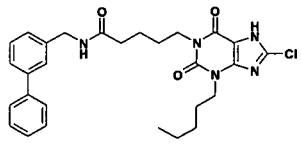
619		5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-methylpentanamide	m/z 356 $[MH]^+$ RT 2.56min
620		4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N,N-dimethylbutanamide	m/z 356 $[MH]^+$ RT 2.59min
621		4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-methylbutanamide	m/z 342 $[MH]^+$ RT 2.48min
622		3-butyl-8-chloro-1-(4-morpholin-4-yl-4-oxobutyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 398 $[MH]^+$ RT 2.58min
623		3-butyl-8-chloro-1-[3-(4-methyl-1,3-thiazol-5-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 382 $[MH]^+$ RT 3.00min
624		5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(4-chlorophenyl)methyl]pentanamide	m/z 466 $[MH]^+$ RT 3.26min
625		8-chloro-1-{3-[4-(methyloxy)phenyl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 405 $[MH]^+$ RT 3.65min

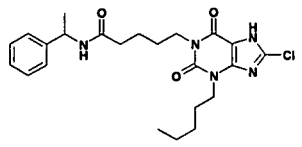
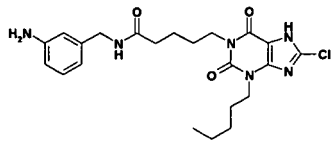
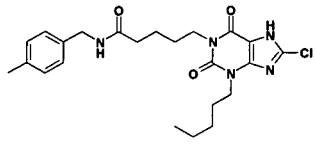
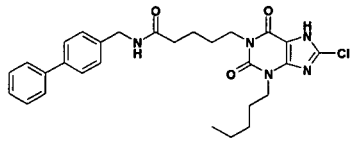
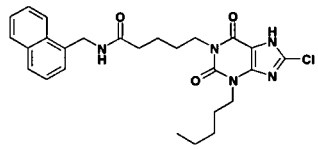
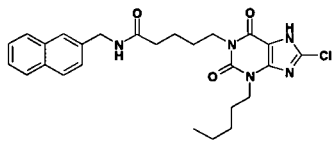
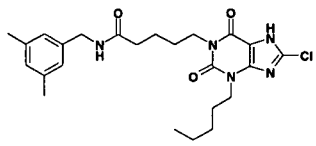
626		8-chloro-1-[3-(4-cyclohexylphenyl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 457 $[MH]^+$ RT 4.42min
627		methyl 4-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]benzoate	m/z 433 $[MH]^+$ RT 3.59min
628		8-chloro-1-[3-(3,4-dichlorophenyl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 443 $[MH]^+$ RT 4.03min
629		8-chloro-3-pentyl-1-(4-phenylbutyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 389 $[MH]^+$ RT 3.87min
630		ethyl 6-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)hexanoate	m/z 399 $[MH]^+$ RT 3.47min
631		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-phenylpentanamide	m/z 432 $[MH]^+$ RT 3.36min
632		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(2-phenylethyl)pentanamide	m/z 460 $[MH]^+$ RT 3.29min

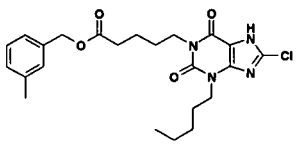
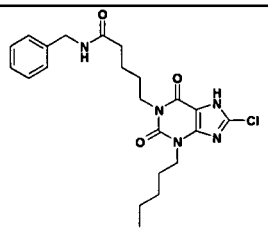
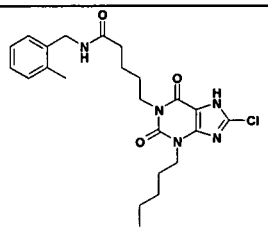
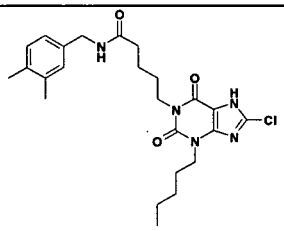
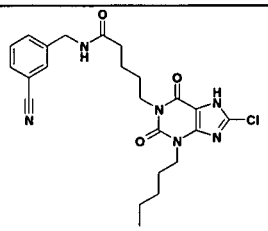
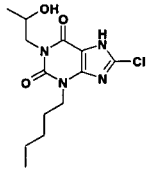
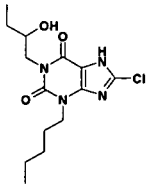
633		8-chloro-1-[5-(1,3-dihydro-2H-isoindol-2-yl)-5-oxopentyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 458 $[MH]^+$ RT 3.35min
634		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(1H-imidazol-2-ylmethyl)pentanamide	m/z 436 $[MH]^+$ RT 2.32min
635		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(2-chlorophenyl)methyl]pentanamide	m/z 480 $[MH]^+$ RT 2.77min
636		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(3-chlorophenyl)methyl]pentanamide	m/z 480 $[MH]^+$ RT 3.42min
637		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(1-methyl-1H-imidazol-2-yl)methyl]pentanamide	m/z 450 $[MH]^+$ RT 2.32min
638		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(pyridin-2-ylmethyl)pentanamide	m/z 447 $[MH]^+$ RT 2.70min
639		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-methyl-N-(phenylmethyl)pentanamide	m/z 460 $[MH]^+$ RT 3.38min

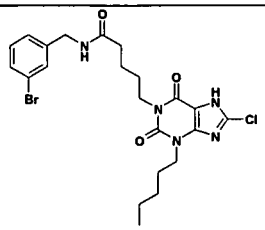
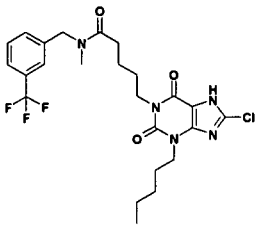
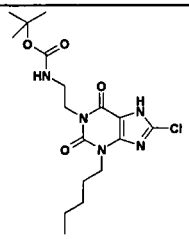
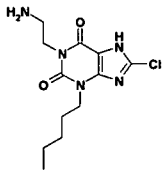
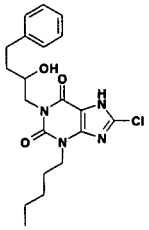
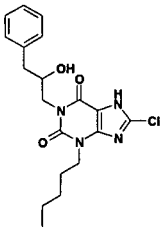
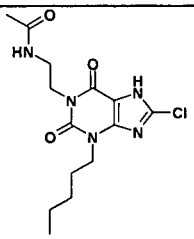
640		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(pyridin-4-ylmethyl)pentanamide	m/z 447 $[MH]^+$ RT 2.42min
641		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(pyridin-3-ylmethyl)pentanamide	m/z 447 $[MH]^+$ RT 2.54min
642		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-{[3-(trifluoromethyl)phenyl]methyl}pentanamide	m/z 514 $[MH]^+$ RT 3.45min
643		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-{[4-(trifluoromethyl)phenyl]methyl}pentanamide	m/z 514 $[MH]^+$ RT 3.47min
644		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-{[4-(methyloxy)phenyl]methyl}pentanamide	m/z 476 $[MH]^+$ RT 2.67min
645		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(4-fluorophenyl)methyl]pentanamide	m/z 464 $[MH]^+$ RT 3.26min
646		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-{[3-(methyloxy)phenyl]methyl}pentanamide	m/z 476 $[MH]^+$ RT 3.21min

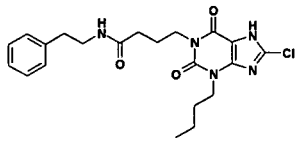
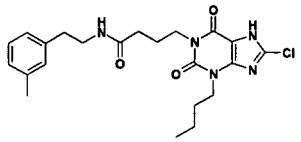
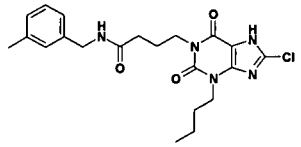
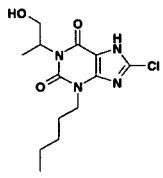
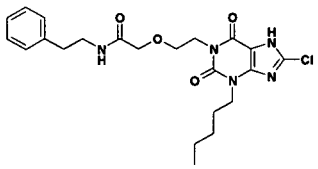
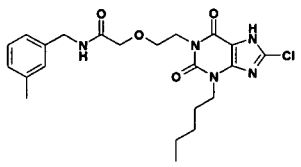
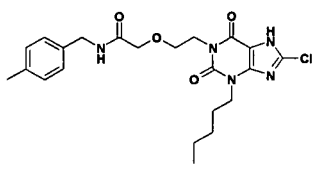
647		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(3,4-dichlorophenyl)methyl]pentanamide	m/z 514 $[MH]^+$ RT 3.56min
648		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-{[3-(methylsulfonyl)phenyl]methyl}pentanamide	m/z 524 $[MH]^+$ RT 2.97min
649		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-{[6-(methyloxy)pyridin-3-yl]methyl}pentanamide	m/z 477 $[MH]^+$ RT 3.01min
650		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(3,4-difluorophenyl)methyl]pentanamide	m/z 482 $[MH]^+$ RT 3.33min
651		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-{[3-(dimethylamino)phenyl]methyl}pentanamide	m/z 489 $[MH]^+$ RT 3.01min
652		N-(1-benzothien-2-ylmethyl)-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanamide	m/z 502 $[MH]^+$ RT 3.48min
653		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(3-thienylmethyl)pentanamide	m/z 452 $[MH]^+$ RT 3.18min

