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Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). **WILLIAMS, Sophie, Caroline** [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB).

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(74) Agent: **THOMPSON, John**; Patent Department, Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB).

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(71) Applicant (for all designated States except US): **CELLTECH R & D LIMITED** [GB/GB]; 208 Bath Road, Slough, Berkshire SL1 3WE (GB).

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(72) Inventors; and

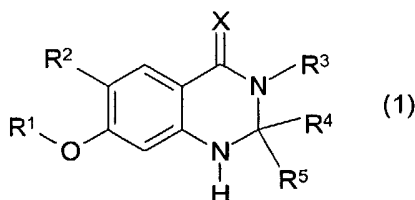
(75) Inventors/Applicants (for US only): **HAUGHAN, Alan, Findlay** [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). **BUCKLEY, George, Martin** [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). **DYKE, Hazel, Joan** [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). **HANNAH, Duncan, Robert** [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). **RICHARD, Marianna, Dilani** [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). **SHARPE, Andrew** [GB/GB]; Celltech R & D

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(54) Title: QUINAZOLINONE DERIVATIVES



(57) Abstract: A compound of formula (1): wherein: X is an oxygen or sulfur atom; R¹ is an aliphatic, cycloaliphatic or cycloalkyl-alkyl-group; R² is an optionally substituted heteroaromatic group or a -CN group; R³ is a group -(Alk¹)_mL¹(Alk²)_nR⁶ in which m and n, which may be the same or different, is each zero or the integer 1, Alk¹ and Alk², which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain, L¹ is a covalent bond or a linker atom or group and R⁶ is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group; R⁴ is a group -(Alk³)_pL²(Alk⁴)_qR⁷ in which p and q, which may be the same or different, is each zero or the integer 1, Alk³ and Alk⁴, which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain, L² is a covalent bond or a linker atom or group and R⁷ is a hydrogen or halogen atom or a -CN group or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group; R⁵ is a hydrogen atom or an optionally substituted aliphatic group; and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof. The compounds of the present invention are potent inhibitors of IMPDH.

QUINAZOLINONE DERIVATIVES

This invention relates to a series of quinazolinones and quinazolinthiones and
5 their derivatives, to processes for their preparation, to pharmaceutical
compositions containing them and to their use in medicine.

Inosine-5'-monophosphate dehydrogenase (IMPDH; EC 1.1.1.205) is an
enzyme involved in the *de novo* synthesis of guanine nucleotides. IMPDH
10 catalyses the β -nicotinamide adenine dinucleotide (NAD)-dependant oxidation
of inosine-5'-monophosphate (IMP) to xanthosine-5'-monophosphate (XMP)
(Jackson R.C. et al., Nature, 256, pp. 331-333, (1975)). Guanine nucleotides
are essential to the cell for RNA and DNA synthesis, intermediates in
signalling pathways and as energy sources for metabolic pathways.

15 IMPDH is ubiquitous in eukaryotes, bacteria and protozoa (Y. Natsumeda &
S.F. Carr, Ann. N.Y. Acad., 696, pp. 88-93, (1993)). Two isoforms of human
IMPDH, designated type I and type II, have been identified and sequenced
(F.R. Collart and E. Huberman, J. Biol. Chem., 263, pp. 15769-15772, (1988);
20 Y. Natsumeda et al J. Biol. Chem., 265, pp 5292-5295, (1990)). Each is 514
amino acids and they share 84% sequence identity. Both IMPDH type I and
type II form active tetramers in solution, with subunit molecular weights of 56
kDa (Y. Yamada et. Al., Biochemistry, 27, pp. 2737-2745, (1988)). It is
thought that type I is the predominant isoform expressed in normal cells,
25 whilst type II is upregulated in neoplastic and replicating cells. Studies have
postulated that selective inhibition of type II IMPDH could provide a
therapeutic advantage by reducing potential toxicity effects caused by
inhibiting the type I isoform (Pankiewicz K.W, Expert Opin. Ther. Patents 11
(7) pp 1161-1170, (2001)).

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The *de novo* synthesis of guanine nucleotides, and thus the activity of IMPDH,
is particularly important in B and T-lymphocytes. These cells depend on the
de novo, rather than the salvage pathway to generate sufficient levels of

nucleotides necessary to initiate a proliferative response to mitogen or antigen (A.C. Allison et. al., Lancet II, 1179, (1975) and A.C. Allison et. al., Ciba Found. Symp., 48, 207, (1977)). Thus, IMPDH is an attractive target for selectively inhibiting the immune system without also inhibiting the proliferation of other cells.

Mycophenolic acid (MPA) and some of its derivatives have been described in United States patents 5,380,879 and 5,444,072 and PCT publications WO 94/01105 and WO 94/12184 as potent, uncompetitive, reversible inhibitors of human IMPDH type I ($K_i = 33$ nM) and type II ($K_i = 9$ nM). MPA has been demonstrated to block the response of B and T-cells to mitogen or antigen (A.C. Allison et. al., Ann. N. Y. Acad. Sci., 696, 63, (1993)).

Immunosuppressants, such as MPA, are useful drugs in the treatment of transplant rejection and autoimmune diseases. (R.E. Morris, Kidney Intl., 49, Suppl. 53, S-26, (1996)). However, MPA is characterized by undesirable pharmacological properties, such as gastrointestinal toxicity. (L.M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995)).

Mycophenolate mofetil, a prodrug which quickly liberates free MPA *in vivo*, was recently approved to prevent acute allograft rejection following kidney transplantation (i.e. renal allograft failure) and heart transplantation. (L.M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995); H.W. Sollinger, Transplantation, 60, pp. 225-232, (1995); J. Kobashigawa Transplant, 66, pp. 507, (1998)). Mycophenolate mofetil has also been used for the treatment of rheumatoid arthritis. The experimental use of mycophenolate mofetil in the treatment of systemic lupus erythematosus, lupus nephritis, myasthenia gravis, inflammatory eye disease, autoimmune and inflammatory skin disorders (including psoriasis) and glomerular disease has also been described (R. Bentley, Chem. Rev., 100, pp. 3801-3825, (2000)). Mycophenolate mofetil has also been postulated to be of use for the treatment of atopic dermatitis (Grundmann-Kollman M et al, Archives of Dermatology, 137 (7), pp. 870-873, (2001)) and has been shown to be effective in predictive animal models of multiple sclerosis (Tran G.T et al,

International Immunopharmacology, 1 (9-10) pp. 1709-1723, (2001)). Several clinical observations, however, limit the therapeutic potential of this drug. (L.M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995)).

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Nucleoside analogues such as tiazofurin, ribavirin and mizoribine also inhibit IMPDH (L. Hedstrom, et. al., Biochemistry, 29, pp. 849-854, (1990)). These nucleoside analogues are competitive inhibitors of IMPDH, but also inhibit other NAD dependant enzymes. This lack of specificity limits the therapeutic application of these compounds. New agents with improved selectivity for IMPDH would represent a significant improvement over these nucleoside analogues. Mizoribine (Bredinin®) has been approved in Japan for multiple indications in transplantation and autoimmune diseases including prevention of rejection after renal transplantation, idiopathic glomerulonephritis, lupus nephritis and rheumatoid arthritis.

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Vertex has recently disclosed a series of novel IMPDH inhibitors (WO 97/40028), of which VX-497 has been evaluated for the treatment of psoriasis.

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It is also known that IMPDH plays a role in other metabolic events. Increased IMPDH activity has been observed in rapidly proliferating human leukemic cell lines and other tumour cell lines, indicating IMPDH as a target for anti-cancer as well as immunosuppressive chemotherapy (M. Nagai et. al., Cancer Res., 51, pp. 3886-3890, (1991), Pankiewicz K.W., Exp. Opin. Ther. Patents, 11, pp. 1161-1170, (2001)). IMPDH has also been shown to play a role in the proliferation of smooth muscle cells, indicating that inhibitors of IMPDH may be useful in preventing restenosis or other hyperproliferative vascular diseases (C.R. Gregory et. al., Transplantation, 59, pp. 655-61, (1995); PCT publication WO 94/12184; and PCT publication WO 94/ 01105).

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Additionally, IMPDH has been shown to play a role in viral replication in some virus-infected cell lines. (S.F. Carr, J. Biol. Chem., 268, pp. 27286-27290, (1993)). VX-497 is currently being evaluated for the treatment of hepatitis C in humans.

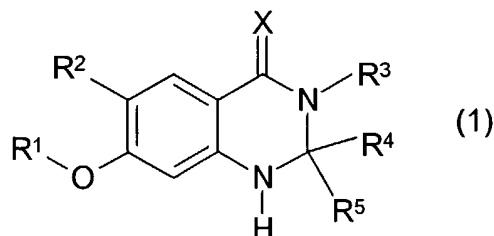
Thus, there remains a need for potent IMPDH inhibitors with improved pharmacological properties. Such inhibitors would have therapeutic potential as immunosuppressants, anti-cancer agents, anti-inflammatory agents, antipsoriatic and anti-viral agents.

International Patent Application WO-A-98/45291 discloses a class of quinazolinone and quinazolinthione derivatives and intermediates thereof having antidiabetic, hypolipidemic and antihypertensive properties.

International Patent Application WO-A-99/42456 generally discloses quinazolinone and quinazolinthione derivatives for use as AMPA receptor modulators for treatment of memory and learning disorders.

The present inventors disclose a class of substituted quinazolinone and quinazolinthione derivatives having activity as IMPDH inhibitors, and to compositions and methods related thereto.

Thus we provide a compound of formula (1):



wherein:

X is an oxygen or sulfur atom;

R¹ is an aliphatic, cycloaliphatic or cycloalkyl-alkyl- group;

R² is an optionally substituted heteroaromatic group or a -CN group;

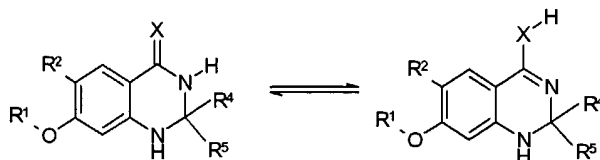
R³ is a group -(Alk¹)_mL¹(Alk²)_nR⁶ in which m and n, which may be the same or different, is each zero or the integer 1, Alk¹ and Alk², which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain, L¹ is a covalent bond or a linker atom or group and R⁶ is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;

R^4 is a group $-(Alk^3)_p L^2 (Alk^4)_q R^7$ in which p and q , which may be the same or different, is each zero or the integer 1, Alk^3 and Alk^4 , which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain, L^2 is a covalent bond or a linker atom or group and R^7 is a hydrogen or halogen atom or a $-CN$ group or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;

R^5 is a hydrogen atom or an optionally substituted aliphatic group;

and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

It will be appreciated that certain compounds of formula (1) may exist as geometric isomers (E or Z isomers). The compounds may also have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such geometric isomers, enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (1) may exist as tautomers, for example keto ($CH_2C=O$) – enol ($CH=CHOH$) tautomers. Quinazolinones may also exist as tautomers; one possible example is illustrated below:



Formula (1) and the formulae hereinafter are intended to represent all individual tautomers and mixtures thereof, unless stated otherwise.

It will also be appreciated that where desired the compounds of the invention may be administered in a pharmaceutically acceptable pro-drug form, for example, as a protected carboxylic acid derivative, e.g. as an acceptable ester. It will be further appreciated that the pro-drugs may be converted *in vivo* to the active compounds of formula (1), and the invention is intended to extend to such pro-drugs. Such prodrugs are well known in the literature, see for example International Patent Application No. WO 00/23419, Bodor N. (Alfred Benson Symposium, 1982, 17, 156-177), Singh G. *et al* (J. Sci. Ind.

Res., 1996, 55, 497-510) and Bundgaard H. (Design of Prodrugs, 1985, Elsevier, Amsterdam).

In the compounds of the invention as represented by formula (1) and the more
 5 detailed description hereinafter certain of the general terms used in relation to
 substituents are to be understood to include the following atoms or groups
 unless specified otherwise.

The term "aliphatic group" is intended to include optionally substituted straight
 10 or branched C₁₋₁₀alkyl, e.g. C₁₋₆ alkyl, C₂₋₁₀alkenyl e.g. C₂₋₆alkenyl or C₂₋₁₀
 alkynyl e.g. C₂₋₆alkynyl groups.

Particular examples of aliphatic groups include optionally substituted straight
 or branched C₁₋₆ alkyl groups such as -CH₃, -CH₂CH₃, -CH(CH₃)₂,
 15 -(CH₂)₂CH₃, -(CH₂)₃CH₃, -CH(CH₃)CH₂CH₃, -CH₂CH(CH₃)₂, -CH₂C(CH₃)₃,
 -C(CH₃)₃, -(CH₂)₄CH₃, -(CH₂)₅CH₃, or C₂₋₆alkenyl or C₂₋₆alkynyl groups such
 as -CHCH₂, -CHCHCH₃, -CH₂CHCH₂, -CHCHCH₂CH₃, -CH₂CHCHCH₃,
 -(CH₂)₂CHCH₂, -CCH, -CCCH₃, -CH₂CCH, -CCCH₂CH₃, -CH₂CCCH₃, or
 -(CH₂)₂CCH groups. More particular examples include optionally substituted
 20 C₁₋₄ alkyl groups selected from -CH₃, -CH₂CH₃, -CH(CH₃)₂, -(CH₂)₂CH₃,
 -CH(CH₃)CH₂CH₃, -CH₂CH(CH₃)₂, -(CH₂)₃CH₃ or -C(CH₃)₃

The term "aliphatic chain" is intended to include those alkyl, alkenyl or alkynyl
 groups as just described where a terminal hydrogen atom is replaced by a
 25 covalent bond to give a divalent chain.

Examples of aliphatic chains include optionally substituted straight or branched
 C₁₋₆ alkylene chains such as -CH₂-, -CH₂CH₂-, -CH(CH₃)CH₂-, -(CH₂)₂CH₂-,
 -(CH₂)₃CH₂-, -CH(CH₃)(CH₂)₂CH₂-, -CH₂CH(CH₃)CH₂-, -C(CH₃)₂-,
 30 -C(CH₃)₂CH₂-, -CH₂C(CH₃)₂CH₂-, -(CH₂)₂CH(CH₃)CH₂-, -CH(CH₃)CH₂CH₂-,
 -CH(CH₃)CH₂CH(CH₃)CH₂-, -CH₂CH(CH₃)CH₂CH₂-, -(CH₂)₂C(CH₃)₂CH₂-,
 -(CH₂)₄CH₂-, -(CH₂)₅CH₂ or C₂₋₆alkenylene or C₂₋₆alkynylene chains such as
 -CHCH-, -CHCHCH₂-, -CH₂CHCH-, -CHCHCH₂CH₂-, -CH₂CHCHCH₂-,

-(CH₂)₂CHCH-, -CC-, -CCCH₂-, -CH₂CC-, -CCCH₂CH₂-, -CH₂CCCH₂- or -(CH₂)₂CCH- chains. More particular examples include optionally substituted C₁₋₃ alkylene chains selected from -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH(CH₃)CH₂-, -C(CH₃)₂- and -CH₂CH(CH₃)- chains.

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Optional substituents that may be present on the aliphatic groups or chains include those optional substituents mentioned hereinafter.

The term "heteroaliphatic chain" is intended to include the aliphatic chains just described but with each additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L³ where L³ is a linker atom or group. Each L³ atom or group may interrupt the aliphatic group, or may be positioned at its terminal carbon atom to connect the group to an adjoining atom or group. Particular examples include optionally substituted -L³CH₂-, -CH₂L³-, -L³CH(CH₃)-, -CH(CH₃)L³-, -CH₂L³CH₂-, -L³CH₂CH₂-, -L³CH₂CH(CH₃)-, -CH(CH₃)CH₂L³-, -CH₂CH₂L³-, -CH₂L³CH₂CH₂-, -CH₂L³CH₂CH₂L³-, -(CH₂)₂L³CH₂-, -(CH₂)₃L³CH₂-, -L³(CH₂)₂CH₂-, -L³CH₂CHCH-, -CHCHCH₂L³-, -(CH₂)₂L³CH₂CH₂-, -(CH₂)₃L³- and -L³CH₂L³CH₂CH₂- chains.

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When L³ is present in heteroaliphatic chains as a linker atom or group it may be any divalent linking atom or group. Particular examples include -O- or -S- atoms or -C(O)-, -C(S)-, -S(O)-, -S(O)₂-, -C(O)O-, -OC(O)-, -N(R⁸)- [where R⁸ is a hydrogen atom or a straight or branched C₁₋₆alkyl group], -N(R⁸)O-, -N(R⁸)N-, -CON(R⁸)-, -OC(O)N(R⁸)-, -CSN(R⁸)-, -N(R⁸)CO-, -N(R⁸)C(O)O-, -N(R⁸)CS-, -S(O)₂N(R⁸)-, -N(R⁸)S(O)₂-, -N(R⁸)CON(R⁸)-, -N(R⁸)CSN(R⁸), -N(R⁸)SO₂N(R⁸)-, -C(=NOR⁸)- or -C(R^{8a})=NO- [where R^{8a} is a straight or branched C₁₋₆alkyl group] groups. Where L³ contains two R⁸ groups these may be the same or different.

30

The term "cycloaliphatic group" includes optionally substituted non-aromatic cyclic or multicyclic, saturated or partially saturated C₃₋₁₀ ring systems, such as, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl,

adamantyl, norbornyl, norbornenyl, bicyclo[2.2.1]heptanyl or bicyclo[2.2.1]heptenyl. Particular examples include optionally substituted C₃₋₆ cycloalkyl ring systems such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. Optional substituents present on those groups include
 5 those substituents mentioned hereinafter.

The term "cycloalkyl-alkyl- group" refers to a C₁₋₆ alkyl group (as described herein) where a terminal hydrogen atom is replaced by a C₃₋₆ cycloalkyl ring (as described herein). Examples include -(CH₂)₁₋₆-cyclopropyl, -(CH₂)₁₋₆-
 10 cyclobutyl, -(CH₂)₁₋₆-cyclopentyl or -(CH₂)₁₋₆-cyclohexyl.

The term "heterocycloaliphatic group" refers to an optionally substituted 3 to 10 membered saturated or partially saturated monocyclic or multicyclic hydrocarbon ring system containing one, two, three or four L⁴ linker atoms or
 15 groups. Particular examples of suitable L⁴ atoms or groups include -O- or -S- atoms or -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, -S(O)₂-, -N(R⁸)- [where R⁸ is as defined above], -N(R⁸)N(R⁸), -N(R⁸)O-, -ON(R⁸)-, -CON(R⁸)-, -OC(O)N(R⁸)-, -CSN(R⁸)-, -N(R⁸)CO-, -N(R⁸)C(O)O-, -N(R⁸)CS-, -S(O)₂N(R⁸), -N(R⁸)S(O)₂-, -N(R⁸)CON(R⁸)-, -N(R⁸)CSN(R⁸)-, -N(R⁸)SO₂N(R⁸)- groups.
 20 Where the linker group contains two R⁸ substituents, these may be the same or different. Optional substituents present on the heterocycloaliphatic groups include those substituents mentioned hereinafter.

Particular examples of heterocycloaliphatic groups include optionally
 25 substituted cyclobutanonyl, cyclopentanonyl, cyclohexanonyl, azetidiny, tetrahydrofuranyl, tetrahydropyranyl, pyrrolinyl, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinonyl, oxazolidinyl, oxazolidinonyl, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, thiazolinyl, thiazolidinyl, pyranyl, e.g. 2- or 4-pyranyl,
 30 pyranonyl, piperidinyl, piperidinonyl, quinuclidinyl, 1,4-dioxanyl, morpholinyl, morpholinonyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, N-C₁₋₆ alkylpiperazinyl, N-C₁₋₆ alkylpyrrolidinyl, N-C₁₋₆ alkylpiperidinyl, N-C₁₋₆ alkylmorpholinyl, homopiperazinyl, dihydrofuran-2-onyl, tetrahydropyran-2-

onyl, isothiazolidinyl 1,1-dioxide, [1,2]thiazinanyl 1,1-dioxide, tetrahydrothiophenyl, tetrahydrothiopyranyl, pyrazolidin-3-onyl, tetrahydrothiopyranyl 1,1-dioxide, tetrahydrothiophenyl 1,1-dioxide, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 5 1,2,5-oxathiazinyl, isoxazinyl, e.g. *o*- or *p*-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5-oxadiazinyl groups.

Cycloaliphatic groups may be linked to the remainder of the compound of formula (1) by any available ring carbon atom. Heterocycloaliphatic groups 10 may be linked to the remainder of the compound of formula (1) by any available ring carbon or, where available, ring nitrogen atom.

The optional substituents which may be present on the aliphatic, cycloaliphatic or heterocycloaliphatic groups described above, include one, two, three or 15 more substituents, which each may be the same or different, selected from halogen atoms, or C₁₋₆alkyl, e.g. methyl, ethyl, propyl or *i*-propyl, C₁₋₆alkoxy, e.g. methoxy, ethoxy or propoxy, haloC₁₋₆alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, haloC₁₋₆alkoxy, e.g. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, C₁₋₆alkylthio, e.g. 20 methylthio, ethylthio or propylthio, or -(Alk⁵)_gR⁹ groups in which Alk⁵ is a straight or branched C₁₋₃alkylene chain, *g* is zero or the integer 1 and R⁹ is a -OH, -SH, -N(R¹⁰)₂ [where R¹⁰ is a hydrogen atom or an optionally substituted C₁₋₆alkyl group], -CN, -CO₂R¹⁰, -OC(O)R¹⁰, -NO₂, -C(O)N(R¹⁰)₂, -C(S)N(R¹⁰)₂, -C(O)R¹⁰, -C(S)R¹⁰, -N(R¹⁰)C(O)R¹⁰, -N(R¹⁰)C(S)(R¹⁰), -SO₂N(R¹⁰)₂, 25 -N(R¹⁰)SO₂R¹⁰, N(R¹⁰)C(O)N(R¹⁰)₂, N(R¹⁰)C(S)N(R¹⁰)₂, N(R¹⁰)SO₂N(R¹⁰)₂, -SO₂R¹⁰, -SO₃R¹⁰, -OCO₂R¹⁰, -OC(O)N(R¹⁰)₂ or an optionally substituted aromatic or heteroaromatic group. When two R¹⁰ atoms or groups are present in these substituents these may be the same or different or joined to form a heterocycloaliphatic ring which contains at least one N atom. This 30 includes, for example, azetidiny, pyrrolidinyl, piperidinyl, imidazolidinyl, thiazolidinyl, pyrazolidinyl, piperazinyl, N-C₁₋₆ alkylpiperazinyl, homopiperazinyl, morpholinyl, thiomorpholinyl, oxazolidinyl and the like. The aromatic and heteroaromatic groups which may be present in these

substituents may optionally be substituted by one, two or three of the R¹² groups described herein.

The optional substituents which may be present on aliphatic or heteroaliphatic chains, for example Alk¹, Alk², Alk³ or Alk⁴, include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or -OH, CN, -CO₂H, -CO₂R¹¹ [where R¹¹ is an optionally substituted C₁₋₆alkyl group] e.g. -CO₂CH₃ or -CO₂C(CH₃)₃; -CONHR¹¹, e.g. -CONHCH₃; -CON(R¹¹)₂, e.g. -CON(CH₃)₂; -COR¹¹, e.g. -COCH₃; C₁₋₆alkoxy, e.g. methoxy or ethoxy; haloC₁₋₆alkoxy, e.g. trifluoromethoxy or difluoromethoxy; -SH, -S(O)R¹¹, e.g. -S(O)CH₃; -S(O)₂R¹¹, e.g. -S(O)₂CH₃; C₁₋₆alkylthio e.g. methylthio or ethylthio; amino; -NHR¹¹, e.g. -NHCH₃ or -N(R¹¹)₂, e.g. -N(CH₃)₂ groups. Where two R¹¹ groups are present in any of the above substituents these may be the same or different.

When R¹⁰ or R¹¹ is present as a C₁₋₆alkyl group it may be a straight or branched C₁₋₆ alkyl group e.g. a C₁₋₃ alkyl group such as methyl, ethyl or *i*-propyl. Optional substituents which may be present on such groups include for example one, two or three substituents which may be the same or different selected from fluorine, chlorine, bromine or iodine atoms or hydroxy or C₁₋₆alkoxy e.g. methoxy or ethoxy groups.

The term "halogen atom" is intended to include fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" is intended to include the alkyl groups mentioned previously substituted by one, two or three of the halogen atoms as described above. Particular examples of such groups include -CF₃, -CCl₃, -CHF₂, -CHCl₂, -CH₂F, and -CH₂Cl groups.

The term "alkoxy" as used herein is intended to include straight or branched C₁₋₁₀alkoxy for example C₁₋₆alkoxy such as methoxy, ethoxy, *n*-propoxy, *i*-propoxy and *t*-butoxy. "Haloalkoxy" as used herein includes any of those

alkoxy groups substituted by one, two or three halogen atoms as described above. Particular examples include -OCF₃, -OCCl₃, -OCHF₂, -OCHCl₂, -OCH₂F and -OCH₂Cl groups.

- 5 As used herein the term "alkylthio" is intended to include straight or branched C₁₋₁₀alkylthio, e.g. C₁₋₆alkylthio such as methylthio or ethylthio groups.

When L¹ and L² are present in compounds of formula (1) as a linker atom or group they may be any such atom or group as hereinbefore described in
10 relation to L³ linker atoms and groups. When m in compounds of formula (1) is zero then L¹, when present, is a -C(O)-, -C(S)-, -S(O)₂-, -CON(R⁸)-, -CSN(R⁸)- or -S(O)₂N(R⁸)- group, where R⁸ is as herein defined.

The terms "aromatic group" and "aryl group" are intended to include for
15 example optionally substituted monocyclic ring C₆₋₁₂ aromatic groups, such as phenyl, or bicyclic fused ring C₆₋₁₂ aromatic groups, such as, 1- or 2-naphthyl groups.

The terms "heteroaromatic group" and "heteroaryl group" are intended to
20 include for example optionally substituted C₁₋₉ heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen atoms (or oxidised versions thereof). In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for
25 example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

30

Each of these aromatic or heteroaromatic groups may optionally be substituted by one, two, three or more R¹² atoms or groups as defined below.

Particular examples of monocyclic ring heteroaromatic groups of this type include pyrrolyl, furyl, thienyl, imidazolyl, N-C₁₋₆alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, tetrazolyl, triazinyl, pyridyl-N-oxide, 5 dihydropyrazolonyl or imidazolonyl.

Particular examples of bicyclic ring heteroaromatic groups of this type include benzofuryl, benzothieryl, benzotriazolyl, indolyl, indazolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, 10 benzopyranyl, quinazolyl, quinoxalyl, naphthyridyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]-pyridyl, quinolyl, isoquinolyl or phthalazyl.

The heteroaromatic groups may be attached to the remainder of the 15 compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

Optional substituents which may be present on the aromatic or heteroaromatic groups include one, two, three or more substituents, each selected from an 20 atom or group R¹² in which R¹² is the group -(Alk⁶)_e(R^{12a})_f in which Alk⁶ is a straight or branched C₁₋₆alkylene, C₂₋₆alkenylene or C₂₋₆alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or -S(O)_h- [where h is an integer 1 or 2] or -N(R¹⁴)- groups; R^{12a} is a halogen atom, or an amino (-NH₂), -NHR¹³ [where R¹³ is the group -(Alk⁶)_e(R^{13a})_f in which R^{13a} is an 25 optionally substituted heterocycloaliphatic, cycloaliphatic, aryl, heteroaryl group and Alk⁶, e and f are as defined hereinafter], -N(R¹³)₂, nitro, cyano, amidino, formyl, hydroxy (OH), carboxyl (-CO₂H), -CO₂R¹³, thiol (-SH), -SR¹³, -OR¹³, -COR¹³, -CSR¹³, -SO₃H, -SOR¹³, -SO₂R¹³, -SO₃R¹³, -SO₂NH₂, -SO₂NHR¹³, SO₂N(R¹³)₂, -CONH₂, -CSNH₂, -CONHR¹³, -CSNHR¹³, 30 -CON(R¹³)₂, -CSN(R¹³)₂, -N(R¹⁴)SO₂R¹³, [where R¹⁴ is a hydrogen atom or a straight or branched C₁₋₆ alkyl group] -N(SO₂R¹³)₂, -N(R¹⁴)SO₂NH₂, -N(R¹⁴)SO₂NHR¹³, -N(R¹³)SO₂N(R¹⁴)₂, -N(R¹⁴)COR¹³, -N(R¹⁴)CONH₂, -N(R¹⁴)CONHR¹³, -N(R¹⁴)CON(R¹³)₂, -N(R¹⁴)CSNH₂, -N(R¹⁴)CSNHR¹³,

-N(R¹⁴)CSN(R¹³)₂, -N(R¹⁴)CSR¹³, -N(R¹⁴)C(O)OR¹³, -SO₂NHet¹ [where -NHet¹ is an optionally substituted C₃₋₇ heterocycloaliphatic group optionally containing one or more other -O- or -S- atoms or -N(R¹⁴)-, -C(O)- or -C(S)- groups], -CONHet¹, -CSNHet¹, -N(R¹⁴)SO₂NHet¹, -N(R¹⁴)CONHet¹,
 5 -N(R¹⁴)CSNHet¹, -SO₂N(R¹⁴)Het² [where Het² is an optionally substituted monocyclic C₃₋₇ cycloaliphatic group optionally containing one or more -O- or -S- atoms or -N(R¹⁴)-, -C(O)- or -C(S)- groups], -CON(R¹⁴)Het², -CSN(R¹⁴)Het², -N(R¹⁴)CON(R¹⁴)Het², -N(R¹⁴)CSN(R¹⁴)Het², optionally substituted aryl, heteroaryl, cycloaliphatic or heterocycloaliphatic group; e is
 10 zero or the integer 1 and f is zero or an integer 1, 2 or 3; provided that when e is zero then f is the integer 1. It will be further appreciated that when two R¹³ or R¹⁴ groups are present in one of the above substituents, the R¹³ or R¹⁴ groups may be the same or different.