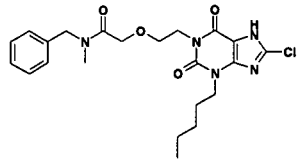
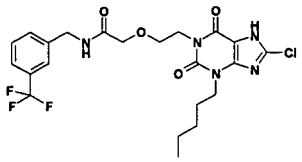
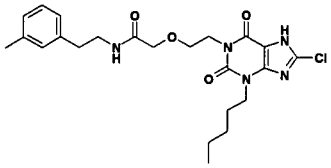
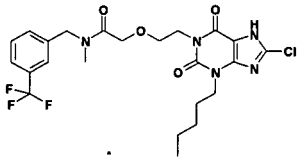
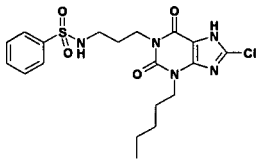
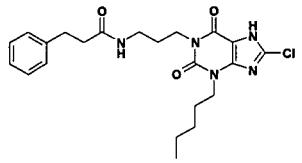
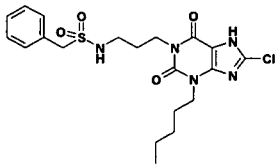
654		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(3-hydroxyphenyl)methyl]pentanamide	m/z 462 $[MH]^+$ RT 3.04min
655		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(3-fluorophenyl)methyl]pentanamide	m/z 464 $[MH]^+$ RT 3.28min
656		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-({4-[(difluoromethyl)oxy]phenyl}methyl)pentanamide	m/z 512 $[MH]^+$ RT 3.34min
657		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-({4-[(trifluoromethyl)oxy]phenyl}methyl)pentanamide	m/z 530 $[MH]^+$ RT 3.50min
658		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(pyrazin-2-ylmethyl)pentanamide	m/z 448 $[MH]^+$ RT 2.74min
659		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(2,3-dichlorophenyl)methyl]pentanamide	m/z 514 $[MH]^+$ RT 3.55min
660		N-(biphenyl-3-ylmethyl)-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanamide	m/z 522 $[MH]^+$ RT 3.61min

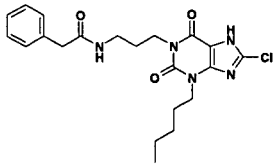
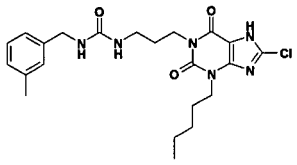
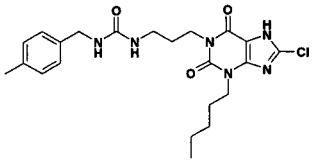
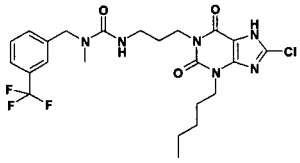
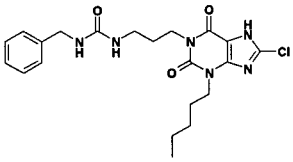
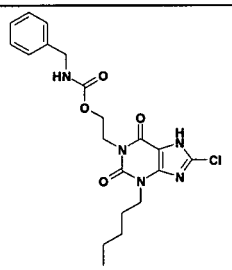
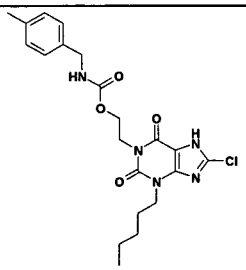
661		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(1-phenylethyl)pentanamide	m/z 460 $[MH]^+$ RT 3.30min
662		N-[(3-aminophenyl)methyl]-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanamide	m/z 461 $[MH]^+$ RT 2.79min
663		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(4-methylphenyl)methyl]pentanamide	m/z 460 $[MH]^+$ RT 3.36min
664		N-(biphenyl-4-ylmethyl)-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanamide	m/z 522 $[MH]^+$ RT 3.63min
665		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(naphthalen-1-ylmethyl)pentanamide	m/z 496 $[MH]^+$ RT 3.48min
666		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(naphthalen-2-ylmethyl)pentanamide	m/z 496 $[MH]^+$ RT 3.50min
667		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(3,5-dimethylphenyl)methyl]pentanamide	m/z 474 $[MH]^+$ RT 3.48min

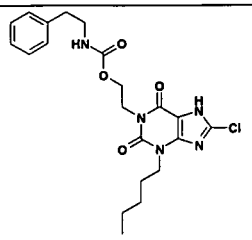
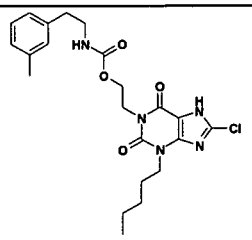
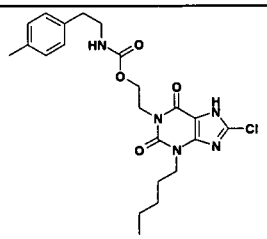
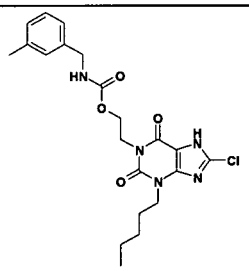
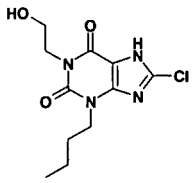
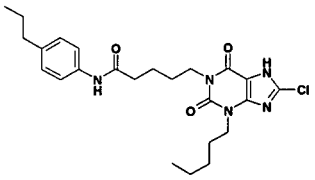
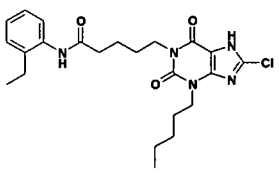
668		(3-methylphenyl)methyl 5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanoate	m/z 461 $[MH]^+$ RT 3.78min
669		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(phenylmethyl)pentanamide	m/z 446 $[MH]^+$ RT 3.12min
670		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(2-methylphenyl)methyl]pentanamide	m/z 460 $[MH]^+$ RT 3.22min
671		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(3,4-dimethylphenyl)methyl]pentanamide	m/z 474 $[MH]^+$ RT 3.34min
672		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(3-cyanophenyl)methyl]pentanamide	m/z 471 $[MH]^+$ RT 3.14min
673		8-chloro-1-(2-hydroxypropyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 315 $[MH]^+$ RT 2.73min
674		8-chloro-1-(2-hydroxybutyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 329 $[MH]^+$ RT 2.91min

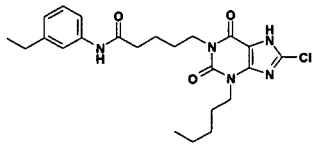
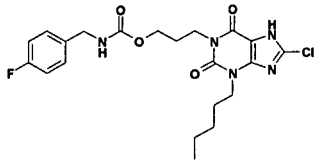
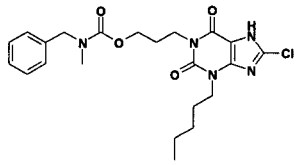
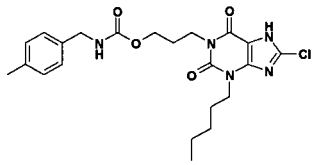
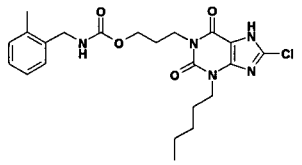
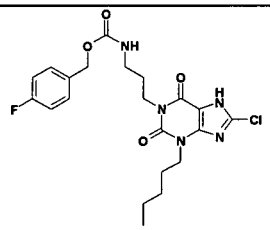
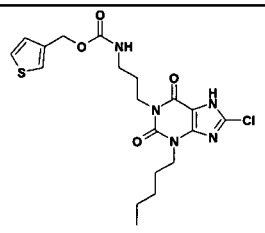
675		N-[(3-bromophenyl)methyl]-5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)pentanamide	m/z 524 $[MH]^+$ RT 3.43min
676		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-methyl-N-{[3-(trifluoromethyl)phenyl]methyl}pentanamide	m/z 528 $[MH]^+$ RT 3.55min
677		1,1-dimethylethyl [2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]carbamate	m/z 400 $[MH]^+$ RT 3.21min
678		1-(2-aminoethyl)-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 300 $[MH]^+$ RT 2.14min
679		8-chloro-1-(2-hydroxy-4-phenylbutyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 405 $[MH]^+$ RT 3.43min
680		8-chloro-1-(2-hydroxy-3-phenylpropyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 391 $[MH]^+$ RT 3.17min
681		N-[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]acetamide	m/z 342 $[MH]^+$ RT 2.61min

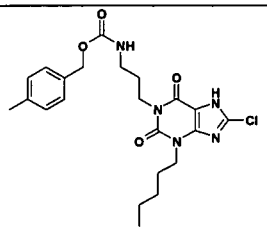
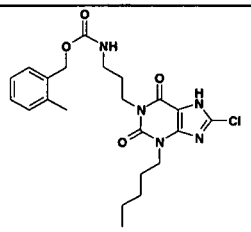
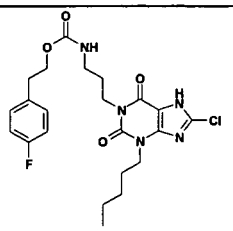
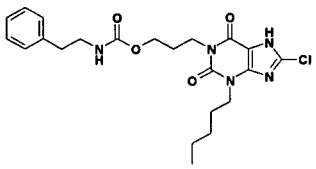
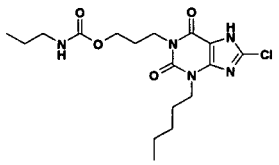
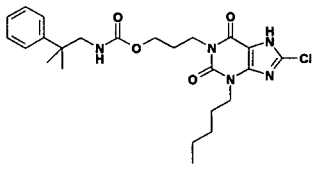
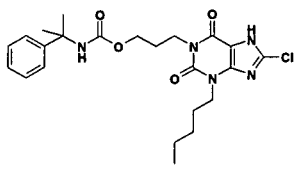
682		4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(2-phenylethyl)butanamide	m/z 432 $[MH]^+$ RT 3.06min
683		4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[2-(3-methylphenyl)ethyl]butanamide	m/z 446 $[MH]^+$ RT 3.19min
684		4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(3-methylphenyl)methyl]butanamide	m/z 432 $[MH]^+$ RT 3.14min
685		8-chloro-1-(2-hydroxy-1-methylethyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 315 $[MH]^+$ RT 2.80min
686		2-{[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]oxy}-N-(2-phenylethyl)acetamide	m/z 462 $[MH]^+$ RT 3.23min
687		2-{[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]oxy}-N-[(3-methylphenyl)methyl]acetamide	m/z 462 $[MH]^+$ RT 3.28min
688		2-{[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]oxy}-N-[(4-methylphenyl)methyl]acetamide	m/z 462 $[MH]^+$ RT 3.27min