15 When in the group -(Alk⁶)_e(R^{12a})_f or -(Alk⁶)_e(R^{13a})_f f is an integer 1, 2 or 3 and e is the integer 1, it is to be understood that the substituent or substituents R^{12a} or R^{13a} may be present on any suitable carbon atom in -Alk⁶. Where more than one R^{12a} or R^{13a} substituent is present these may be the same or different and may be present on the same or different atom in -Alk⁶. It will be
 20 understood that, when f is zero and no substituent R^{12a} or R^{13a} is present the chain represented by Alk⁶ contains a terminal hydrogen atom and becomes a corresponding group.

When -NHet¹ or -Het² forms part of a substituent R^{12a} each may be for
 25 example an optionally substituted 2- or 3-pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperazinyl, imidazolinyl, imidazolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, oxazolidinyl or thiazolidinyl group. Additionally Het² may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -NHet¹ or
 30 -Het² include those substituents described above in relation to aromatic groups.

Particularly useful atoms or groups represented by R^{12} include fluorine, chlorine, bromine or iodine, C_{1-6} alkyl, e.g. methyl, ethyl, *i*-propyl, halo C_{1-6} alkyl, e.g. $-CF_3$, halo C_{1-6} alkoxy, e.g. $-OCF_3$, $-OCF_2H$, $-(Alk^6)_eNH_2$, $-(Alk^6)_eNHR^{13}$, $-(Alk^6)_eN(R^{13})_2$, $-(Alk^6)_eCN$, $-(Alk^6)_eCO_2H$, $-(Alk^6)_eCO_2R^{13}$, $-(Alk^6)_eSR^{13}$, $-(Alk^6)_eOR^{13}$, $-(Alk^6)_eCOR^{13}$, $-(Alk^6)_eCSR^{13}$, $-(Alk^6)_eSO_2R^{13}$, $-(Alk^6)_eSO_2NH_2$, $-(Alk^6)_eSO_2NHR^{13}$, $-(Alk^6)_eSO_2N(R^{13})_2$, $-(Alk^6)_eCONH_2$, $-(Alk^6)_eCSNH_2$, $-(Alk^6)_eCONHR^{13}$, $-(Alk^6)_eCSNHR^{13}$, $-(Alk^6)_eCON(R^{13})_2$, $-(Alk^6)_eCSN(R^{13})_2$, $-(Alk^6)_eN(R^{14})SO_2R^{13}$, $-(Alk^6)_eN(R^{14})COR^{13}$, $-(Alk^6)_eN(R^{14})CONH_2$, $-(Alk^6)_eN(R^{14})CONHR^{13}$, $-(Alk^6)_eN(R^{14})CSR^{13}$, $-(Alk^6)_eN(R^{14})C(O)OR^{13}$, $-(Alk^6)_eSO_2NHet^1$, $-(Alk^6)_eCONHet^1$, $-(Alk^6)_eCSNHet^1$, optionally substituted $-(Alk^6)_e$ phenyl, $-(Alk^6)_e$ monocyclic heteroaryl, $-(Alk^6)_e$ monocyclic heterocycloaliphatic or $(Alk^6)_e$ cycloaliphatic.

Particularly useful R^{13} groups include a C_{1-6} alkyl group (where *f* is zero), or an optionally substituted $-(Alk^6)_e$ phenyl, $-(Alk^6)_e$ monocyclic heteroaryl, $-(Alk^6)_e$ monocyclic heterocycloaliphatic or $-(Alk^6)_e$ cycloaliphatic.

When Alk^6 is present in the above R^{12} and R^{13} groups it may be for example a methylene, ethylene, *n*-propylene, *i*-propylene, *n*-butylene, *i*-butylene, *s*-butylene, *t*-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three $-O-$ or $-S-$, atoms or $-S(O)-$, $-S(O)_2-$ or $-N(R^{14})-$ groups. Particular examples of Alk^6 include C_{1-4} alkylene chains e.g. methylene, ethylene, propylene, *i*-propylene or *t*-butylene.

R^{13} is most especially a C_{1-3} alkyl group. R^{14} is particularly hydrogen or methyl.

When, in R^{12} or R^{13} , *f* is zero Alk^6 is in particular a C_{1-4} alkyl group as defined herein. When *f* is the integer 1, 2 or 3 Alk^6 is in particular a C_{1-3} alkylene chain.

Particular examples of aryl, heteroaryl, heterocycloaliphatic or cycloaliphatic groups which may be present in the group $-R^{12a}$ or $-R^{13a}$ include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, azetidiny,

- pyrrolidinyl, pyrrolidinonyl, piperidinyl, imidazolidinyl, thiazolidinyl, piperazinyl, N-C₁₋₆ alkylpiperazinyl, especially N-methylpiperazinyl, N-C₁₋₆ alkylpyrrolidinyl, especially N-methylpyrrolidinyl, N-C₁₋₆ alkylpiperidinyl, especially N-methylpiperidinyl, homopiperazinyl, morpholinyl, thiomorpholinyl, oxazolidinyl, 5 tetrahydrofuranyl, tetrahydropyranyl, phenyl, pyrrolyl, furyl, thienyl, imidazolyl, N-C₁₋₆alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, tetrazolyl, triazinyl, pyridyl-N-oxide, dihydropyrazolonyl or imidazolonyl.
- 10 Optional substituents which may in particular be present on the aryl, heteroaryl, heterocycloaliphatic or cycloaliphatic groups represented by -R^{12a} or -R^{13a} include one, two, three or more atoms or groups selected from fluorine, chlorine, C₁₋₃ alkoxy, especially -OCH₃, OCF₃, OCF₂H, CF₃, C₁₋₃ alkylthio, straight or branched C₁₋₃ alkyl, -CN, NHCH₃, N(CH₃)₂, CONH₂, 15 CONHCH₃, CON(CH₃)₂, CO₂CH₃, CO₂CH₂CH₃, -CO₂C(CH₃)₃, or -COCH₃, -SO₂CH₃, -NHCOCH₃, -N(CH₃)COCH₃ or CO₂H.

Where desired, two adjacent R¹² substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C₁₋₆alkylenedioxy group such as 20 methylenedioxy or ethylenedioxy or a C₃₋₆ cycloalkyl or 3-10 membered monocyclic heterocycloaliphatic group as defined herein.

It will be appreciated that where two or more R¹² substituents are present, these need not necessarily be the same atoms and/or groups. In general, the 25 substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include 30 pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulfonates, e.g. methanesulfonates, ethanesulfonates, or isothionates, arylsulfonates, e.g. *p*-toluenesulfonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

Particular examples of the group R^4 , in compounds of formula (1), include $-Alk^3-L^2-Alk^4-R^7$, $-Alk^3-L^2-R^7$, $-Alk^3-R^7$, $-L^2-Alk^4-R^7$, $-L^2-R^7$ or $-R^7$ wherein Alk^3 , L^2 , Alk^4 and R^7 are as herein defined.

Alk^3 and Alk^4 , when present in compounds of formula (1), may be the same or different and is each preferably an optionally substituted aliphatic chain, in particular a C_{1-6} alkylene chain, most especially a C_{1-3} alkylene chain. In one particular embodiment of the invention Alk^3 and/or Alk^4 is each a $-CH_2-$, $-(CH_2)_2-$ or $-(CH_2)_3-$ chain, most especially a $-CH_2-$ or $-(CH_2)_2-$ chain.

One particular group of compounds of the invention has the formula (1) wherein Alk^3 is an optionally substituted C_{2-6} alkenylene or C_{2-6} alkynylene chain, especially an ethenylene or ethynylene chain. In one particular group of compounds of the invention Alk^3 is an ethenylene chain.

In one particular embodiment of the invention p is zero.

In another particular embodiment of the invention p is the integer 1.

q in one particular aspect of the invention is zero.

Particular examples of L^2 , when present in compounds of formula (1), include
5 -O- or -S- atoms or -C(O)-, -C(S)-, -S(O)-, -S(O)₂-, -C(O)O-, -OC(O)-, -N(R⁸)-
[where R⁸ is as defined hereinbefore], -CON(R⁸)-, -CSN(R⁸)-, -N(R⁸)CO-,
-N(R⁸)CS-, -S(O)₂N(R⁸)- or -N(R⁸)S(O)₂- groups. More particular examples of
 L^2 include -O- or -S- atoms or -CO-, -C(O)O-, -CON(R⁸)- or -N(R⁸)CO-
10 groups. R⁸ is especially a hydrogen atom or a C₁₋₃ alkyl group, particularly
methyl.

L^2 in one particular group of compounds of the invention is a covalent bond.

R⁷ in one particular group of compounds of the invention is a hydrogen atom.

15

In another particular group of compounds of the invention R⁷ is an optionally
substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic
group especially an optionally substituted C₃₋₆ cycloalkyl, 3-10 membered,
especially 3-7 membered, saturated monocyclic heterocycloalkyl, phenyl or
20 heteroaromatic group. Particular examples include optionally substituted
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, azetidiny, pyrrolidiny,
pyrrolidinonyl, piperidiny, imidazolidiny, thiazolidiny, piperaziny, N-C₁₋₆
alkylpiperaziny, especially N-methylpiperaziny, N-C₁₋₆ alkylpyrrolidiny,
especially N-methylpyrrolidiny, N-C₁₋₆ alkylpiperidiny, especially N-
25 methylpiperidiny, homopiperaziny, morpholiny, thiomorpholiny, oxazolidiny,
tetrahydrofurany, tetrahydropyrany, phenyl, pyrroly, furyl, thienyl, imidazolyl,
N-C₁₋₆alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl,
triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidiny, pyridaziny, pyraziny,
tetrazolyl, triaziny, pyridyl-N-oxide, dihydropyrazolonyl, imidazolonyl,
30 benzofuryl, benzothienyl, indolyl, benzimidazolyl, benzothiazolyl,
benzoxazolyl, benzisoxazolyl, quinoliny or isoquinoliny. More particular
examples include optionally substituted cyclohexyl, piperidiny,
tetrahydrofurany, phenyl, furyl, thienyl, imidazolyl, N-C₁₋₆alkylimidazolyl,

pyridyl, pyridyl-N-oxide, benzofuryl, indolyl or quinoliny. Particular values of R^7 include cyclohexyl, piperidin-1-yl, tetrahydrofuran-2-yl, 2,6-dichlorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 2-acetylamino-phenyl, 4-acetylamino-phenyl, [2,3]methylenedioxyphenyl, fur-2-yl, 5-phenylfur-2-yl, 5 thien-2-yl, 5-methoxycarbonylthien-2-yl, 4-methoxycarbonylthien-2-yl, 1-methylimidazol-2-yl, imidazol-2-yl, imidazol-4-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyrid-2-yl-N-oxide, pyrid-3-yl-N-oxide, pyrid-4-yl-N-oxide, 2-chloropyrid-5-yl, benzofur-2-yl, 7-methoxybenzofur-2-yl, 5-chlorobenzofur-2-yl, 1-methylindol-3-yl, quinolin-2-yl.

10

One class of compounds of the invention has the formula (1) wherein R^4 is the chain $-Alk^3-L^2-R^7$ in which Alk^3 is an optionally substituted aliphatic chain, L^2 is a covalent bond and R^7 is a hydrogen atom. Alk^3 in compounds of this type is preferably a straight or branched C_{1-6} alkylene chain as herein defined, especially $-CH_2-$, $-CH_2CH_2-$, $-(CH_2)_2CH_2-$, $-(CH_2)_3CH_2-$ or $-CH_2C(CH_3)_2-$. Optional substituents present on these chains include those as herein defined for Alk^3 substituents, especially $-CN$, $-CO_2H$, $-CO_2R^{11}$ [where R^{11} is as herein defined] $-CONHR^{11}$, $-CON(R^{11})_2$, $-COR^{11}$, C_{1-6} alkoxy, particularly methoxy or ethoxy; halo C_{1-6} alkoxy, particularly trifluoromethoxy or difluoromethoxy; $-S(O)R^{11}$, $-S(O)_2R^{11}$, amino, $-NHR^{11}$ or $-N(R^{11})_2$ groups. R^{11} is in particular a C_{1-3} alkyl group. In one particular group of compounds of this type Alk^1 is a $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$ chain substituted with a $-NH(CH_3)$, $-N(CH_3)_2$, $-CN$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2C(CH_3)_3$, $-CONH_2$, $-CONHCH_3$ or $-CON(CH_3)_2$ group. In another particular group of compounds of this type Alk^3 is a $-CH_2-$ or $-(CH_2)_2-$ chain substituted with a $-OCOCH_3$, $-OH$, $-SCH_3$, $-OCH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_3$, $-CONHCH_3$, $-CN$ or $-NHCO_2^tBu$ group or a $-CHCH-$ chain substituted with a $-CO_2CH_3$, $-CO_2H$ or $-CN$ group.

Another class of compounds of the invention has the formula (1) wherein R^4 is the chain $-Alk^3-L^2-R^7$ in which Alk^3 is an optionally substituted aliphatic chain, L^2 is a covalent bond or a linker atom or group and R^7 is an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic

group especially an optionally substituted heterocycloaliphatic, aromatic or heteroaromatic group.

In one particular embodiment of compounds of this type Alk^3 is an optionally substituted C_{1-6} alkylene chain, especially $-\text{CH}_2-$, CH_2CH_2- or $-\text{CH}_2\text{CH}_2\text{CH}_2-$. R^7 in compounds of this type is especially an optionally substituted 3-10 membered saturated monocyclic heterocycloaliphatic, phenyl or monocyclic or bicyclic heteroaromatic group. Particular R^7 examples include optionally substituted azetidiny, pyrrolidiny, pyrrolidinonyl, piperidiny, imidazolidiny, thiazolidiny, piperaziny, $N\text{-C}_{1-6}$ alkylpiperaziny, especially N -methylpiperaziny, $N\text{-C}_{1-6}$ alkylpyrrolidiny, especially N -methylpyrrolidiny, $N\text{-C}_{1-6}$ alkylpiperidiny, especially N -methylpiperidiny, homopiperaziny, morpholiny, thiomorpholiny, oxazolidiny, tetrahydrofurany, tetrahydropyrany, phenyl, pyrroly, furyl, thienyl, imidazolyl, $N\text{-C}_{1-6}$ alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidiny, pyridaziny, pyraziny, tetrazolyl, triaziny, pyridyl- N -oxide, dihydropyrazolonyl or imidazolonyl. In one group of compounds R^7 is a morpholiny, thiomorpholiny, pyrrolidiny, N -methylpyrrolidiny, piperidiny, N -methylpiperidiny, piperaziny, N -methylpiperaziny, imidazolyl, phenyl, pyridyl, pyrimidiny or pyrazolyl group. One particular group of compounds of this type has the formula (1) wherein Alk^3 is a $-\text{CH}_2-$ or $-(\text{CH}_2)_2-$ chain and L^2 is a covalent bond or a $-\text{O}-$, $-\text{S}-$ or $-\text{NHCO}-$ linker atom or group. R^7 is in particular a phenyl, 4-chlorophenyl, 2-acetylaminophenyl, tetrahydrofuran-2-yl or piperidin-1-yl group.

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In another particular embodiment of compounds of this type Alk^3 is an optionally substituted C_{2-6} alkenylene chain, especially $-\text{CHCH}-$ or C_{2-6} alkynylene chain, especially $-\text{CC}-$. L^2 in one embodiment is preferably a covalent bond. L^2 in another embodiment is a $-\text{CO}-$ or $-\text{CON}(\text{CH}_3)-$ group. R^7 is especially an optionally substituted 3-10 membered saturated monocyclic heterocycloaliphatic, phenyl or heteroaromatic group. Particular R^7 groups include optionally substituted furyl, thienyl or phenyl. Other particular

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examples include optionally substituted piperidiny, pyridyl, imidazolyl, indolyl, benzofuryl or quinoliny.

In another class of compounds of the invention R^4 is the chain $-L^2-(Alk^4)_q-R^7$ in which L^2 is a linker atom or group, Alk^4 is an optionally substituted aliphatic or heteroaliphatic chain, q is zero or the integer 1 and R^7 is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group. Alk^4 in compounds of this type is preferably an optionally substituted straight or branched C_{1-6} alkylene chain as defined herein or a $-CH_2L^3-$ [where L^3 is as defined herein], $-CH(CH_3)L^3-$, $-CH_2L^3CH_2-$, $-CH(CH_3)CH_2L^3-$, $-CH_2CH_2L^3-$, $-CH_2L^3CH_2CH_2-$, $-(CH_2)_2L^3CH_2-$, $-(CH_2)_3L^3CH_2-$ or $-(CH_2)_3L^3-$ chain and R^7 is preferably a hydrogen atom or an optionally substituted C_{3-6} cycloalkyl, 3-10 membered saturated monocyclic heterocycloaliphatic, phenyl or monocyclic heteroaromatic group. In compounds of this class L^2 is in particular $-O-$, $-N(R^8)-$, $-C(O)-$, $-C(S)-$, $-S(O)_2-$, $-C(O)O-$, $-OC(O)-$, $-CON(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$ or $-N(R^8)CS-$, [where R^8 is especially a hydrogen atom or a methyl group] and Alk^4 is most preferably an optionally substituted C_{1-3} alkylene chain, especially $-CH_2-$, CH_2CH_2- or $-CH_2CH_2CH_2-$. Optional substituents which may in particular be present on Alk^4 include $-CN$, $-CO_2H$, $-CO_2R^{11}$ [where R^{11} is as herein defined] $-CONHR^{11}$, $-CON(R^{11})_2$, $-COR^{11}$, C_{1-6} alkoxy, particularly methoxy or ethoxy; halo C_{1-6} alkoxy, particularly trifluoromethoxy or difluoromethoxy; $-S(O)R^{11}$, $-S(O)_2R^{11}$, amino, $-NHR^{11}$ or $-N(R^{11})_2$ groups. R^{11} is in particular a C_{1-3} alkyl group. In one particular group of compounds of this type L^2 is a linker atom or group, most especially a $-CONH-$ group, q is zero and R^7 is an optionally substituted C_{3-6} cycloalkyl, 3-7 membered saturated monocyclic heterocycloalkyl, phenyl or heteroaromatic group, most especially a phenyl group.

Another class of compounds has the formula (1) wherein R^4 is the group R^7 . In compounds of this class R^7 is in particular a halogen atom a $-CN$ group or an optionally substituted C_{3-6} cycloalkyl, 3-10 membered saturated monocyclic heterocycloaliphatic, phenyl or monocyclic or bicyclic heteroaromatic group. In one particular embodiment of compounds of this type R^4 is an optionally substituted phenyl or heteroaromatic group, typically phenyl, fur-2-yl,

benzofur-2-yl, 7-methoxybenzofur-2-yl, 5-chlorobenzofur-2-yl and quinolin-2-yl.

- In another class of compounds of the invention R^4 is the chain $-Alk^3-L^2-Alk^4-R^7$ in which Alk^3 is an optionally substituted aliphatic chain, L^2 is a linker atom or group, Alk^4 is an optionally substituted aliphatic or heteroaliphatic chain and R^7 is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group.
- One particular group of compounds according to the invention has the formula (1) wherein R^4 is a C_{1-6} alkyl group, especially a C_{1-3} alkyl group, most especially a methyl group. R^5 in compounds of this type is in particular a hydrogen atom or a C_{1-6} alkyl group.
- R^5 in compounds of formula (1) is in particular a hydrogen atom or a C_{1-3} alkyl group, especially methyl. R^5 is also in particular a $-CF_3$ group.

When R^4 , in one particular group of compounds of formula (1), is a hydrogen atom then R^5 is other than a hydrogen atom.

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In one particular group of compounds of formula (1) X is an O atom.

- Examples of cycloaliphatic groups which may represent R^1 include C_{3-6} cycloalkyl groups, such as those described previously. Examples of cycloalkyl-alkyl- groups which may represent R^1 include C_{1-3} alkyl groups (as described herein) where a terminal hydrogen atom is replaced by a C_{3-6} cycloalkyl ring (as described herein), for example, cyclopropylCH₂-.

- R^1 , in compounds of formula (1), is in particular a C_{1-6} alkyl group. Especially preferred is when R^1 is a C_{1-3} alkyl group. Most especially preferred is when R^1 is a methyl group.

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In another group of compounds of formula (1) R^1 is a haloalkyl group, especially a CHF₂ or CH₂F group.

A particularly preferred group of compounds of the invention has the formula (1) wherein R^2 is an optionally substituted monocyclic heteroaromatic group, especially a five-membered heteroaromatic group containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Particular preferred heteroaromatic groups which may represent R^2 include optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, N- C_{1-6} alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl or pyrazolyl. Especially preferred is when R^2 is an oxazolyl group. Most especially preferred is where R^2 is an oxazol-5-yl group.

Particular examples of the group R^3 , in compounds of formula (1), include $-Alk^1-L^1-Alk^2-R^6$, $-Alk^1-L^1-R^6$, $-Alk^1-R^6$, $-L^1-Alk^2-R^6$, $-L^1-R^6$ or $-R^6$ wherein Alk^1 , L^1 , Alk^2 and R^6 are as herein defined. One particular group of compounds of the invention has the formula (1) wherein R^3 is the group $-Alk^1-L^1-R^6$.

Alk^1 and Alk^2 , when present in compounds of formula (1), may be the same or different and is each preferably an optionally substituted aliphatic chain, in particular a C_{1-6} alkylene chain, especially an optionally substituted $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$ or $-CH_2CH(CH_3)-$ chain, most especially a C_{1-3} alkylene chain such as $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ chain.

In one particular embodiment of the invention m is zero.

In another particular embodiment of the invention m is the integer 1.

n in one particular aspect of the invention is zero.

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Particular examples of L^1 , when present in compounds of formula (1), include $-O-$ or $-S-$ atoms or $-C(O)-$, $-C(S)-$, $-S(O)-$, $-S(O)_2-$, $-C(O)O-$, $-OC(O)-$, $-N(R^8)-$ [where R^8 is as defined hereinbefore], $-CON(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-$

$N(R^8)CS-$, $-S(O)_2N(R^8)-$ or $-N(R^8)S(O)_2-$ groups. R^8 is especially a hydrogen atom or a C_{1-3} alkyl group, particularly methyl.

L^1 in one particular group of compounds of the invention is a covalent bond.

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In one particular group of compounds of the invention R^6 is a hydrogen atom.

In another particular group of compounds of the invention R^6 is an optionally substituted C_{3-6} cycloalkyl, 3-7 membered saturated monocyclic
10 heterocycloalkyl, phenyl or heteroaromatic group as described herein for R^7 .
Typical examples of R^6 include morpholin-1-yl, pyrid-4yl and imidazol-1-yl.

One class of compounds of the invention has the formula (1) wherein R^3 is the chain $-Alk^1-L^1-R^6$ in which Alk^1 is an optionally substituted aliphatic chain, L^1 is
15 a covalent bond and R^6 is a hydrogen atom. In one particular group of compounds of this class R^3 is especially a straight or branched C_{1-6} alkyl group, particularly $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_2CH_3$ or $-C(CH_3)_3$. In this group of compounds R^3 is preferably a $-CH_3$ group. In another particular group of compounds of this class Alk^1 is a substituted aliphatic chain, L^1 is a
20 covalent bond and R^6 is a hydrogen atom. Alk^1 in compounds of this type is preferably a straight or branched C_{1-6} alkylene chain as herein defined, especially $-CH_2-$, $-CH_2CH_2-$, $-(CH_2)_2CH_2-$, $-(CH_2)_3CH_2-$ or $-CH_2C(CH_3)_2-$. Substituents present on these chains include those as herein defined for Alk^1 substituents, especially $-CN$, $-CO_2H$, $-CO_2R^{11}$ [where R^{11} is as herein defined]
25 $-CONHR^{11}$, $-CON(R^{11})_2$, $-COR^{11}$, C_{1-6} alkoxy, particularly methoxy or ethoxy; halo C_{1-6} alkoxy, particularly trifluoromethoxy or difluoromethoxy; $-S(O)R^{11}$, $-S(O)_2R^{11}$, amino, $-NHR^{11}$ or $-N(R^{11})_2$ groups. R^{11} is in particular a C_{1-3} alkyl group. In one particular group of compounds of this type Alk^1 is a $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$ chain substituted with a
30 $-NH(CH_3)$, $-N(CH_3)_2$, $-CN$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2C(CH_3)_3$, $-CONH_2$, $-CONHCH_3$ or $-CON(CH_3)_2$ group.

Another class of compounds of the invention has the formula (1) wherein R^3 is the chain $-Alk^1-L^1-R^6$ in which Alk^1 is an optionally substituted aliphatic chain, L^1 is a covalent bond or a linker atom or group and R^6 is an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group especially an optionally substituted heterocycloaliphatic, aromatic or heteroaromatic group. Alk^1 in compounds of this type is in particular an optionally substituted C_{1-6} alkylene chain, especially $-CH_2-$, CH_2CH_2- or $-CH_2CH_2CH_2-$. R^6 in compounds of this type is especially an optionally substituted 3-10 membered saturated monocyclic heterocycloaliphatic, phenyl or monocyclic heteroaromatic group. Particular R^6 examples include optionally substituted azetidiny, pyrrolidiny, pyrrolidinonyl, piperidiny, imidazolidiny, thiazolidiny, piperaziny, N- C_{1-6} alkylpiperaziny, especially N-methylpiperaziny, N- C_{1-6} alkylpyrrolidiny, especially N-methylpyrrolidiny, N- C_{1-6} alkylpiperidiny, especially N-methylpiperidiny, homopiperaziny, morpholiny, thiomorpholiny, oxazolidiny, tetrahydrofurany, tetrahydropyrany, phenyl, pyrroly, furyl, thienyl, imidazolyl, N- C_{1-6} alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidiny, pyridaziny, pyraziny, tetrazolyl, triaziny, pyridyl-N-oxide, dihydropyrazolonyl or imidazolonyl. In one group of compounds R^6 is a morpholiny, thiomorpholiny, pyrrolidiny, N-methylpyrrolidiny, piperidiny, N-methylpiperidiny, piperaziny, N-methylpiperaziny, imidazolyl, pyridyl, pyrimidiny or pyrazolyl group. One particular group of compounds of this class are those wherein L^1 is a covalent bond. In one particular embodiment of compounds of this type R^3 is a $-(CH_2)_2$ morpholin-1-yl, $-(CH_2)_2$ pyrid-4-yl and $-(CH_2)_2$ imidazol-1-yl group.

R^3 in another class of compounds of formula (1) is the chain $-L^1-R^6$ in which L^1 is a linker group and R^6 is an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group. L^1 in compounds of this type is especially a $-C(O)-$, $-C(S)-$ or $-S(O)_2$ group. One preferred group of compounds of this type is where R^6 is an optionally substituted phenyl or monocyclic heteroaromatic group. In compounds of this type R^6 is in particular

an optionally substituted phenyl, pyridyl, pyrimidinyl, pyridazinyl or pyrazinyl group.

In another class of compounds of the invention R^3 is the chain $-Alk^1-L^1-Alk^2-R^6$ in which Alk^1 is an optionally substituted aliphatic chain, L^1 is a linker atom or group, Alk^2 is an optionally substituted aliphatic or heteroaliphatic chain and R^6 is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group. Alk^1 in compounds of this type is preferably an optionally substituted straight or branched C_{1-6} alkylene chain such as herein defined, especially optionally substituted $-CH_2-$, $-CH_2CH_2-$, $-(CH_2)_2CH_2-$, $-(CH_2)_3CH_2-$ or $-CH_2C(CH_3)_2-$; Alk^2 is preferably an optionally substituted straight or branched C_{1-6} alkylene chain as defined herein or a $-CH_2L^3-$ [where L^3 is as defined herein], $-CH(CH_3)L^3-$, $-CH_2L^3CH_2-$, $-CH(CH_3)CH_2L^3-$, $-CH_2CH_2L^3-$, $-CH_2L^3CH_2CH_2-$, $-(CH_2)_2L^3CH_2-$, $-(CH_2)_3L^3CH_2-$ or $-(CH_2)_3L^3-$ chain and R^6 is preferably a hydrogen atom or an optionally substituted C_{3-6} cycloalkyl, 3-10 membered saturated monocyclic heterocycloaliphatic, phenyl or monocyclic heteroaromatic group. In compounds of this class Alk^1 is most especially a C_{1-3} alkylene chain, particularly $-CH_2-$, CH_2CH_2- or $-CH_2CH_2CH_2-$; L^1 is in particular $-O-$, $-N(R^8)-$, $-CON(R^8)-$ or $-N(R^8)CO-$ [where R^8 is especially a hydrogen atom or a methyl group] and Alk^2 is most preferably an optionally substituted C_{1-3} alkylene chain, especially $-CH_2-$, CH_2CH_2- or $-CH_2CH_2CH_2-$. Optional substituents which may in particular be present on Alk^2 include $-CN$, $-CO_2H$, $-CO_2R^{11}$ [where R^{11} is as herein defined] $-CONHR^{11}$, $-CON(R^{11})_2$, $-COR^{11}$, C_{1-6} alkoxy, particularly methoxy or ethoxy; halo C_{1-6} alkoxy, particularly trifluoromethoxy or difluoromethoxy; $-S(O)R^{11}$, $-S(O)_2R^{11}$, amino, $-NHR^{11}$ or $-N(R^{11})_2$, groups. R^{11} is in particular a C_{1-3} alkyl group.

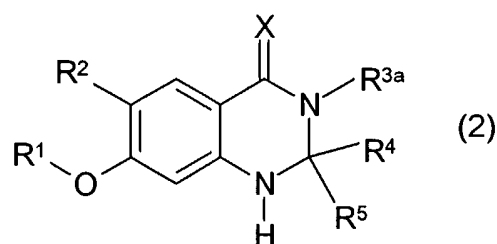
A further class of compounds of the invention has the formula (1) wherein R^3 is the group R^6 . In compounds of this class R^6 is in particular an optionally substituted C_{3-6} cycloalkyl, 3-10 membered saturated monocyclic heterocycloaliphatic, phenyl or monocyclic heteroaromatic group.