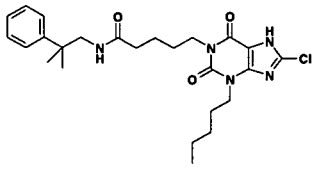
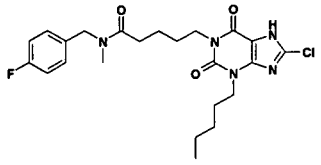
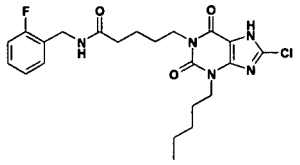
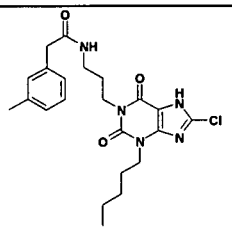
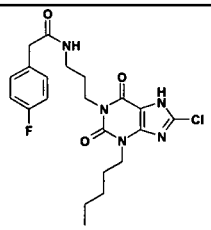
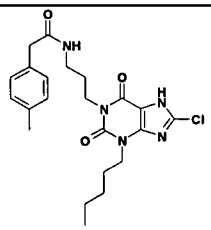
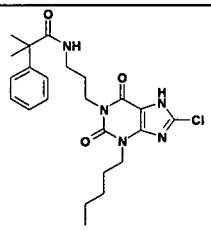
689		2-{[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]oxy}-N-methyl-N-(phenylmethyl)acetamide	m/z 462 $[MH]^+$ RT 3.27min
690		2-{[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]oxy}-N-{[3-(trifluoromethyl)phenyl]methyl}acetamide	m/z 516 $[MH]^+$ RT 3.39min
691		2-{[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]oxy}-N-[2-(3-methylphenyl)ethyl]acetamide	m/z 476 $[MH]^+$ RT 3.36min
692		2-{[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]oxy}-N-methyl-N-{[3-(trifluoromethyl)phenyl]methyl}acetamide	m/z 530 $[MH]^+$ RT 3.41min
693		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]benzenesulfonamide	m/z 454 $[MH]^+$ RT 3.29min
694		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-3-phenylpropanamide	m/z 446 $[MH]^+$ RT 3.27min
695		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-1-phenylmethanesulfonamide	m/z 468 $[MH]^+$ RT 3.29min

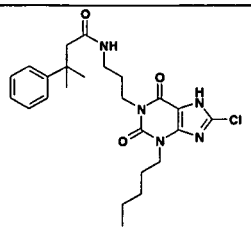
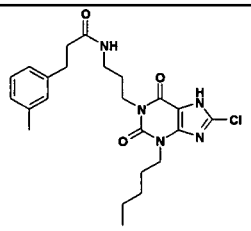
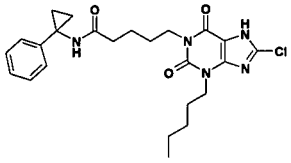
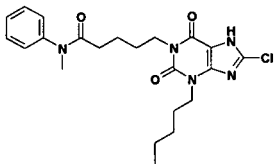
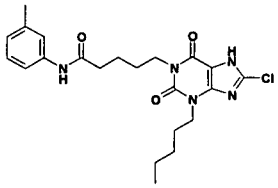
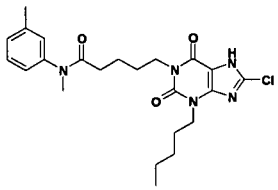
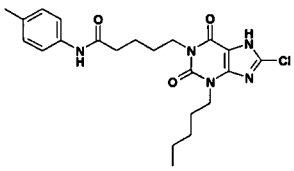
696		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-2-phenylacetamide	m/z 432 $[MH]^+$ RT 3.18min
697		1-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-3-[(3-methylphenyl)methyl]urea	m/z 461 $[MH]^+$ RT 3.29min
698		1-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-3-[(4-methylphenyl)methyl]urea	m/z 461 $[MH]^+$ RT 3.29min
699		3-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-1-methyl-1-{[3-(trifluoromethyl)phenyl]methyl}urea	m/z 529 $[MH]^+$ RT 3.51min
700		1-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-3-(phenylmethyl)urea	m/z 447 $[MH]^+$ RT 3.17min
701		2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl (phenylmethyl)carbamate	m/z 434 $[MH]^+$ RT 3.24min
702		2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl [(4-methylphenyl)methyl]carbamate	m/z 448 $[MH]^+$ RT 3.34min

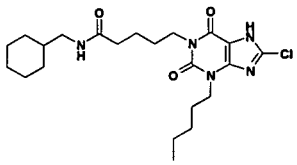
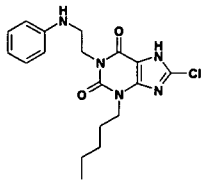
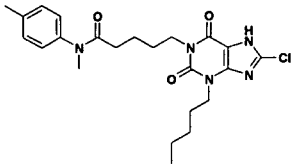
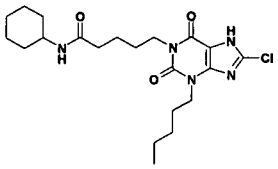
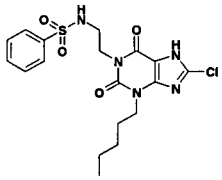
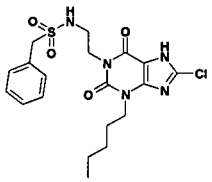
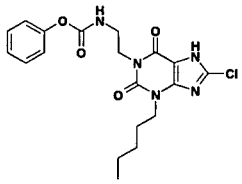
703		2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl (2-phenylethyl)carbamate	m/z 448 $[MH]^+$ RT 3.34min
704		2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl [2-(3-methylphenyl)ethyl]carbamate	m/z 462 $[MH]^+$ RT 3.48min
705		2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl [2-(4-methylphenyl)ethyl]carbamate	m/z 462 $[MH]^+$ RT 3.48min
706		2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl [(3-methylphenyl)methyl]carbamate	m/z 448 $[MH]^+$ RT 3.37min
707		3-butyl-8-chloro-1-(2-hydroxyethyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 287 $[MH]^+$ RT 2.42min
708		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(4-propylphenyl)pentanamide	m/z 474 $[MH]^+$ RT 3.73min
709		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(2-ethylphenyl)pentanamide	m/z 460 $[MH]^+$ RT 3.41min

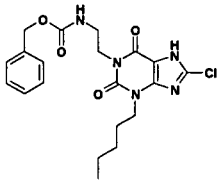
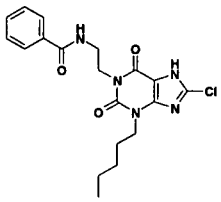
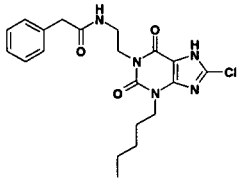
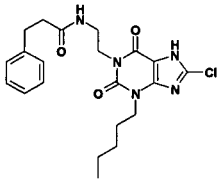
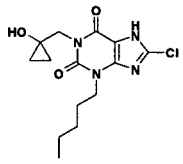
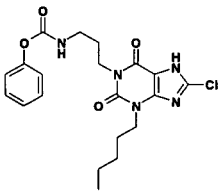
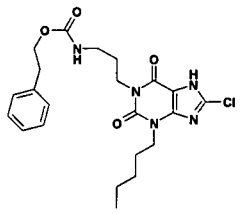
710		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(3-ethylphenyl)pentanamide	m/z 460 $[MH]^+$ RT 3.58min
711		3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl [(4-fluorophenyl)methyl]carbamate	m/z 466 $[MH]^+$ RT 3.43min
712		3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl methyl(phenylmethyl)carbamate	m/z 462 $[MH]^+$ RT 3.54min
713		3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl [(4-methylphenyl)methyl]carbamate	
714		3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl [(2-methylphenyl)methyl]carbamate	m/z 462 $[MH]^+$ RT 3.50min
715		(4-fluorophenyl)methyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 466 $[MH]^+$ RT 3.36min
716		3-thienylmethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 454 $[MH]^+$ RT 3.27min