In one particular embodiment R^3 is a hydrogen atom or a C_{1-6} alkyl group, especially a C_{1-3} alkyl group, most especially a methyl group.

One group of cycloaliphatic or heterocycloaliphatic substituents, which may be present on the groups R^6 or R^7 , are one, two, three or more groups selected from C_{1-3} alkoxy, OCF_3 , OCF_2H , CF_3 , C_{1-3} alkylthio, optionally substituted straight or branched C_{1-3} alkyl (wherein the optional alkyl substituent is in particular an optionally substituted phenyl or monocyclic heteroaromatic group), $-CN$, $NHCH_3$, $N(CH_3)_2$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, CO_2CH_3 , $CO_2CH_2CH_3$, $-CO_2C(CH_3)_3$, or $-COCH_3$, $-NHCOCH_3$, $-N(CH_3)COCH_3$ or CO_2H .

One group of aromatic or heteroaromatic substituents, which may be present on the groups R^6 or R^7 , are one, two, three or more atoms or groups selected from fluorine, chlorine, straight or branched C_{1-6} alkyl, optionally substituted morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, methoxy, $-OCF_3$, $-OCF_2H$, $-CF_3$, $-CN$, $-NHCH_3$, $-N(CH_3)_2$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2C(CH_3)_3$, or $-COCH_3$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, $-SCH_3$, $-SO_2CH_3$ or CO_2H . More particular examples include fluorine, chlorine, methyl, methoxy, $-CO_2CH_3$ and $-NHCOCH_3$.

One particularly preferred group of compounds of the invention has the formula (2):

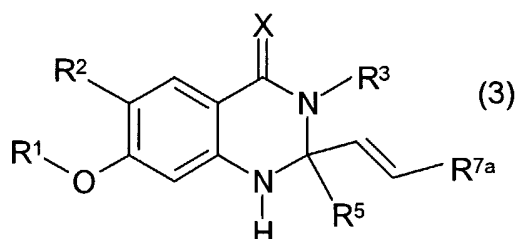


wherein R^1 , R^2 , R^4 , R^5 and X are as defined and further defined herein;
 R^{3a} is a hydrogen atom or a C_{1-6} alkyl group;
 and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

R^{3a} in compounds of this type is in particular a hydrogen atom or a C_{1-3} alkyl group, especially a methyl or ethyl group, most especially a methyl group.

One particular group of compounds of the invention has the formulae (1) or (2)
 5 wherein R^5 is a hydrogen atom or C_{1-6} alkyl group, especially C_{1-3} alkyl, most especially methyl and R^4 is the group $-(Alk^3)_p L^2 (Alk^4)_q R^7$.

Another particularly preferred group of compounds of the invention has the formula (3):



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wherein R^1 , R^2 , R^3 , R^5 and X are as defined herein;

R^{7a} is an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group as defined herein for R^7 ;

and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

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Particular examples of the group R^{7a} present in compounds of formula (3) include optionally substituted cyclohexyl, phenyl, furyl, thienyl, pyridyl, pyridyl-N-oxide, imidazolyl, benzofuryl and quinolinyl. Typical values for R^{7a} include cyclohexyl, phenyl, 2,6-dichlorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl,
 20 4-acetylamino-phenyl, 5-phenylfur-2-yl, [2,3]methylenedioxyphenyl, fur-2-yl, thien-2-yl, 5-methoxycarbonylthien-2-yl, 4-methoxycarbonylthien-2-yl, imidazol-2-yl, imidazol-4-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyrid-2-yl-N-oxide, pyrid-3-yl-N-oxide, pyrid-4-yl-N-oxide, 2-chloropyrid-5-yl, benzofur-2-yl, 1-methylindol-3-yl and quinolin-2-yl.

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Particularly useful compounds of the invention include:

2-(2-furan-2-yl-vinyl)-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one;

7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2-(2-thiophen-2-yl-vinyl)-2,3-dihydro-

30 1H-quinazolin-4-one;

7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2-styryl-2,3-dihydro-1*H*-quinazolin-4-one;

7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2-phenylethynyl-2,3-dihydro-1*H*-quinazolin-4-one;

- 5 7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2-phenethyl-2,3-dihydro-1*H*-quinazolin-4-one;

and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

10 Compounds of formula (1) are potent inhibitors of IMPDH. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

Thus the compounds of the invention may be used in the treatment of IMPDH-associated disorders. The invention extends to such a use and in general to
15 the use of the compounds of formula (1) for the manufacture of a medicament for treating such diseases and disorders.

"IMPDH-associated disorders" refers to any disorder or disease state in which inhibition of the enzyme IMPDH (inosine monophosphate dehydrogenase,
20 EC1.1.1.205, of which there are presently two known isozymes referred to as IMPDH type 1 and IMPDH type 2) would modulate the activity of cells (such as lymphocytes or other cells) and thereby ameliorate or reduce the symptoms or modify the underlying cause(s) of that disorder or disease. There may or may not be present in the disorder or disease an abnormality
25 associated directly with the IMPDH enzyme. Examples of IMPDH-associated disorders include transplant rejection and autoimmune disorders, such as rheumatoid arthritis, lupus, multiple sclerosis, juvenile diabetes, asthma, and inflammatory bowel disease, as well as inflammatory disorders, cancer and tumors, T-cell mediated hypersensitivity diseases, ischemic or reperfusion
30 injury, viral replication diseases, proliferative disorders and vascular diseases.

Use of the compounds of the present invention is exemplified by, but is not limited to, treating a range of disorders such as: treatment of transplant rejection (e.g. kidney, liver, heart, lung, pancreas (e.g., islet cells), bone

marrow, cornea, small bowel, skin allografts, skin homografts (such as employed in burn treatment), heart valve xenografts, serum sickness, and graft vs. host disease, in the treatment of autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, juvenile diabetes, 5 asthma, inflammatory bowel disease (such as Crohn's disease and ulcerative colitus), pyoderma gangrenum, lupus (systemic lupus erythematosus), myasthenia gravis, psoriasis, eczema, dermatitis, dermatomyositis, atopic dermatitis; multiple sclerosis, seborrhoea, pulmonary inflammation, eye uveitis, hepatitis, Grave's disease, Hashimoto's thyroiditis, autoimmune 10 thyroiditis, Behcet's or Sjorgen's syndrome (dry eyes/mouth), pernicious or immunohaemolytic anaemia, Addison's disease (autoimmune disease of the adrenal glands), idiopathic adrenal insufficiency, autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome) glomerulonephritis, scleroderma, morphea, lichen planus, viteligo 15 (depigmentation of the skin), alopecia areata, autoimmune alopecia, autoimmune hypopituitarism, cicatricial pemphigoid, Gullivan-Barre syndrome, and alveolitis; in the treatment of T-cell mediated hypersensitivity diseases, including contact hypersensitivity, delayed-type hypersensitivity, contact dermatitis (including that due to poison ivy), urticaria, skin allergies, 20 respiratory allergies (hayfever, allergic rhinitis) and gluten-sensitive enteropathy (Celiac disease); in the treatment of inflammatory diseases such as osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, acute respiratory distress syndrome, Sezary's syndrome and vascular diseases which have an inflammatory and or a proliferatory component such as 25 restenosis, stenosis and artherosclerosis; in the treatment of cancer and tumor disorders, such as solid tumors, lymphomas and leukemia; in the treatment of fungal infections such as mycosis fungoides; in protection from ischemic or reperfusion injury such as ischemic or reperfusion injury that may have been incurred during organ transplantation, myocardial infarction, stroke 30 or other causes; in the treatment of DNA or RNA viral replication diseases, such as herpes simplex type 1 (HSV-1), herpes simplex type 2 (HSV-2), hepatitis (including hepatitis B and hepatitis C) cytomegalovirus, Epstein-Barr, human immunodeficiency virus (HIV) and influenza.

Additionally, IMPDH is also known to be present in bacteria and thus may regulate bacterial growth. As such, the IMPDH-inhibitor compounds of the present invention may be useful in treatment or prevention of bacterial infection, alone or in combination with other antibiotic agents.

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In a particular embodiment, the compounds of the present invention are useful for the treatment of the afore mentioned exemplary disorders irrespective of their etiology, for example, for the treatment of lupus, psoriasis, inflammatory bowl disease, multiple sclerosis, atopic dermatitis, transplant rejection or
10 rheumatoid arthritis.

In another particular embodiment the compounds of the present invention are of particular use for the treatment of DNA or RNA viral replication diseases, such as hepatitis (including hepatitis B and hepatitis C) cytomegalovirus,
15 human immunodeficiency virus (HIV) and influenza.

In an additional particular embodiment the compounds of the present invention are of particular use for the treatment of cancer and tumour disorders, such as solid tumors, lymphoma, leukemia and other forms of
20 cancer.

The compounds of formula (1) can be used alone or in combination with other therapeutic or prophylactic agents, such as anti-virals, anti-inflammatory agents, antibiotics, anticancer agents and immunosuppressants.

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For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or
30 more pharmaceutically acceptable carriers, excipients or diluents.

Alternate compositions of this invention comprise a compound formula (1) or a salt thereof; an additional agent selected from an immunosuppressant, an anti-cancer agent, an anti-viral agent, anti-inflammatory agent, anti-fungal agent,

anti-vascular hyperproliferation agent or an antibiotic agent; and any pharmaceutically acceptable carrier, adjuvant or vehicle.

Thus, for example, additional immunosuppression agents include, but are not limited to, cyclosporin A, FK506, rapamycin, leflunomide, deoxyspergualin, prednisone, azathioprine, OKT3, ATAG, interferon and mizoribine. Additional anti-cancer agents include, but are not limited to, cis-platin, actinomycin D, doxorubicin, vincristine, vinblastine, etoposide, amsacrine, mitoxantrone, tenipaside, taxol, colchicine, cyclosporin A, phenothiazines, interferon and thioxantheres. Additional anti-viral agents include, but are not limited to, Cytovene, Ganiclovir, trisodium phosphonoformate, Ribavirin, d4T, ddI, AZT and acyclovir. Additional anti-vascular hyperproliferative agents include, but are not limited to, HMG Co-A reductase inhibitors such as lovastatin, thromboxane A2 synthetase inhibitors, eicosapentanoic acid, ciprostone, trapidil, ACE inhibitors, low molecular weight heparin, and rapamycin.

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physician's Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

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

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in

the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with
5 pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

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

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

15

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take
20 such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. For particle mediated administration the compounds of
25 formula (1) may be coated on particles such as microscopic gold particles.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

30

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichloro-

fluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

5 For vaginal or rectal administration the compounds of formula (1) may be formulated as a suppository. These formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is a solid at room temperature but liquid at the body temperature. Such materials include for example cocoa butter and polyethylene glycols.

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

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

The compounds of the invention may be prepared by a number of processes
25 as generally described below and more specifically in the Examples hereinafter. Many of the reactions described are well-known standard synthetic methods which may be applied to a variety of compounds and as such can be used not only to generate compounds of the invention, but also where necessary the intermediates thereto.

30

In the following process description, the symbols R^1 , R^2 , R^3 , R^4 and R^5 when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional

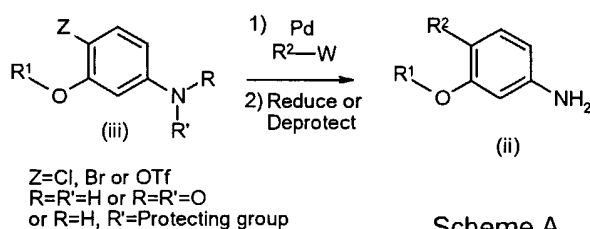
groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Greene, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, (1999) and the examples herein]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups. It will be appreciated that the syntheses described herein for the preparation of compounds of formula (1) also applies to the compounds of formulae (2) and (3), unless otherwise stated.

Compounds of formula (1) may be prepared according to one of several general methods, including the method shown in Scheme D, below.

An appropriate starting material for the preparation of compounds of formula (1) is an amine of formula (ii), as shown below.

Amines of general formula (ii) may be prepared in a variety of ways. For example, the amine of formula (ii) where R^1 is a methyl group and R^2 is an oxazole group may be prepared using methods known in the literature (CAS 198821-79-3).

Alternatively amines of formula (ii), where R^2 is an optionally substituted heteroaromatic group, may be prepared using the route as shown in Scheme A:



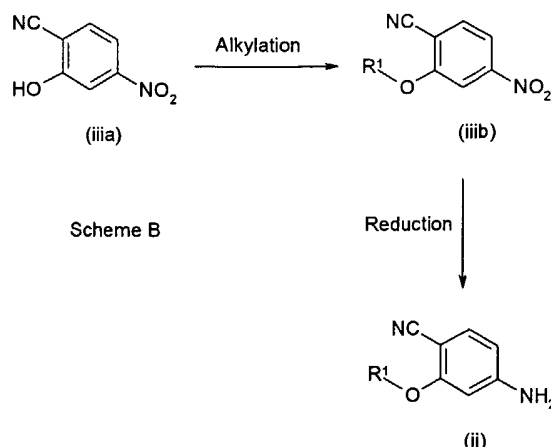
Scheme A

For example, a compound of formula (iii), where Z is a halogen atom e.g. Cl or Br or a suitable leaving group e.g. trifluoromethylsulfonyloxy (OTf) and $-\text{NRR}'$

is a nitro group or an amine group (which may be suitably protected), may be reacted with a derivative of the desired heteroaromatic group (R^2 -W, where W is as described below) utilising a palladium catalysed cross coupling reaction. The following literature methodology may be used to perform this coupling reaction according to the nature of the W group; e.g. when W is a hydrogen atom (Heterocycles, 31, pp. 1951-1958, (1990)); the zinc species ($W=ZnCl$) (J. Organomet. Chem., 390, pp. 389-398, (1990); Tetrahedron, 53, pp. 7237-7254, (1997)); the mercury species ($W=HgBr$) (Chem. Heterocycl. Compd., 19, pp. 1159-1162, (1983)) or a boron derivative ($W=B(OH)_2$, $W=BEt_2$) (J. Med. Chem., 40, pp. 3542-3550, (1997); J. Org. Chem., 63, pp. 8295-8303, (1998)). The resulting coupled product may require further manipulation, depending on the nature of the $-NRR'$ group, in order to obtain an amine of formula (ii). For example, when $-NRR'$ is a nitro group this may be reduced to an amine using standard techniques such as those methods as described hereinafter, or when $-NRR'$ is a protected amine the protecting group may be removed using standard methodology, for example a carbamate protecting group e.g. *tert*-butoxycarbonyl may be removed under acidic conditions e.g. trifluoroacetic acid. It will be appreciated that the various R^2 -W derivatives are either commercially available or may be prepared using methods known to those skilled in the art. In a similar manner the compounds of formula (iii) are either commercially available or may be prepared using methods known to those skilled in the art. For example, the compound of formula (iii) may be prepared by alkylation of the phenol precursor of (iii) using standard techniques.