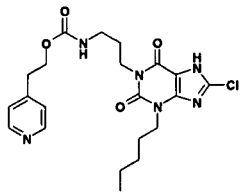
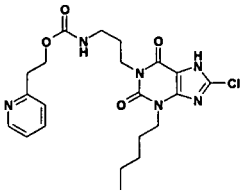
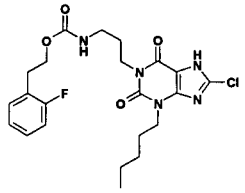
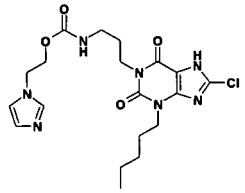
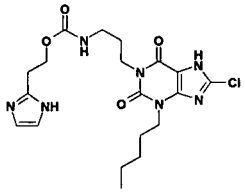
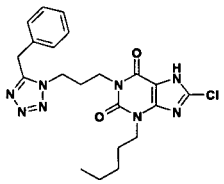
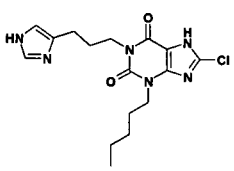
717		(4-methylphenyl)methyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 462 $[MH]^+$ RT 3.45min
718		(2-methylphenyl)methyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 462 $[MH]^+$ RT 3.42min
719		2-(4-fluorophenyl)ethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 480 $[MH]^+$ RT 3.49min
720		3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl (2-phenylethyl)carbamate	m/z 462 $[MH]^+$ RT 3.50min
721		3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl propylcarbamate	m/z 400 $[MH]^+$ RT 3.20min
722		3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl (2-methyl-2-phenylpropyl)carbamate	m/z 490 $[MH]^+$ RT 3.66min
723		3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl (1-methyl-1-phenylethyl)carbamate	m/z 476 $[MH]^+$ RT 3.59min

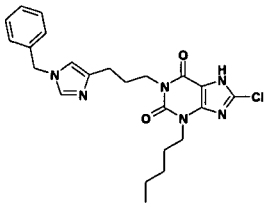
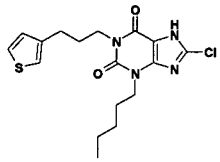
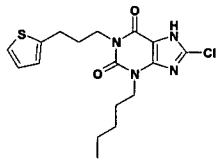
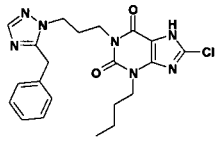
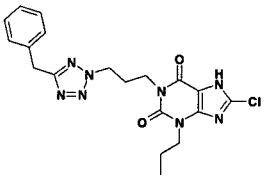
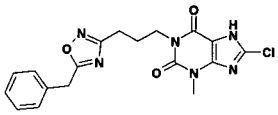
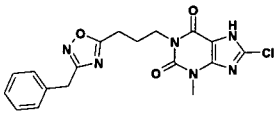
724		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(2-methyl-2-phenylpropyl)pentanamide	m/z 488 $[MH]^+$ RT 3.53min
725		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(4-fluorophenyl)methyl]-N-methylpentanamide	m/z 478 $[MH]^+$ RT 3.46min
726		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-[(2-fluorophenyl)methyl]pentanamide	m/z 464 $[MH]^+$ RT 3.32min
727		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-2-(3-methylphenyl)acetamide	m/z 446 $[MH]^+$ RT 3.37min
728		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-2-(4-fluorophenyl)acetamide	m/z 450 $[MH]^+$ RT 3.28min
729		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-2-(4-methylphenyl)acetamide	m/z 446 $[MH]^+$ RT 3.36min
730		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-2-methyl-2-phenylpropanamide	m/z 460 $[MH]^+$ RT 3.50min

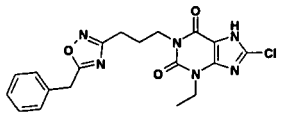
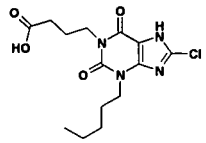
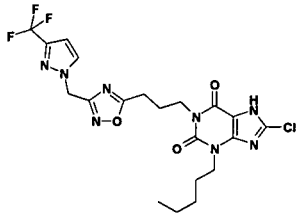
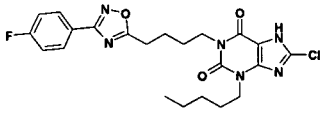
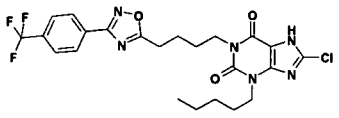
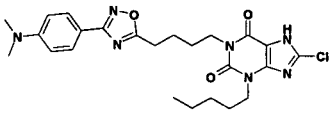
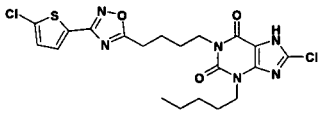
731		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-3-methyl-3-phenylbutanamide	m/z 474 $[MH]^+$ RT 3.51min
732		N-[3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]-3-(3-methylphenyl)propanamide	m/z 460 $[MH]^+$ RT 3.45min
733		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(1-phenylcyclopropyl)pentanamide	m/z 472 $[MH]^+$ RT 3.29min
734		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-methyl-N-phenylpentanamide	m/z 446 $[MH]^+$ RT 3.27min
735		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(3-methylphenyl)pentanamide	m/z 446 $[MH]^+$ RT 3.41min
736		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-methyl-N-(3-methylphenyl)pentanamide	m/z 460 $[MH]^+$ RT 3.41min
737		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(4-methylphenyl)pentanamide	m/z 446 $[MH]^+$ RT 3.40min

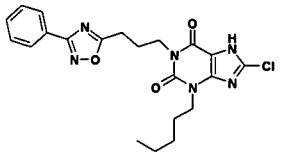
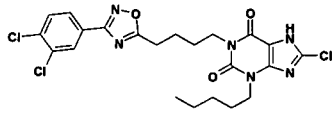
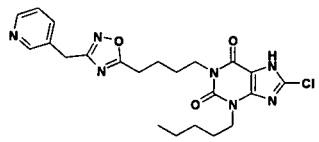
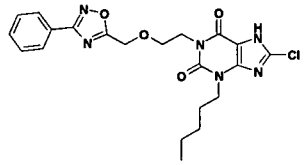
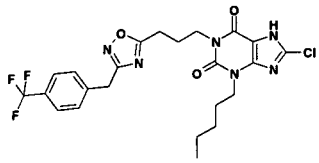
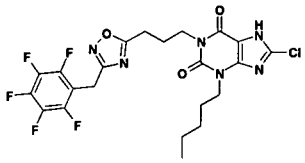
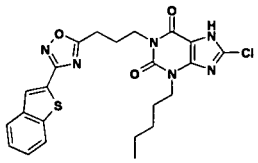
738		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(cyclohexylmethyl)pentanamide	m/z 452 $[MH]^+$ RT 3.40min
739		8-chloro-3-pentyl-1-[2-(phenylamino)ethyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 376 $[MH]^+$ RT 3.55min
740		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-methyl-N-(4-methylphenyl)pentanamide	m/z 460 $[MH]^+$ RT 3.41min
741		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-cyclohexylpentanamide	m/z 438 $[MH]^+$ RT 3.25min
742		N-[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]benzenesulfonamide	m/z 440 $[MH]^+$ RT 3.08min
743		N-[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]-1-phenylmethanesulfonamide	m/z 454 $[MH]^+$ RT 3.15min
744		phenyl [2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]carbamate	m/z 420 $[MH]^+$ RT 3.18min

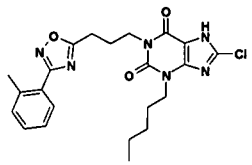
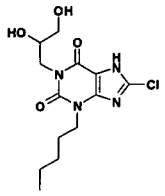
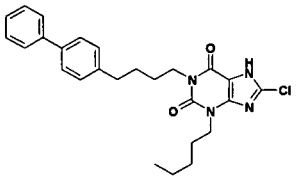
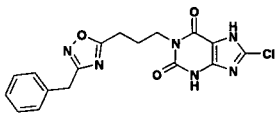
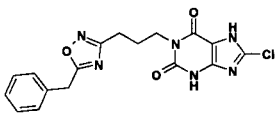
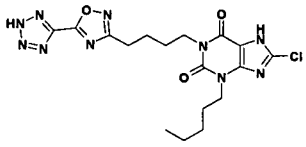
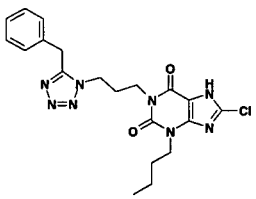
745		phenylmethyl [2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]carbamate	m/z 434 $[MH]^+$ RT 3.23min
746		N-[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]benzamide	m/z 404 $[MH]^+$ RT 3.04min
747		N-[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]-2-phenylacetamide	m/z 418 $[MH]^+$ RT 2.99min
748		N-[2-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)ethyl]-3-phenylpropanamide	m/z 432 $[MH]^+$ RT 3.14min
749		8-chloro-1-[(1-hydroxycyclopropyl)methyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 327 $[MH]^+$ RT 2.82min
750		phenyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 434 $[MH]^+$ RT 3.31min
751		2-phenylethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 462 $[MH]^+$ RT 3.48min

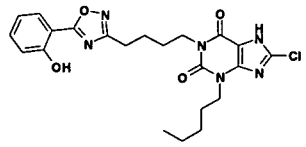
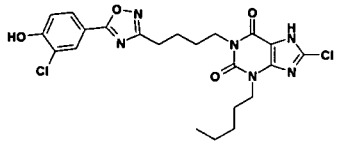
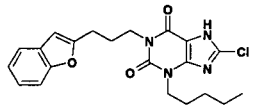
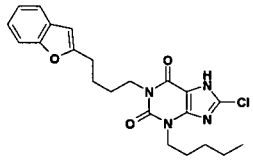
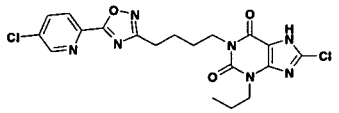
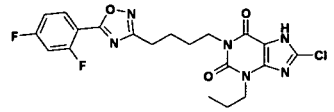
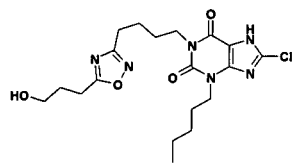
752		2-pyridin-4-ylethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 463 $[MH]^+$ RT 2.44min
753		2-pyridin-2-ylethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 463 $[MH]^+$ RT 2.44min
754		2-(2-fluorophenyl)ethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 480 $[MH]^+$ RT 3.46min
755		2-(1H-imidazol-1-yl)ethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 452 $[MH]^+$ RT 2.30min
756		2-(1H-imidazol-2-yl)ethyl [3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)propyl]carbamate	m/z 452 $[MH]^+$ RT 2.31min
757		8-chloro-3-pentyl-1-{3-[5-(phenylmethyl)-1H-tetrazol-1-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 457 $[MH]^+$ RT 3.32min
758		8-chloro-1-[3-(1H-imidazol-4-yl)propyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 365 $[MH]^+$ RT 2.27min

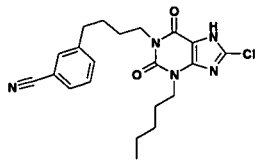
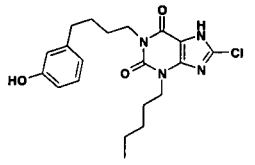
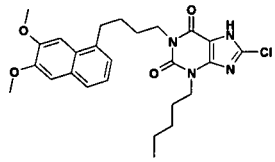
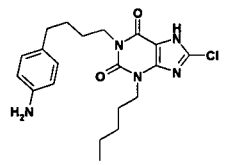
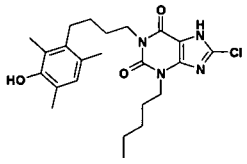
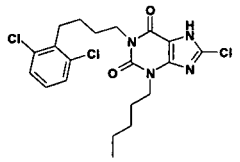
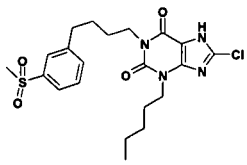
759		8-chloro-3-pentyl-1-{3-[1-(phenylmethyl)-1H-imidazol-4-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 455 $[MH]^+$ RT 2.61min
760		8-chloro-3-pentyl-1-[3-(3-thienyl)propyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 381 $[MH]^+$ RT 3.61min
761		8-chloro-3-pentyl-1-[3-(2-thienyl)propyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 381 $[MH]^+$ RT 3.69min
762		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
763		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
764		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
765		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

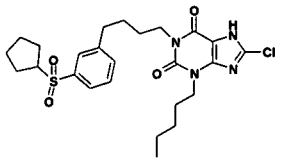
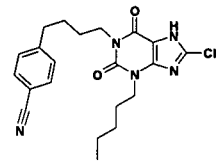
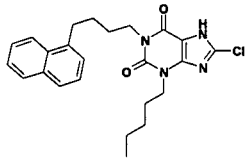
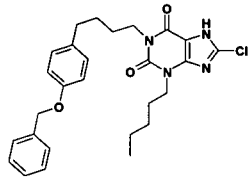
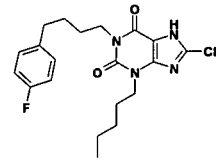
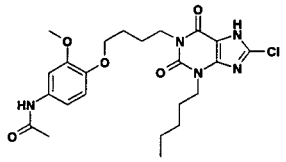
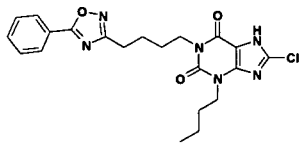
766		8-chloro-3-ethyl-1-{3-[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]propyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 415 $[MH]^+$ RT 2.97min
767		4-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)butanoic acid	m/z 343 $[MH]^+$ RT 2.81min
768		8-chloro-3-pentyl-1-[3-(3-{[3-(trifluoromethyl)-1H-pyrazol-1-yl]methyl}-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 515 $[MH]^+$ RT 3.43min
769		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
770		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
771		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
772		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

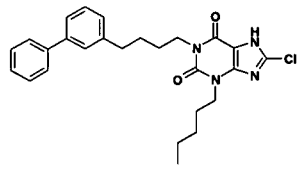
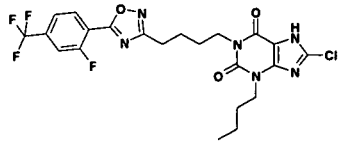
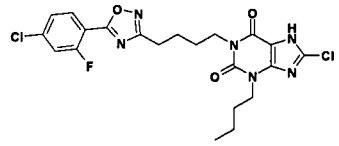
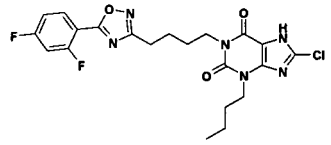
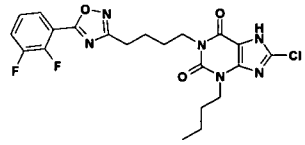
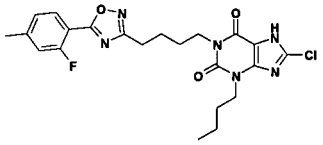
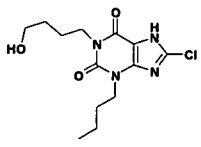
773		8-chloro-3-pentyl-1-[3-(3-phenyl-1,2,4-oxadiazol-5-yl)propyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 443 $[MH]^+$ RT 3.51min
774		8-chloro-1-{4-[3-(3,4-dichlorophenyl)-1,2,4-oxadiazol-5-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 525 $[MH]^+$ RT 4.12min
775		8-chloro-3-pentyl-1-{4-[3-(pyridin-3-ylmethyl)-1,2,4-oxadiazol-5-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 472 $[MH]^+$ RT 2.90min
776		8-chloro-3-pentyl-1-(2-{[(3-phenyl-1,2,4-oxadiazol-5-yl)methyl]oxy}ethyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 459 $[MH]^+$ RT 3.45min
777		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
778		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
779		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

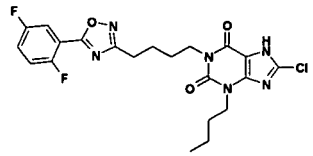
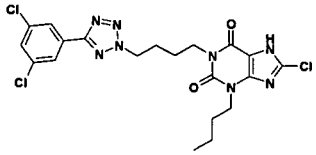
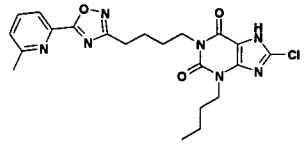
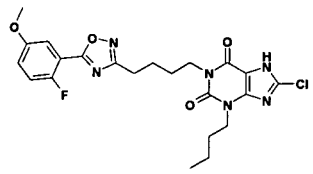
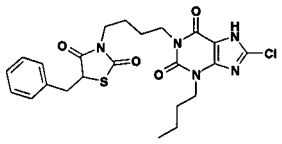
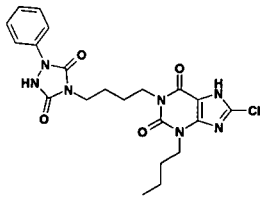
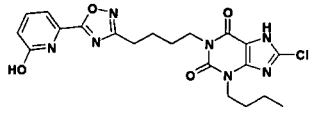
780		8-chloro-1-{3-[3-(2-methylphenyl)-1,2,4-oxadiazol-5-yl]propyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 457 $[MH]^+$ RT 3.62min
781		8-chloro-1-(2,3-dihydroxypropyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 331 $[MH]^+$ RT 2.48min
782		1-(4-biphenyl-4-ylbutyl)-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 465 $[MH]^+$ RT 4.18min
783		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
784		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
785		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
786		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

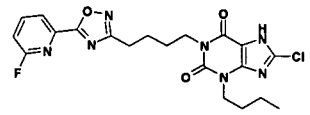
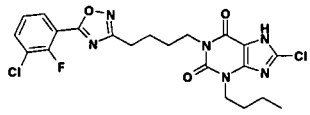
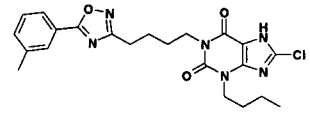
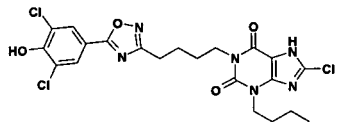
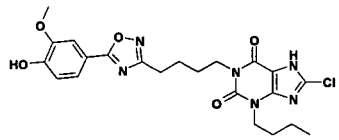
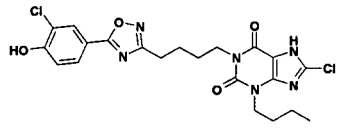
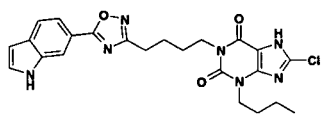
787		8-chloro-1-{4-[5-(2-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 473 $[MH]^+$ RT 3.84min
788		8-chloro-1-{4-[5-(3-chloro-4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 507 $[MH]^+$ RT 3.74min
789		1-[3-(1-benzofuran-2-yl)propyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 415 $[MH]^+$ RT 5.10min
790		1-[4-(1-benzofuran-2-yl)butyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 429 $[MH]^+$ RT 3.88min
791		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
792		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
793		8-chloro-1-{4-[5-(3-hydroxypropyl)-1,2,4-oxadiazol-3-yl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 439 $[MH]^+$ RT 2.93min