25

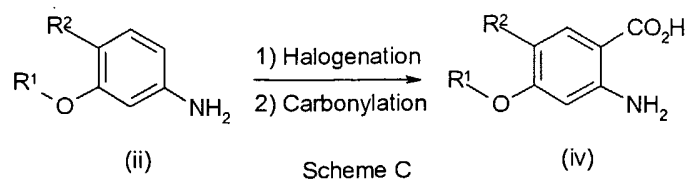
Further, when R^2 is a CN group amines of formula (ii) may be prepared from 2-hydroxy-4-nitrobenzonitrile (iiia) (CAS No. 39835-14-8) as shown in the general Scheme B below:



Thus a phenol of formula (iiiia) may be alkylated using conditions known to those skilled in the art, typically using an alkyl halide e.g. iodoethane and sodium hydride in *N,N*-dimethylformamide, to give an ether of formula (iiib).

- 5 Alternatively these compounds may be commercially available, for example $R^1 = \text{Me}$ (CAS No. 101084-96-2). The compound of formula (iiib) may then be reduced to give the desired amine of formula (ii) using standard methods, for example hydrogenolysis using palladium catalysis.

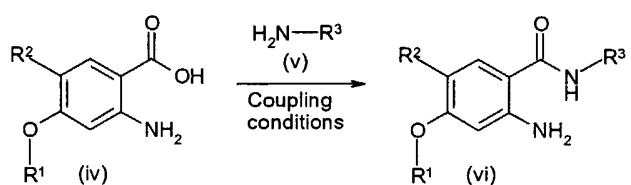
- 10 The amine of formula (ii) may then be converted to an amino acid of general formula (iv) using a two-step process as shown in Scheme C. Thus an amine of formula (ii) may be treated with a halogen source such as bromine or a halosuccinimide e.g. chloro or bromosuccinimide. The reaction may be performed in a solvent such as acetonitrile or an ether e.g. a cyclic ether such as tetrahydrofuran at a temperature from about 0° to 30°. When bromine is used as halogen source the reaction may optionally be performed in the presence of added base such as an amine e.g. triethylamine. The intermediate thus formed may be converted into a carboxylic acid of formula (iv) using methods known to those skilled in the art. For example the
- 15 as tetrahydrofuran at a temperature from about 0° to 30°. When bromine is used as halogen source the reaction may optionally be performed in the presence of added base such as an amine e.g. triethylamine. The intermediate thus formed may be converted into a carboxylic acid of formula (iv) using methods known to those skilled in the art. For example the
- 20 halogenated intermediate may be treated with carbon monoxide under reduced pressure in the presence of a catalyst e.g. a palladium catalyst such as dichlorobis(triphenylphosphine)palladium(II) in for example water and an appropriate solvent e.g. *N,N*-dimethylformamide or tetrahydrofuran. It may be appropriate to carry out the reaction at an elevated temperature, such as 90-
- 25 100°C.



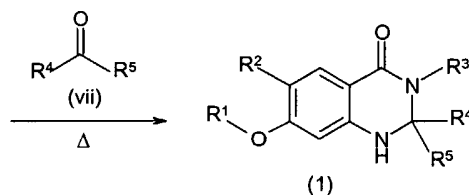
Amino acids of formula (iv) may also be known compounds (e.g. $R^1 = \text{Me}$, $R^2 = \text{Oxazole}$; CAS No. 371251-38-6).

5

In one aspect of the invention quinazolinones of formula (1) may be prepared by reacting an amine of formula (vi) with a carbonyl compound of formula (vii). Thus, quinazolinones of formula (1) may be prepared using the general route as shown in Scheme D:



Scheme D



10

Thus amino acids of formula (iv) may be reacted with amines of formula (v) using coupling reaction conditions familiar to those skilled in the art to give amides (vi). For example, an acid of formula (iv) may be activated *in situ* using for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, advantageously in the presence of a catalyst such as a N-hydroxy compound, e.g. *N*-hydroxybenzotriazole, using suitable conditions, e.g. in *N,N*-dimethylformamide, prior to the subsequent addition of an amine of formula (v). A base such as an amine base e.g. triethylamine or diisopropylethylamine may also be employed in the reaction. Alternatively acids of formula (iv) may be reacted with oxalyl chloride in an inert solvent (such as dichloromethane) to give an intermediate acid chloride, which may or may not be isolated, but which in turn is reacted with an amine of formula (v) at a suitable temperature such as room temperature to give the amide (vi). The reaction may be performed in the presence of a base, such as a hydride,

25

e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide at for example ambient temperature.

5

Amines of formula (v) may be commercially available, known compounds in the literature or may be prepared using methods known to those skilled in the art.

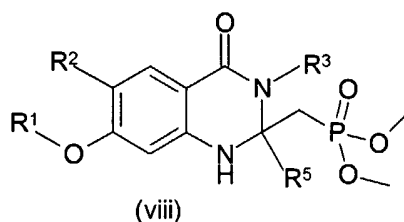
- 10 Formation of quinazolinones of formula (1) may be achieved by condensation of amino amides (vi) with aldehydes or ketones of formula (vii) typically using acid, e.g. p-toluenesulfonic acid, catalysed conditions similar to those employed by Bhavani and Reddy (Org. Prep. Proced. Int. 1992, 24, 1) or Bonala *et al* (J. Med. Chem. 1968, 11, 1136), Bonala *et al* (J. Med. Chem.
- 15 1968, 11, 1136), Gould *et al* (Tetrahedron, 1991, 47, 7209) or Larsen *et al* (J. Med. Chem. 2001, 44, 1217). The acid used as a catalyst may be hydrochloric acid (Klemm *et al*; J. Heterocycl. Chem. 1998, 35, 1269), trichloroacetic acid (Yamato *et al*; Chem. Pharm. Bull. 1981, 29, 3124) or a Lewis acid such as zinc chloride (Yamato *et al*; Chem. Pharm. Bull. 1981, 29, 3124) or cerium
- 20 chloride or borontrifluoride diethyl etherate, or acetic acid. The reaction may be performed in a sealed tube, for example, using microwaves as an energy source or under vacuum. Suitable solvents for use in this reaction include halogenated hydrocarbons, e.g. dichloromethane or dichloroethane, amides, e.g. dimethylformamide, ethers such as cyclic ethers e.g. 1-4-dioxane,
- 25 alcohols e.g. ethanol or esters e.g. isopropylacetate. Drying agents such as magnesium sulfate or molecular sieves may be added or the reaction may be performed using Dean Stark conditions. The reaction may be achieved at a range of temperatures e.g. from room temperature to reflux.

- 30 Carbonyl compounds of formula (vii) are either commercially available or may be prepared using methods known to those skilled in the art. Alternatively a carbonyl compound protected as an acetal may be used in the condensation reaction rather than the carbonyl compound itself. Such compounds are either

commercially available or prepared using methods previously reported in the literature.

Quinazolinethiones of formula (1) (where $X=S$) may be prepared from the corresponding quinazolinone ($X=O$) for example, by reaction with a thiation reagent, such as Lawesson's Reagent or P_2S_5 , in an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, or toluene at an elevated temperature such as the reflux temperature (see for example Tetrahedron 1985, 41, 5061).

Compounds of formula (1) wherein Alk^3 is a $-CHCH-$ chain may be prepared using phosphorus ylides e.g. Wittig methodology, as known to those skilled in the art. Thus a phosphonate e.g. of formula (viii):



may be prepared using the methodology described herein for the preparation of compounds of formula (1). The phosphonate may then be reacted with an aldehyde of formula $OHCL^2(Alk_4)_qR^7$ in the presence of a base e.g. potassium hydroxide in a suitable solvent such as an alcohol e.g. ethanol to give a compound of formula (1) wherein Alk^3 is a $-CHCH-$ chain.

It will be appreciated that compounds of formula (1) or any preceding intermediates may be further derivatised by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of any of formula (1) or any preceding intermediates where appropriate functional groups exist in these compounds.

For example, ester groups may be converted to the corresponding acid [-CO₂H] by acid- or base-catalysed hydrolysis depending on the nature of the ester. Acid- or base- catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol. Similarly an acid [-CO₂H] may be prepared by hydrolysis of the corresponding nitrile [-CN], using for example a base such as sodium hydroxide in a refluxing alcoholic solvent, such as ethanol.

10

In another example, -OH groups may be generated from the corresponding ester or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as tetrahydrofuran. Alternatively an alcohol may be prepared by reduction of the corresponding acid [-CO₂H], using for example lithium aluminium hydride in a solvent such as tetrahydrofuran.

15

Alcohol groups may be converted into leaving groups, such as halogen atoms or sulfonyloxy groups such as an alkylsulfonyloxy, e.g. trifluoromethylsulfonyloxy or arylsulfonyloxy, e.g. p-toluenesulfonyloxy group using conditions known to those skilled in the art. For example, an alcohol may be reacted with thionyl chloride in a halogenated hydrocarbon e.g. dichloromethane to yield the corresponding chloride. A base e.g. triethylamine may also be used in the reaction.

25

In another example, alcohol or phenol groups may be converted to ether groups by coupling a phenol with an alcohol in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate. Alternatively ether groups may be prepared by deprotonation of an alcohol, using a suitable base e.g. sodium hydride followed by subsequent addition of an alkylating agent, such as an alkylhalide.

30

Aldehyde [-CHO] groups may be obtained by oxidation of a corresponding alcohol using well known conditions. For example using an oxidising agent such as a periodinane e.g. Dess Martin, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane. An alternative oxidation may be suitably activating dimethyl sulfoxide using for example, oxalyl chloride, followed by addition of an alcohol, and subsequent quenching of the reaction by the addition of an amine base, such as triethylamine. Suitable conditions for this reaction may be using an appropriate solvent, for example, a halogenated hydrocarbon, e.g. dichloromethane at -78°C followed by subsequent warming to room temperature.

In a further example primary amine (-NH₂) or secondary amine (-NH-) groups may be alkylated using a reductive alkylation process employing an aldehyde or ketone and a borohydride, for example sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [-NH₂] groups may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [-NO₂] group may be reduced to an amine [-NH₂], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

In a further example amine (-CH₂NH₂) groups may be obtained by reduction of nitriles (-CN), for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon, or Raney nickel, in a solvent such as an ether e.g. a

cyclic an ether, e.g. a cyclic ether such as tetrahydrofuran, at a temperature from -78°C to the reflux temperature.

5 Alkyl groups may be prepared by reduction of a corresponding alkyne or alkene group, for example, by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol.

10 Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange by treatment with a base, for example a lithium base such as *n*-butyl or *t*-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl
15 group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile. Aromatic halogen substituents may also be subjected to palladium catalysed reactions, to introduce, for example, acid, ester, cyano or amino substituents.

20

In another example, sulfur atoms in the compounds, for example when present in a linker group L¹, L² or L³ may be oxidised to the corresponding sulfoxide or sulfone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated
25 hydrocarbon, e.g. dichloromethane, at around ambient temperature.

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an
30 elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid or a peroxy acid e.g. 3-chloroperoxybenzoic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base or acid in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol or an aqueous solvent using conventional procedures. Salts of compounds of formula (1) may be exchanged for other salts by use of conventional ion-exchange chromatography procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention. All temperatures are in °C. Where experimental detail is not given for the preparation of a reagent it is either commercially available, or it is known in the literature, for which the CAS number is quoted. The compounds are named with the aid of Beilstein Autonom supplied by MDL Information Systems GmbH, Theodor-Heuss-Allee 108, D-60486 Frankfurt, Germany.

¹H NMR spectra were obtained at 300MHz or 400MHz unless otherwise indicated.

The following LCMS conditions were used to obtain the retention times (RT) as described herein:

LCMS conditions:

HP1100 (Diode Array) linked to a Finnigan LC-Q Mass Spectrometer, ESI mode with Pos/Neg ionization

10	Column:	Luna C18(2) 100×4.6mm, 5µm particle size Analytical column
	Column Temp:	35°C
	Mobile Phase:	A: Water + 0.08% formic acid B: Acetonitrile + 0.08% formic acid
	Flow rate:	3ml/min
15	Gradient:	Time (mins): % Composition B:
		0 5
		4.4 95
		5.30 95
		5.32 5
20		6.5 5
	Run time:	6.5 mins
	Typical Injection Vol:	10µl
	Detector Wavelength:	DAD 200-400nm

Preparative LC conditions (Method A):

Gilson 215 liquid handler setup.

30	Column:	Luna C18(2) 250×21.2mm, 5µM particle size prep column
	Column Temp:	Ambient
	Gradient:	Variable – depends on retention time of sample in LC-MS analysis.
	Run Time:	20 mins
	Flow rate:	25ml/min
	Typical Injection Vol:	0.5 – 4.0ml at 25mg/ml
	Detector Wavelength:	210 and 254nm
35	Mobile Phase:	A: Water + 0.08% formic acid B: Acetonitrile + 0.08% formic acid

Preparative LC conditions (Method B):

Gilson 215 liquid handler setup.

40	Column:	Luna C18(2) 250×21.2mm, 5µM particle size prep column
	Column Temp:	Ambient
	Gradient:	Variable – depends on retention time of sample in LC-MS analysis.

Run Time: 20 mins
 Flow rate: 25ml/min
 Typical Injection Vol: 0.5 – 4.0ml at 25mg/ml
 Detector Wavelength: 210 and 254nm
 5 Mobile Phase: A: 10mM NH₄OAc in water
 B: 10mM NH₄OAc in acetonitrile

Preparative LC conditions (Method C):

Gilson 215 liquid handler setup.

10 Column: Luna C18(2) 100x21mm, 5μM particle size Prep column.
 Column Temp: Ambient.
 Gradient: Variable- depends on retention of sample in LCMS screen.
 15 Run Time: 10 mins
 Flow rate: 20ml/min
 Typical Injection volume: 500μl
 Detector Wavelength: 210 and 254nm
 Mobile phase: A: Water + 0.08% formic acid
 20 B: MeCN + 0.08 % formic acid

Abbreviations used :-

CDCl₃ - Chloroform-d; DCE - Dichloroethane;
 DCM - Dichloromethane; DEA - Diethylamine;
 25 Et₂O - Diethyl ether; DIPEA - Di-*iso*-propylethylamine;
 EDC - 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride;
 DMF - *N,N*-Dimethylformamide; DMSO - Dimethyl sulphoxide;
 EtOH - Ethanol; d₆-DMSO - Dimethyl-d₆ sulphoxide;
 EtOAc - Ethyl acetate; HOBT - 1-Hydroxybenzotriazole hydrate;
 30 MeOH - Methanol; d₄-MeOH - Methanol-d₄
 THF - Tetrahydrofuran; TEA - Triethylamine;
 PTSA - *para*-Toluenesulfonic acid monohydrate;
 HBTU - 2-[1*H*-Benzotriazole-1-yl]-1,1,3,3-tetramethyluronium
 hexafluorophosphate

35

Intermediate 1. 2-Amino-4-methoxy-N-(2-morpholin-4-yl-ethyl)-5-oxazol-5-yl-benzamide

To a solution of 2-amino-4-methoxy-5-oxazol-5-yl-benzoic acid (CAS 371251-38-6) (0.13g) in dry DCM (10ml) stirring at room temperature was added 4-(2-

aminoethyl)morpholine (0.17ml) and TEA (0.33ml) followed by EDC (0.16g). The reaction mixture was allowed to stir for 22 hours. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica eluting with 10% MeOH/DCM to yield the title compound as a yellow solid (82mg, 45%). TLC R_f 0.28 (10% MeOH/DCM). LCMS 347 [M+H]⁺, RT 1.38 mins. ¹H NMR 300MHz (d₄-MeOH) 8.15 (1H, s), 7.93 (1H, s), 7.30 (1H, s), 6.45 (1H, s), 3.95 (3H, s), 3.75-3.70 (4H, m), 3.55-3.50 (2H, m), 2.65-2.55 (6H, m).