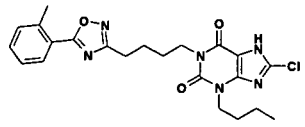
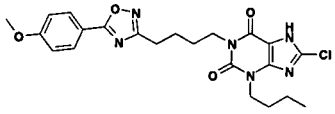
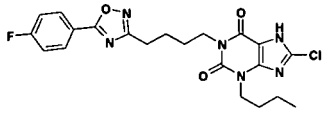
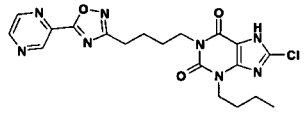
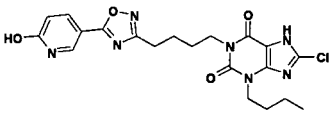
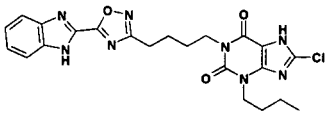
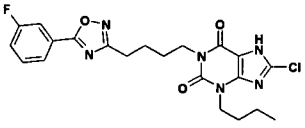
794		3-[4-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)butyl]benzonitrile	m/z 414 $[MH]^+$ RT 3.62min
795		8-chloro-1-[4-(3-hydroxyphenyl)butyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 405 $[MH]^+$ RT 3.48min
796		1-{4-[6,7-bis(methyloxy)naphthalen-1-yl]butyl}-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 499 $[MH]^+$ RT 3.78min
797		1-[4-(4-aminophenyl)butyl]-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 404 $[MH]^+$ RT 3.02min
798		8-chloro-1-[4-(3-hydroxy-2,4,6-trimethylphenyl)butyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 447 $[MH]^+$ RT 3.78min
799		8-chloro-1-[4-(2,6-dichlorophenyl)butyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 457 $[MH]^+$ RT 4.10min
800		8-chloro-1-{4-[3-(methylsulfonyl)phenyl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 467 $[MH]^+$ RT 3.33min

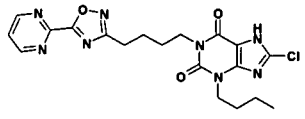
801		8-chloro-1-{4-[3-(cyclopentylsulfonyl)phenyl]butyl}-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 521 $[MH]^+$ RT 3.65min
802		4-[4-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)butyl]benzonitrile	m/z 414 $[MH]^+$ RT 3.61min
803		8-chloro-1-(4-naphthalen-1-ylbutyl)-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 439 $[MH]^+$ RT 4.00min
804		8-chloro-3-pentyl-1-(4-{4-[(phenylmethyl)oxy]phenyl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 495 $[MH]^+$ RT 4.06min
805		8-chloro-1-[4-(4-fluorophenyl)butyl]-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 407 $[MH]^+$ RT 3.78min
806		N-[4-{[4-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)butyl]oxy}-3-(methyloxy)phenyl]acetamide	m/z 492 $[MH]^+$ RT 3.09min
807		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

808		1-(4-biphenyl-3-ylbutyl)-8-chloro-3-pentyl-3,7-dihydro-1H-purine-2,6-dione	m/z 465 $[MH]^+$ RT 4.13min
809		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
810		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
811		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
812		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
813		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
814		3-butyl-8-chloro-1-(4-hydroxybutyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 315 $[MH]^+$ RT 2.54min

815		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
816		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
817		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
818		3-butyl-8-chloro-1-(4-{5-[2-fluoro-5-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 491 $[MH]^+$ RT 3.51min
819		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
820		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
821		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

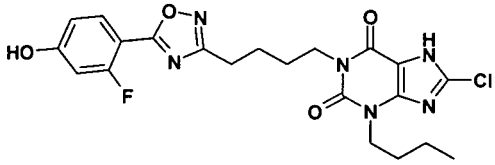
822		3-butyl-8-chloro-1-{4-[5-(6-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 462 $[MH]^+$ RT 3.23min
823		3-butyl-8-chloro-1-{4-[5-(3-chloro-2-fluorophenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 495 $[MH]^+$ RT 3.69min
824		3-butyl-8-chloro-1-{4-[5-(3-methylphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1H-purine-2,6-dione	m/z 457 $[MH]^+$ RT 3.67min
825		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
826		3-butyl-8-chloro-1-(4-{5-[4-hydroxy-3-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 489 $[MH]^+$ RT 3.27min
827		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
828		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

829		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
830		3-butyl-8-chloro-1-(4-{5-[4-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 473 $[MH]^+$ RT 3.51min
831		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
832		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
833		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
834		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
835		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

836		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

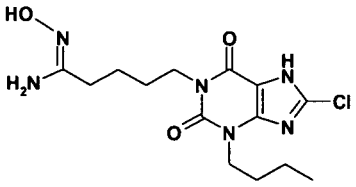
Example 837: 3-Butyl-8-chloro-1-{4-[5-(2-fluoro-4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione

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



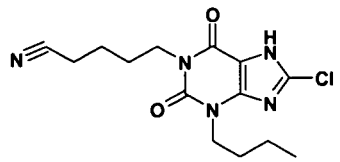
CDI (45mg, 0.28mmol) in anhydrous DMSO (0.5ml) was added to 2-fluoro-4-hydroxybenzoic acid (40mg, 0.25mmol) and stirred at rt for 2h. 5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide (100mg, 0.28mmol) in DMSO (0.4ml) was added and the resulting mixture heated 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.
^{1}H 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-1*H*-purin-1-yl)-*N*-hydroxypentanimidamide



5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-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.

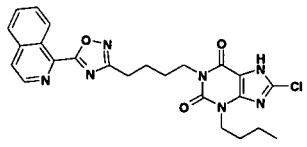
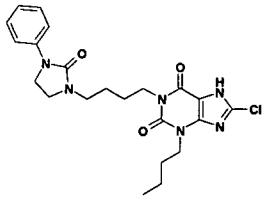
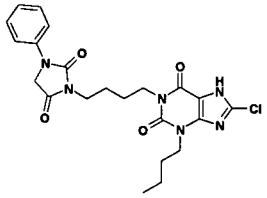
c) 5-(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanenitrile

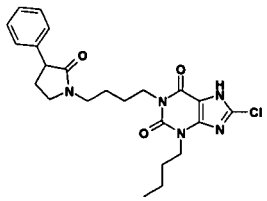
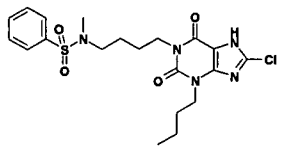
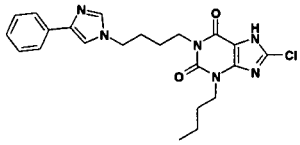
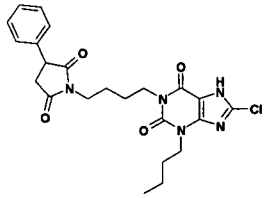
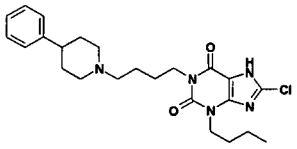
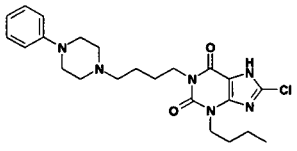
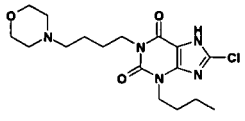


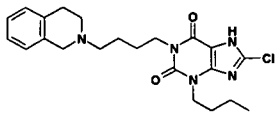
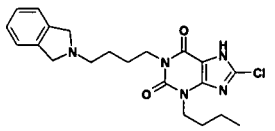
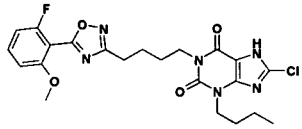
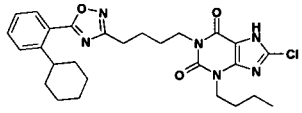
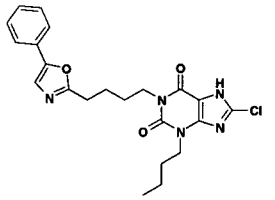
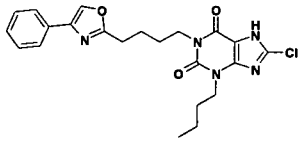
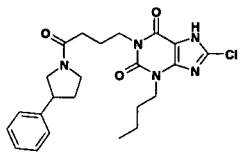
5-Bromopentanenitrile (4.54ml, 39mmol) and cesium carbonate (12.7g) were added to a solution of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (10g, 35mmol) in DMF (100ml) and the mixture stirred under nitrogen at 40°C overnight and allowed to cool.

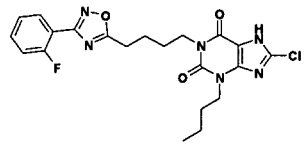
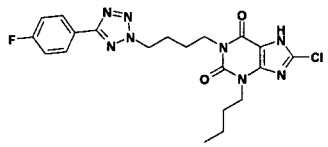
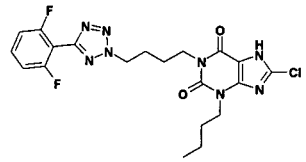
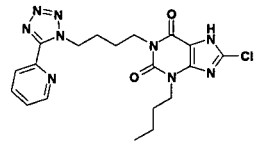
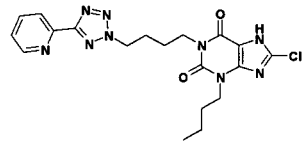
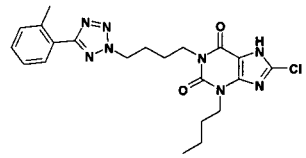
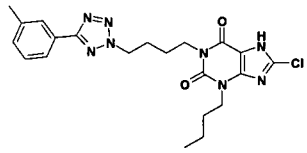
The mixture was then degassed by the repeated successive application of a vacuum and then nitrogen pressure. The mixture was then treated with tetrakis(triphenylphosphine)palladium(0) (2.86g, 2.5mmol) and morpholine (30.8ml, 350mmol). The mixture was stirred in a nitrogen atmosphere for 3h and then partitioned 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.

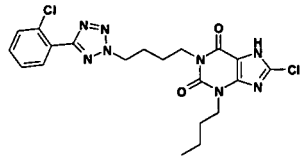
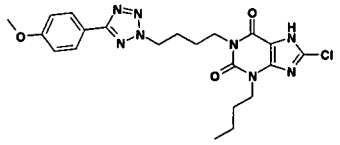
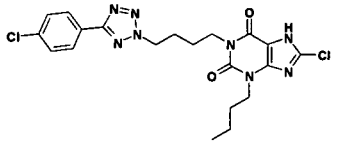
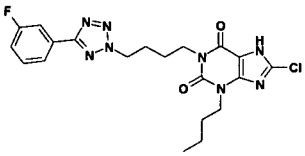
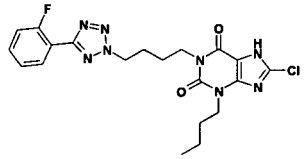
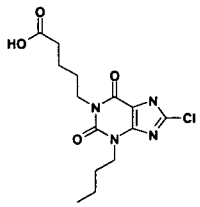
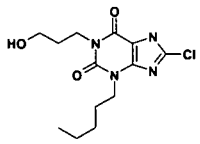
The following compounds (**Table 35**) were prepared using a method analogous to that for **Example 837**, using the appropriate carboxylic acid.

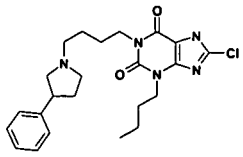
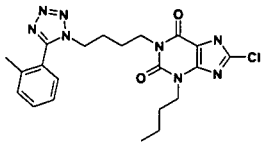
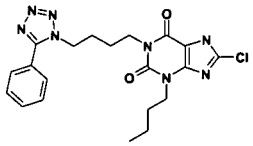
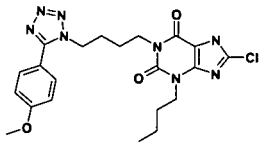
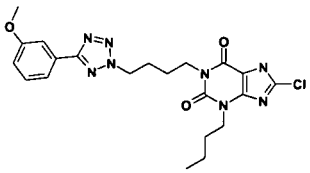
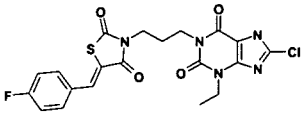
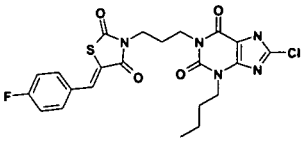
844		3-butyl-8-chloro-1-[4-(5-isoquinolin-1-yl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 494 $[MH]^+$ RT 3.49min
845		3-butyl-8-chloro-1-[4-(2-oxo-3-phenylimidazolidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 459 $[MH]^+$ RT 3.23min
846		3-butyl-8-chloro-1-[4-(2,5-dioxo-3-phenylimidazolidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 473 $[MH]^+$ RT 3.19min

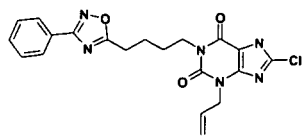
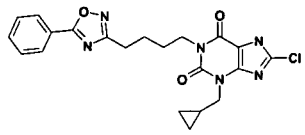
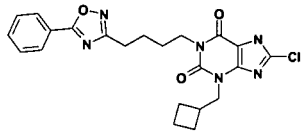
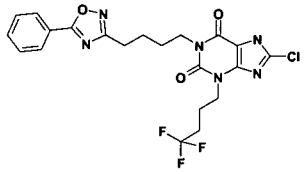
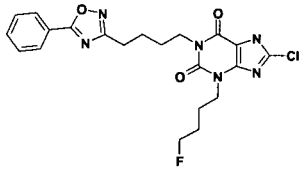
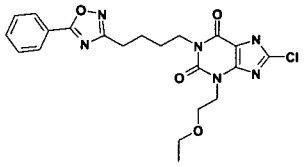
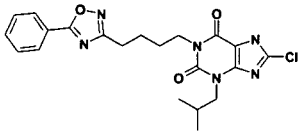
847		3-butyl-8-chloro-1-[4-(2-oxo-3-phenylpyrrolidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 458 $[MH]^+$ RT 3.12min
848		N-[4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)butyl]-N-methylbenzenesulfonamide	m/z 468 $[MH]^+$ RT 3.28min
849		3-butyl-8-chloro-1-[4-(4-phenyl-1H-imidazol-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 441 $[MH]^+$ RT 2.60min
850		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
851		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
852		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
853		3-butyl-8-chloro-1-(4-morpholin-4-ylbutyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 384 $[MH]^+$ RT 2.11min

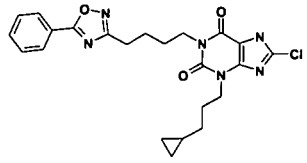
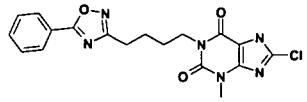
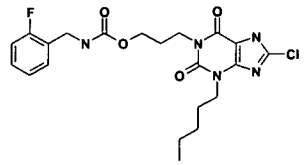
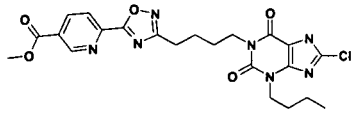
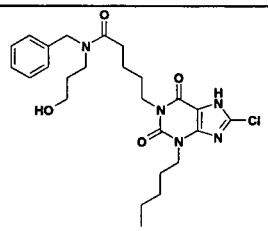
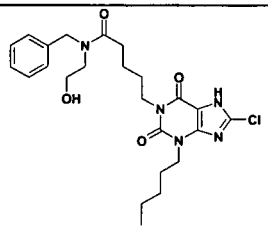
854		3-butyl-8-chloro-1-[4-(3,4-dihydroisoquinolin-2(1H)-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 430 $[MH]^+$ RT 2.40min
855		3-butyl-8-chloro-1-[4-(1,3-dihydro-2H-isoindol-2-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 416 $[MH]^+$ RT 2.33min
856		3-butyl-8-chloro-1-(4-{5-[2-fluoro-6-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 491 $[MH]^+$ RT 3.33min
857		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
858		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
859		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
860		3-butyl-8-chloro-1-[4-oxo-4-(3-phenylpyrrolidin-1-yl)butyl]-3,7-dihydro-1H-purine-2,6-dione	m/z 458 $[MH]^+$ RT 3.16min

861		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
862		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
863		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
864		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
865		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
866		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
867		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

868		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
869		3-butyl-8-chloro-1-(4-{5-[4-(methyloxy)phenyl]-2H-tetrazol-2-yl}butyl)-3,7-dihydro-1H-purine-2,6-dione	m/z 473 $[MH]^+$ RT 3.40min
870		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
871		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
872		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
873		5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	m/z 343 $[MH]^+$ RT 2.76min
874		5-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)pentanoic acid	m/z 315 $[MH]^+$ RT 2.74min

875		3-butyl-8-chloro-1-[4-(3-phenyl-1-pyrrolidinyl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 444 $[MH]^+$ RT 2.51min
876		3-butyl-8-chloro-1-{4-[5-(2-methylphenyl)-1*H*-tetrazol-1-yl]butyl}-3,7-dihydro-1*H*-purine-2,6-dione	m/z 457 $[MH]^+$ RT 3.16min
877		3-butyl-8-chloro-1-[4-(5-phenyl-1*H*-tetrazol-1-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 443 $[MH]^+$ RT 3.08min
878		3-butyl-8-chloro-1-(4-{5-[4-(methyloxy)phenyl]-1*H*-tetrazol-1-yl}butyl)-3,7-dihydro-1*H*-purine-2,6-dione	m/z 473 $[MH]^+$ RT 3.10min
879		3-butyl-8-chloro-1-(4-{5-[3-(methyloxy)phenyl]-2*H*-tetrazol-2-yl}butyl)-3,7-dihydro-1*H*-purine-2,6-dione	m/z 473 $[MH]^+$ RT 3.40min
880		8-chloro-3-ethyl-1-(3-{(5*Z*)-5-[(4-fluorophenyl)methylidene]-2,4-dioxo-1,3-thiazolidin-3-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	m/z 478 $[MH]^+$ RT 3.31min
881		3-butyl-8-chloro-1-(3-{(5*Z*)-5-[(4-fluorophenyl)methylidene]-2,4-dioxo-1,3-thiazolidin-3-yl}propyl)-3,7-dihydro-1*H*-purine-2,6-dione	m/z 506 $[MH]^+$ RT 3.63min

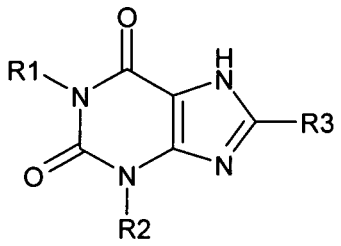
882		8-chloro-1-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)butyl]-3-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione	m/z 427 $[MH]^+$ RT 3.20min
883		8-chloro-3-(cyclopropylmethyl)-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 441 $[MH]^+$ RT 3.38min
884		8-chloro-3-(cyclobutylmethyl)-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 455 $[MH]^+$ RT 3.53min
885		8-chloro-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione	m/z 497 $[MH]^+$ RT 3.46min
886		8-chloro-3-(4-fluorobutyl)-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 461 $[MH]^+$ RT 3.26min
887		8-chloro-3-[2-(ethyloxy)ethyl]-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 459 $[MH]^+$ RT 3.16min
888		8-chloro-3-(2-methylpropyl)-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 443 $[MH]^+$ RT 3.44min