10 The compound of intermediate 2 was prepared in a similar manner to the method in Intermediate 1:-

Intermediate 2. 2-Amino-4-methoxy-N-methyl-5-oxazol-5-yl-benzamide

From 2-amino-4-methoxy-5-oxazol-5-yl-benzoic acid (0.2g) and methylamine hydrochloride (0.13g). Purification by column chromatography on silica eluting with EtOAc afforded the title compound as a pale yellow solid (76mg, 36%). TLC R_f 0.31 (EtOAc). LCMS 248 [M+H]⁺, RT 2.04 mins. ¹H NMR 300MHz (d₆-DMSO) 8.33 (1H, s), 8.25-8.20 (1H, m, br), 7.85 (1H, s), 7.25 (1H, s), 6.95-6.85 (2H, s, br), 6.40 (1H, s), 3.85 (3H, s), 2.75-2.70 (3H, d).

20 **Intermediate 3. 2-Amino-4-methoxy-5-oxazol-5-yl-N-(2-pyridin-4-yl-ethyl)-benzamide**

To a solution of 2-amino-4-methoxy-5-oxazol-5-yl-benzoic acid (CAS 371251-38-6) (0.13g) in dry DCM (10ml) stirring at room temperature was added 4-(aminoethyl)pyridine (0.24g) and TEA (0.33ml) followed by EDC (0.25g) and HOBT (0.17g). The reaction mixture was allowed to stir for 22 hours. The reaction mixture was filtered, extracted with DCM (50ml) and washed with water (20ml). The organic layer was separated, dried over MgSO₄, filtered, and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica eluting with 10% MeOH/DCM to yield the title compound as a yellow oil (93mg, 32%). LCMS 339 [M+H]⁺, RT 1.40 mins. ¹H NMR 300MHz (d₄-MeOH) 8.45-8.40 (2H, m), 8.15 (1H, s), 7.78 (1H, s), 7.40-7.35 (2H, m), 7.28 (1H, s), 6.42 (1H, s), 3.95 (3H, s), 3.65-3.60 (2H, m), 3.00-2.93 (2H, m).

The compound of intermediate 4 was prepared in a similar manner to the method in Intermediate 3:-

Intermediate 4. 3-(2-Amino-4-methoxy-5-oxazol-5-yl-benzoylamino)-propionic acid ethyl ester

- 5 From 2-amino-4-methoxy-5-oxazol-5-yl-benzoic acid (0.2g) and β -alanine ethyl ester hydrochloride (0.3g). The reaction mixture was diluted with H₂O (20ml) and extracted with DCM (3x50ml). The organic layers were combined, dried over MgSO₄, filtered and concentrated *in vacuo* to afford the title compound as a pale yellow solid (356mg, quantitative). TLC R_f 0.31 (EtOAc).
10 LCMS 334 [M+H]⁺, RT 2.63 mins. ¹H NMR 300MHz (CDCl₃) 7.83 (1H, s), 7.70 (1H, s), 7.34 (1H, s), 6.70-6.64 (1H, s, br), 6.18 (1H, s), 5.95-5.90 (2H, s, br), 4.25-4.15 (2H, q), 3.90 (3H, s), 3.90-3.82 (2H, m), 2.67-2.50 (2H, m), 1.30-1.20 (3H, m).

Intermediate 5. 2-Amino-N-(2-imidazol-1-yl-ethyl)-4-methoxy-5-oxazol-5-yl-benzamide

- 15 To a stirred solution under nitrogen of 2-amino-4-methoxy-5-oxazol-5-yl-benzoic acid (826mg) in DMF (60ml) was added HBTU (1.34g) and DIPEA (3.14ml) followed by N-(ethylamino)imidazole, bishydrochloride (CAS 93668-43-0) (649mg). The mixture was stirred at room temperature overnight and
20 concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting with 5-20% MeOH/DCM to afford the title compound as a brown gum (957mg, 83%). LCMS 328 [M+H]⁺, RT 1.42 mins. ¹H NMR 300MHz (d₄-MeOH) 8.16 (1H, s), 7.97 (1H, s), 7.84 (1H, s), 7.30 (2H, s), 7.24 (1H, s), 6.45 (1H, s), 4.36-4.30 (2H, tr), 3.95 (3H, s), 3.73-3.68 (2H, tr).

Intermediate 6. 2-Amino-4-methoxy-5-oxazol-5-yl-benzamide

- 25 2-Amino-4-methoxy-5-oxazol-5-yl-benzoic acid (3.5g), EDC (2.87g) and HOBt (2.02g) were combined in a 0.5M ammonia in dioxane solution (100ml), and stirred at room temperature for 21 hours. The reaction mixture was evaporated directly onto silica and purified by column chromatography on
30 silica eluting with 75-100% EtOAc/heptane rising to 5% MeOH/EtOAc to give the title compound as a yellow solid (1.90 g, 55%). TLC R_f 0.15 (75% EtOAc/Heptane). LCMS 234 [M+H]⁺, RT 1.95 mins. ¹H NMR 300MHz (d₆-

DMSO) 8.36 (1H, s), 7.94 (1H, s), 7.85 (1H, brs), 7.30 (1H, s), 7.05 (3H, brs), 6.45 (1H, s), 3.91 (3H, s).

Intermediate 7 **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydro-quinazolin-2-ylmethyl)-phosphonic acid dimethylester.**

5 A mixture of Intermediate 2 (100mg) dimethyloxopropylphosphonate (200mg) and PTSA (2mg) in DMF (2ml) and toluene (5ml) was stirred at room temperature for 2 hours and then heated to 110°C for 2 hours. The solvent was removed *in vacuo* and the residue was purified by column chromatography eluting with 5% MeOH/DCM to yield the title compound as a yellow solid (112mg, 71%). LCMS 396 [M+H]⁺, RT 2.16 mins. ¹H NMR 300MHz (CDCl₃) 8.30 (1H, s), 7.85(1H, s), 7.35 (1H, s), 6.25 (1H, s), 5.85 (1H, br s), 3.95 (3H, s), 3.80 (3H, d), 3.65 (3H, d), 3.05 (3H, s), 2.50 (1H, t), 2.25 (1H, t), 1.90 (3H, s).

15 **Intermediate 8** **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-2-[2-(1-trityl-1H-imidazole-4-yl)-vinyl]-2,3-dihydro-1H-quinazolin-4-one**

A mixture of Intermediate 7 (150mg), 1-trityl-1H-imidazole-4-carboxaldehyde (128mg) and KOH (20mg) in EtOH (1ml) was heated to 60°C for 3 hours. The solvent was removed *in vacuo* and the residue was purified by column chromatography eluting with 2.5% MeOH/DCM to yield the title compound as a solid (30mg, 13%). LCMS 607 [M+H]⁺, RT 3.31 mins

20 **Intermediate 9** **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-2-trimethylsilylanylethynyl-2,3-dihydro-1H-quinazolin-4-one**

25 A mixture of Intermediate 2 (1.01g), 4-trimethylsilyl-3-butyne-2-one (1.34ml) and PTSA (31mg) was combined in isopropyl acetate (120ml) and heated to reflux in a Dean-Stark apparatus for 20 hours. The reaction was then allowed to cool slowly to room temperature, and the product filtered from the reaction, washed with ice-cold isopropyl acetate (3 x 5 ml) and dried further *in vacuo* to yield the title compound as a yellow solid (1.07 g, 71%). TLC R_f 0.42 (5% MeOH/DCM). LCMS 370 [M+H]⁺, RT 3.64 mins. ¹H NMR 400MHz (d₄-MeOH) 8.25 (1H, s), 8.13 (1H, s), 7.43 (1H, s), 6.50 (1H, s), 4.07 (3H, s), 3.15 (3H, s), 1.91 (3H, s), 0.15 (9H, s).

30 **Intermediate 10** **5-(3-Oxobut-1-enyl)thiophene-3-carboxylic acid**

methyl ester

Methyl 5-formyl-3-thiophenecarboxylate (68mg) and 1-triphenylphosphoranylidene-2-propanone (128mg) were combined in THF (5ml) and stirred at room temperature for 18 hours. The solvent was evaporated and the residue purified by column chromatography on silica eluting with 20% EtOAc/heptane to furnish the title compound as a pale pink solid (64mg, 76%). TLC R_f 0.41 (1:2 EtOAc/Heptane). LCMS 211 [M+H]⁺, RT 3.00 mins. ¹H NMR 300MHz (CDCl₃) 8.11 (1H, s), 7.68 (1H, s), 7.59 (1H, d), 6.55 (1H, d), 3.89 (3H, s), 2.35 (3H, s).

10 **Intermediate 11** **2-[2-(7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)ethyl]isoindole-1,3-dione**

A mixture of Intermediate 2 (205mg) and *N*-(3-oxobutyl)phthalimide (CAS 3783-77-5) (216mg) in acetic acid (10ml) was heated to 70°C, under a slight reduced pressure, for 1.5 hours. After cooling, the acetic acid was removed *in vacuo* and the residue triturated with EtOAc to provide the title compound as a pale yellow solid (238 mg, 65%). LCMS 447 [M+H]⁺, RT 2.92 mins. ¹H NMR 300MHz (d₆-DMSO) 8.30 (1H, s), 7.92 (1H, s), 7.81 (4H, m), 7.25 (2H, m), 6.30 (1H, s), 3.87 (3H, s), 3.50-3.80 (2H, m), 2.99 (3H, s), 1.95-2.20 (2H, m), 1.43 (3H, s).

20 **Intermediate 12.** **2-(2-Amino-ethyl)-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one**

Hydrazine hydrate (0.04ml) was added to a solution of Intermediate 11 (193 mg), and stirred at room temperature for 4 hours. The reaction mixture was evaporated under reduced pressure to give a crude product (243mg). A sample (25mg) was purified by preparative HPLC (Method A) to give the title compound as a pale yellow glass (7.2mg). LCMS 317 [M+H]⁺, RT 1.47 mins. ¹H NMR 400MHz (d₄-MeOH) 8.52 (1H, s, br), 8.16 (1H, s), 8.11 (1H, s), 7.30 (1H, s), 6.37 (1H, s), 3.96 (3H, s), 3.14 (1H, m), 3.03 (3H, s), 2.94 (1H, s), 2.38 (1H, m), 2.08 (1H, m), 1.60 (3H, s).

30 **Intermediate 13** **4-(1-Methyl-1H-imidazol-2-yl)-but-3-en-2-one.**

A mixture of 1-methyl-2-imidazolecarboxaldehyde (1g) and 1-triphenylphosphoranylidene-2-propanone (2.86g) in DMF (2ml) was stirred at room temperature for 12 hours. The solvent was removed *in vacuo* and the

residue was purified by column chromatography eluting with 50-100% EtOAc/heptane to yield the title compound as an off-white solid (548mg, 40%).

TLC R_f 0.23 (EtOAc).

Example 1. **7-Methoxy-2,2-dimethyl-3-(2-morpholin-4-yl-ethyl)-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one**

To a solution of Intermediate 1 (0.082g) in acetone (1ml) stirring at room temperature was added MgSO₄ (0.5g) followed by PTSA (0.3mg). The reaction mixture was heated to reflux for 6 hours. The solvent was removed *in vacuo* and the residue purified by preparative HPLC (Method A) to afford the title compound as an off-white solid (15mg, 16%). TLC R_f 0.1 (5% MeOH/DCM). LCMS 387 [M+H]⁺, RT 1.49 mins. ¹H NMR 300MHz (d₄-MeOH) 8.09 (1H, s), 8.03 (1H, s), 7.22 (1H, s), 6.24 (1H, s), 3.88 (3H, s), 3.68-3.61 (4H, m), 3.60-3.53 (2H, m), 2.60-2.50 (6H, m), 1.50 (6H, s).

Examples 2-6 were prepared in a similar manner to the method in Example 1:-

Example 2. **7-Methoxy-2,2,3-trimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one**

From Intermediate 2 (0.2g). The reaction mixture was left to cool overnight and the precipitated solid collected by filtration to give the title compound as an off-white solid (127mg, 55%). TLC R_f 0.23 (EtOAc). LCMS 288 [M+H]⁺, RT 2.35 mins. ¹H NMR 300MHz (d₆-DMSO) 8.30 (1H, s), 7.95 (1H, s), 7.28 (1H, s), 7.15 (1H, s), 6.32 (1H, s), 3.90 (3H, s), 2.90 (3H, s), 1.45 (6H, s).

Example 3. **7-Methoxy-2,2-dimethyl-6-oxazol-5-yl-3-(2-pyridin-4-yl-ethyl)-2,3-dihydro-1H-quinazolin-4-one**

From Intermediate 3 (93mg). The reaction mixture was filtered and the solvent removed *in vacuo* to give a yellow solid, which was washed with water and filtered to afford the title compound as a pale yellow solid (22.2mg, 21%). TLC R_f 0.56 (5% MeOH/DCM). LCMS 379 [M+H]⁺, RT 1.67 mins. ¹H NMR 300MHz (d₄-MeOH) 8.52-8.48 (2H, m), 8.20 (1H, s), 8.16 (1H, s), 7.45-7.40 (2H, m), 7.35 (1H, s), 6.37 (1H, s), 4.00 (3H, s), 3.80-3.72 (2H, m), 3.10-3.02 (2H, m), 1.58 (6H, s).

Example 4. **3-(7-methoxy-2,2-dimethyl-6-oxazol-5-yl-4-oxo-1,4-dihydro-2H-quinazolin-3-yl)-propionic acid ethyl ester**

From Intermediate 4 (0.36g). The reaction mixture was purified by column chromatography on silica eluting with 2% MeOH/DCM to yield the title compound as an off-white solid (190mg, 48%). LCMS 374 [M+H]⁺, RT 2.88 mins. ¹H NMR 300MHz (d₄-MeOH) 8.15 (1H, s), 8.10 (1H, s), 7.23 (1H, s), 6.30 (1H, s), 4.15-4.08 (2H, q), 3.92 (3H, s), 3.75-3.67 (2H, m), 2.69-2.62 (2H, m), 1.55 (6H, s), 1.24-1.17 (3H, t).