889		8-chloro-3-(3-cyclopropylpropyl)-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 469 $[MH]^+$ RT 3.63min
890		8-chloro-3-methyl-1-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione	m/z 401 $[MH]^+$ RT 2.98min
891		3-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)propyl [(2-fluorophenyl)methyl]carbamate	m/z 466 $[MH]^+$ RT 3.44min
892		methyl 6-{3-[4-(3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)butyl]-1,2,4-oxadiazol-5-yl}-3-pyridinecarboxylate	m/z 502 $[MH]^+$ RT 3.22min
893		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(3-hydroxypropyl)-N-(phenylmethyl)pentanamide	m/z 504 $[MH]^+$ RT 2.64min
894		5-(8-chloro-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(2-hydroxyethyl)-N-(phenylmethyl)pentanamide	m/z 490 $[MH]^+$ RT 3.13min

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)



(I)

and pharmaceutically acceptable derivatives thereof, wherein

R^1 represents $-(alkylene)_m-X-(alkylene)_n-Y$;

Wherein X represents A, A1, A2 or a direct link;

A represents a group selected from
cycloalkylene, cycloalkenylene, aryl, heteroaryl, heterocyclyl, and $-CH_2-OC(O)-$;

A1 represents a group selected from
$-CH_2-O-(CH_2)_q$aryl$-O-$, $-CH_2-O-(CH_2)_wN(R^5)C(O)O-$, $-CH_2-N(R^5)C(O)O-$,
$-CH_2-N(R^5)C(O)-$, $-CH_2-(O)_p-(CH_2)_qC(O)NR^5-$, $-CH_2-N(R^5)C(O)N(R^5)-$,
$-CH_2-C(O)N((CH_2)_wOH)-$, $-CH_2-NR^5-S(O)_2-$, $CH_2-S(O)_2NR^5-$, $-CH_2-C(O)O-$, $-O-$,
$-NR^5-$, and $-S-$;

A2 represents $-CH(OH)-$;

When X is A, A1 or A2, Y represents a group selected from
heteroaryl, heterocyclyl, aryl, cycloalkyl, cycloalkenyl, -NH-aryl, $-O(CH_2)_n$-aryl,
-O-heteroaryl, $-OR^5$, $-C(O)OR^5$, $-C(O)O-C_6$ aryl, $-OC(O)R^4$, $-CH(aryl)_2$,
$-CH(heteroaryl)_2$, and $-C_{1-6}$ haloalkyl;

When X is A1 and Y is selected from
$-O(CH_2)_n$-aryl, -O-heteroaryl, $-OR^5$, $-OC(O)R^4$, and -NH-aryl,
n is an integer selected from 2, 3, 4 and 5;

When X is A1 and Y is $-C_{1-6}$ haloalkyl, or when X is A2, n is an integer selected from 1, 2, 3, 4 and 5;

When X is a direct link, (m + n) is an integer selected from 2 to 10;

When X is a direct link and (m + n) is an integer selected from 3 to 10, Y represents a group selected from
-C(O)$(CH_2)_q$OR^4, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocyclyl, heteroaryl, heterocyclyl, Aryl, 3 or 4 ring fused system, -CH(aryl)$_2$, -CH(heteroaryl)$_2$, -OR^5, -NR^{5}R^6, -NR^{5}C(O)OR^7, -$(O)_p$C(O)NR^{5}R^7, and -NR^{5}C(O)R^7;

When X is a direct link and (m + n) is 2, Y represents a group selected from
-OR^5, -NH_2, and -NR^{5}C(O)OR^8;

When Y incorporates a ring, that ring may be optionally substituted by one or more of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -$(CH_2)_q$NR^{5}R^7, -$(CH_2)_q$-$(O)_p$-$(CH_2)_q$-N(R^5)C(O)OR^8, -$(CH_2)_q$-N(R^5)C(O)R^8, -$(CH_2)_q$-$(O)_p$-$(CH_2)_q$-C(O)NR^{5}R^6, -$(CH_2)_q$-N(R^5)C(O)N(R^5)R^6, -$(CH_2)_q$-C(O)N((CH$_2$)$_m$OH)R^5, -$(CH_2)_q$-N(R^5)-S(O)$_2$R^8, -CH_2-S(O)$_2$N(R^5)R^6, -C_{1-6} haloalkyl, -OCF_3, -OCH(F)$_2$, -OCH_2F, -C(O)OR^5, -OR^5, -R^{8}CN, -CN, -SO_2R^9, -$(CH_2)_n$heteroaryl, -$(CH_2)_n$heterocycyl, -$(CH_2)_n$cycloalkyl, -$(CH_2)_n$cycloalkenyl, and -$(CH_2)_n$aryl;

Provided that when X is A1, A1 is -O- and Y is a ring which is substituted by aryl or heteroaryl, then m is an integer selected from 3, 4 and 5;

R^2 is selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, and heteroaryl, each of which may be optionally substituted by one or more of a group independently selected from: C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_{1-6} haloalkyl, halogen, -CN, -OR^4, -$(CH_2)_n$COR^4, -C(O)OR^4, -OCOR^4, -$(CH_2)_n$NR^{5}R^6, -$(NH)_p$CONR^{5}R^6, -OCONR^{5}R^7, and -NR^{5}C(O)OR^7;

R^3 represents a group selected from halogen and CN;

R^4 is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -$(CH_2)_n$ cycloalkyl, -$(CH_2)_n$ cycloalkenyl, -$(CH_2)_n$ heterocyclyl, -$(CH_2)_n$ aryl, and -$(CH_2)_n$ heteroaryl;

R^5 and R^6 are independently selected from hydrogen and C_{1-4} alkyl;

R^7 represents a group selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -$(CH_2)_t$ cycloalkyl, -$(CH_2)_n$ cycloalkenyl, -$(CH_2)_t$ heterocyclyl, -$(CH_2)_t$ aryl, and -$(CH_2)_t$ heteroaryl;

R^8 represents a group selected from C_{1-4} alkyl;

R^9 represents a group selected from C_{1-6} alkyl C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_n$ cycloalkyl, $-(CH_2)_n$cycloalkenyl, $-(CH_2)_n$heterocyclyl, $-(CH_2)_n$ aryl, $-(CH_2)_n$heteroaryl, and CN;

m represents an integer selected from 1, 2, 3, 4 and 5;

n represents an integer selected from 0, 1, 2, 3, 4 and 5;

p represents an integer selected from 0 and 1;

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

t represents an integer selected from 1 and 2; and

w represents an integer selected from 2, 3 and 4.

2. At least one chemical entity according to claim 1 wherein X is selected from A and A1.

3. At least one chemical entity according to claim 1 or 2 wherein R^2 is selected from C_{3-6} alkyl.

4. At least one chemical entity according to any preceding claim wherein X is selected from A and A1, and A represents a group selected from heteroaryl and heterocyclyl, and A1 represents a group selected from CH_2-O-$(CH_2)_w$N(R^5)C(O)O-, CH_2-N(R^5)C(O)O-, CH_2-N(R^5)C(O)-, CH_2-$(O)_p$-$(CH_2)_q$C(O)NR^5-, CH_2-N(R^5)C(O)N(R^5)-, CH_2-C(O)N($(CH_2)_m$OH)-, CH_2-NR^5-S$(O)_2$-, CH_2-S$(O)_2$NR^5-, and CH_2-C(O)O-.

5. At least one chemical entity according to claim 4 wherein X represents A and A represents a group selected from heteroaryl.

6. At least one chemical entity according to claim 5 wherein A represents a group selected from heteroaryl comprising a nitrogen heteroatom.

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

8. At least one chemical entity according to any preceding claim wherein R^3 represents halogen.

9. At least one chemical entity according to any preceding claim wherein R^3 represents chlorine.

10. At least one chemical entity according to any preceding claim for use in human or veterinary medicine.

11. At least one chemical entity according to any one of claims 1 to 9, for use in the treatment of disorders of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia and/or of inflammatory diseases or conditions.

12. At least one chemical entity according to any one of claims 1 to 9 for use in the treatment of diabetic dyslipidaemia, mixed dyslipidaemia, heart failure, hypercholesteraemia, 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.

13. At least one chemical entity according to any one of claims 1 to 9 for use in the manufacture of a medicament for treating diabetic dyslipidaemia, mixed dyslipidaemia, heart failure, hypercholesteraemia, 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.

14. 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 9.

15. A method according to claim 14 wherein the human or animal subject has a disorder of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia or an inflammatory disease or condition.

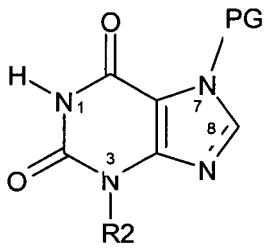
16. A pharmaceutical formulation comprising at least one chemical entity according to any one of claims 1 to 9 and at least one pharmaceutically acceptable diluents, excipients or carriers.

17. 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 9 together with another therapeutically active agent.

18. A pharmaceutical formulation comprising:
    (i) at least one chemical entity according to any one of claims 1 to 9;
    (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.

19. A method for the preparation of at least one chemical entity according to any one of claims 1 to 9 in which R^3 is halogen from an appropriate starting material, for example compound(s) of formula (II):



(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.