Example 5. 7-Methoxy-2,2-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one

From Intermediate 6 (0.10 g). Purification by column chromatography on silica eluting with 75% EtOAc/heptane rising to 5% MeOH/EtOAc followed by trituration with DCM/Et₂O afforded the title compound as an off-white solid (25mg, 22%). TLC R_f 0.24 (EtOAc). LCMS 274 [M+H]⁺, RT 2.18 mins. ¹H NMR 300MHz (d₆-DMSO) 8.31 (1H, s), 7.92 (2H, s), 7.30 (1H, s), 7.12 (1H, s), 6.30 (1H, s), 3.91 (3H, s), 1.40 (6H, s).

Example 6. 3-(2-Imidazol-1-yl-ethyl)-7-methoxy-2,2-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one

To a solution of Intermediate 5 (106mg) in DMF (2ml) stirring at room temperature was added acetone (1ml) and MgSO₄ (0.5g) followed by PTSA (6.8mg). The reaction mixture was heated to 80°C for 1 hour then to 100°C for 10 mins in a sealed tube using microwaves. The solvent was removed *in vacuo* and the residue purified by preparative HPLC (Method B) to afford the title compound as a brown oil (3.7mg, 3%). LCMS 368 [M+H]⁺, RT 1.53 mins. ¹H NMR 300MHz (d₄-MeOH) 8.19 (1H, s), 8.15 (1H, s), 7.70 (1H, s), 7.33 (1H, s), 7.19 (1H, s), 7.02 (1H, s), 6.33 (1H, s), 4.35-4.25 (2H, tr), 3.97 (3H, s), 3.80-3.73 (2H, tr), 1.35 (6H, s).

Examples 7-9 were prepared in a similar manner to the method in Example 6:-

Example 7. Acetic acid 7-methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydro-quinazolin-2-yl methyl ester

From Intermediate 2 (50mg) and methyl acetoacetate (0.07ml). Purification by preparative HPLC (Method A) afforded the title compound (17mg, 24%). LCMS 346 [M+H]⁺, RT 2.42 mins. ¹H NMR 300MHz (d₄-MeOH) 8.20 (1H, s),

8.15 (1H, s), 7.35 (1H, s), 6.35 (1H, s), 4.40-4.20 (2H, m), 4.0 (3H, s), 3.15 (3H, s), 1.90 (3H, s), 1.7 (3H, s).

Example 8. **7-Methoxy-2,3-dimethyl-2-(2-methylsulfanyl-ethyl)-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one**

5 From Intermediate 2 (50mg) and 4-(methylthio)-2-butanone (0.07ml). Purification by preparative HPLC (Method A) afforded the title compound (13mg, 18%). LCMS 348 [M+H]⁺, RT 2.84 mins. ¹H NMR 300MHz (d₄-MeOH) 8.20 (1H, s), 8.15 (1H, s), 7.35 (1H, s), 6.35 (1H, s), 4.0 (3H, s), 3.05 (3H, s), 2.8-2.65 (1H, m), 2.55-2.45 (1H, m), 2.4-2.25 (1H, m), 2.10 (3H, s),
10 2.10-1.95 (1H, m), 1.60 (3H, s).

Example 9. **7-Methoxy-2-methoxymethyl-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one**

From Intermediate 2 (50mg) and methoxyacetone (0.06ml). Purification by preparative HPLC (Method A) afforded the title compound (7mg, 10%).
15 LCMS 318 [M+H]⁺, RT 2.45 mins. ¹H NMR 300MHz (d₄-MeOH) 8.20 (1H, s), 8.15 (1H, s), 7.30 (1H, s), 6.35 (1H, s), 4.0 (3H, s), 3.60-3.45 (2H, m), 3.40 (3H, s), 3.1 (3H, s), 1.6 (3H, s).

Example 10. **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one**

20 To a solution of Intermediate 2 (0.2g) in dioxane (10ml) was added acetaldehyde (40mg) and MgSO₄ (2g). The reaction mixture was heated to 100°C for 5 hours. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica eluting with 5-10% MeOH/DCM to yield the title compound as an off-white solid (42mg, 19%). TLC R_f 0.33
25 (10% MeOH/DCM). LCMS 274 [M+H]⁺, RT 2.15 mins. ¹H NMR 300MHz (CDCl₃) 8.30 (1H, s), 7.86 (1H, s), 7.35 (1H, s), 6.15 (1H, s), 4.92-4.84 (1H, m), 4.60 (1H, s, br), 3.94 (3H, s), 3.08 (3H, s), 1.48-1.42 (3H, d).

Example 11. **7-Methoxy-3-methyl-6-oxazol-5-yl-2-phenyl-2,3-dihydro-1h-quinazolin-4-one**

30 To a solution of Intermediate 2 (0.1g) in DCM (10ml), stirring at room temperature was added benzaldehyde (0.04ml) and MgSO₄ (50mg) followed by PTSA (catalytic). The reaction mixture was stirred at room temperature overnight, filtered and concentrated *in vacuo*. The residue was extracted with DCM (30ml) and washed with 1N hydrochloric acid (2x15ml). The organic

layer was separated, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting with 50-100% EtOAc/heptane to afford the title compound as a pale yellow solid (16mg, 12%). TLC R_f 0.48 (EtOAc). LCMS 336 $[\text{M}+\text{H}]^+$, RT 2.84 mins. ^1H NMR 300MHz (d_4 -MeOH) 8.20 (1H, s), 8.19 (1H, s), 7.40 (5H, m), 7.35 (1H, s), 6.34 (1H, s), 5.88 (1H, s), 3.95 (3H, s), 2.98 (3H, s).

Example 12 was prepared in a similar manner to the method in Example 11:-

Example 12. **7-Methoxy-3-methyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydro-quinazoline-2-carboxylic acid ethyl ester**

From Intermediate 2 (0.1g) and ethylglyoxalate solution (50% in toluene, 0.08ml). Purification was by column chromatography on silica eluting with 5% MeOH/DCM followed by triturating with EtOAc/ Et_2O to afford the title compound as an orange solid (5.8mg, 22%). TLC R_f 0.41 (EtOAc). LCMS 336 $[\text{M}+\text{H}]^+$, RT 2.45 mins. ^1H NMR 300MHz (d_4 -MeOH) 8.29 (1H, s), 8.22 (1H, s), 7.45 (1H, s), 6.57 (1H, s), 5.38 (1H, s), 4.30 (2H, q), 4.08 (3H, s), 3.22 (3H, s), 1.32 (3H, t).

Example 13. **7-Methoxy-3-methyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydro-quinazoline-2-carboxylic acid**

To a solution of Intermediate 2 (0.1g) in DCM (10ml), stirring at room temperature was added glyoxylic acid monohydrate (36.8mg) and MgSO_4 (50mg) followed by PTSA (catalytic). The reaction mixture was heated at reflux for 4 hours, allowed to cool, filtered and concentrated *in vacuo*. Water (10ml) was added and the mixture acidified with 2N hydrochloric acid. The solid formed was filtered off and dried *in vacuo* to afford the title compound as a pale orange solid (36.6mg, 30%). TLC R_f 0.03 (10%MeOH/DCM). LCMS 304 $[\text{M}+\text{H}]^+$, RT 2.01 mins. ^1H NMR 300MHz (d_4 -MeOH) 8.10 (1H, s), 7.99 (1H, s), 7.25 (1H, s), 6.4 (1H, s), 5.14 (1H, s), 3.89 (3H, s), 3.00 (3H, s).

Example 14. **(7-Methoxy-3-methyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydro-quinazolin-2-yl)-acetic acid ethyl ester**

To a solution of Intermediate 2 (0.1g) in DMF (4ml) in a microwave tube was added ethyl (3,3-diethoxy) propionate (0.08ml) and molecular sieves (50mg) followed by PTSA (catalytic). The reaction tube was sealed and heated in the microwave reactor at 100°C for 90mins. The reaction mixture was allowed to

cool down, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting with 50-100% EtOAc/heptane to afford the title compound as a yellow solid (29.5mg, 21%). TLC R_f 0.45 (10% MeOH/DCM). LCMS 346 $[M+H]^+$, RT 2.51 mins. ^1H NMR 300MHz (d_4 -MeOH) 8.42 (1H, s), 8.39 (1H, s), 7.58 (1H,s), 6.68 (1H, s), 5.48 (1H, dd), 4.33 (2H, q), 4.20 (3H, s), 3.33 (3H, s), 3.03 (2H, d), 1.49 (3H, t).

Example 15. **2-(7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydro-quinazolin-2-yl)-N-methyl-acetamide**

Intermediate 2 (0.05g) and N-methylacetoacetamide (0.08ml) were combined in acetic acid (3ml) and heated to 100°C under a slight vacuum. After 2 hours, fresh acetic acid was introduced, and the reaction heated as before for a further 2 hours. The reaction mixture was further concentrated *in vacuo* and the residue purified by column chromatography on silica eluting with EtOAc followed by 5% MeOH/DCM. The residue was triturated with Et_2O /hexane and further purified by preparative silica TLC eluting with 10% MeOH/DCM to afford the title compound as a fluffy yellow solid (12mg, 17%). TLC R_f 0.48 (10% MeOH/DCM). LCMS 345 $[M+H]^+$, RT 1.98 mins. ^1H NMR 300MHz (d_4 -MeOH) 8.08 (1H, s), 8.05 (1H, s), 7.24 (1H, s), 6.33 (1H, s), 3.90 (3H, s), 2.95 (3H, s), 2.58 (5H, m), 1.64 (3H, s).

The following examples 16-22 were prepared in a similar manner to the method in Example 15:-

Example 16. **2-Benzofuran-2-yl-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one**

From Intermediate 2 (58mg) and benzofuran-2-yl methyl ketone (190mg). Purification was by column chromatography on silica eluting with 50% EtOAc/heptane followed by preparative HPLC (Method A) to afford the title compound as an off-white solid (31mg, 33%). TLC R_f 0.43 (50% EtOAc/heptane). LCMS 390 $[M+H]^+$, RT 3.29 mins. ^1H NMR 300MHz ($CDCl_3$) 8.35 (1H, s), 7.85 (1H, s), 7.15-7.50 (5H, m), 6.57, (1H, s), 6.15 (1H, s), 4.92 (1H, s, br), 3.90 (3H, s), 3.18 (3H, s), 2.05 (3H, s).

Example 17. **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-2-(2-phenyl-cyclopropyl)-2,3-dihydro-1H-quinazolin-4-one.**

From Intermediate 2 (50mg) and *trans*-phenyl-2-acetylcyclopropane (CAS 827-92-9) (120mg). Purification was by column chromatography on silica eluting with 50% EtOAc/heptane followed by preparative HPLC (Method A) to afford the title compound as an off-white solid (47mg, 60%). LCMS 390
5 [M+H]⁺, RT 3.44 mins. ¹H NMR 300MHz (CDCl₃) 8.30 (1H, s), 7.85 (1H, s), 7.05-7.40 (6H, m), 6.20 (1H, d), 4.50 and 4.70 (1H, 2xs, br, diastereomers), 3.90 (3H, d), 3.05 (3H, d), 1.65-2.15 (2H, m), 1.40 (3H, d), 1.0-1.20 (2H, m).

Example 18. **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-2-phenoxymethyl-2,3-dihydro-1H-quinazolin-4-one.**

10 From Intermediate 2 (50mg) and phenoxy-2-propanone (150mg). Purification was by column chromatography on silica eluting with 50% EtOAc/heptane followed by preparative HPLC (Method A) to afford the title compound as an off-white solid (66mg, 88%). TLC R_f 0.08 (50% EtOAc/heptane). LCMS 380 [M+H]⁺, RT 3.23 mins. ¹H NMR 300MHz (CDCl₃) 8.30 (1H, s), 7.85 (1H, s),
15 7.35 (1H, s), 7.20-7.30 (2H, m), 7.00 (1H, t), 6.85 (1H, d), 6.15 (1H, s), 4.90 (1H, s, br), 4.25 (1H, d), 3.95 (1H, d), 3.90 (3H, s), 3.18 (3H, s), 1.75 (3H, s).

Example 19. **2-[2-(2,6-Dichloro-phenyl)-vinyl]-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one.**

20 From Intermediate 2 (66mg) and 2,6-dichlorobenzylidene acetone (190mg). Purification was by column chromatography on silica eluting with 50% EtOAc/heptane followed by preparative HPLC (Method A) to afford the title compound as an off-white solid (26mg, 20%). TLC R_f 0.39 (50% EtOAc/heptane). LCMS 380 [M+H]⁺, RT 3.62 mins. ¹H NMR 300MHz (CDCl₃)
25 8.35 (1H, s), 7.85 (1H, s), 7.35 (1H, s), 7.25-7.30 (2H, m), 7.10 (1H, t), 6.55 (1H, d), 6.20 (2H, dd), 4.55 (1H, s, br), 3.95 (1H, d), 3.90 (3H, s), 3.15 (3H, s), 1.75 (3H, s).

Example 20. **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl—2-(2-thiophen-2-yl-vinyl)-2,3-dihydro-1H-quinazolin-4-one.**

30 From Intermediate 2 (50mg) and *trans*-4-(2-thienyl)-3-buten-2-one (86mg). Purification was by column chromatography on silica eluting with 50% EtOAc/heptane followed by preparative HPLC (Method A) to afford the title compound as an off-white solid (24mg, 31%). TLC R_f 0.21 (50% EtOAc/heptane). LCMS 382 [M+H]⁺, RT 3.23 mins. ¹H NMR 300MHz

(CDCl₃) 8.35 (1H, s), 7.85 (1H, s), 7.35 (1H, s), 7.20 (1H, d), 6.95 (2H, m), 6.70 (1H, d), 6.15 (1H, s), 6.05 (1H, d), 4.45 (1H, s, br), 3.95 (3H, s), 3.10 (3H, s), 1.75 (3H, s).

Example 21 **2-[2-(4-Chlorophenyl)-vinyl]-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one.**

5 From Intermediate 2 (60mg) and 4-(4-chlorophenyl)but-3-ene-2-one (88mg). Purification was by column chromatography on silica eluting with 5% MeOH/DCM followed by preparative HPLC (Method A) to afford the title compound as an off-white solid (29mg, 29%). TLC R_f 0.29 (5% MeOH/DCM).
10 LCMS 410 [M+H]⁺, RT 3.54 mins. ¹H NMR 300MHz (d₆-DMSO) 8.30 (1H, s), 7.95 (1H, s), 7.25-7.40 (3H, m), 7.35 (1H, d), 7.25 (1H, s), 6.40-6.50 (2H, m), 6.35 (1H, s), 3.90 (3H, s), 2.95 (3H, s), 1.70 (3H, s).

Example 22. **2-(2-Furan-2-yl-vinyl)-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one.**

15 From Intermediate 2 (50mg) and 4-(2-furyl)-3-buten-2-one (75mg). Purification was by column chromatography on silica eluting with 50% EtOAc/heptane followed by preparative HPLC (Method A) to afford the title compound as an off-white solid (21mg, 29%). LCMS 366 [M+H]⁺, RT 3.06 mins. ¹H NMR 300MHz (CDCl₃) 8.35 (1H, s), 7.85 (1H, s), 7.36 (1H, s), 7.34 (1H, s), 6.10-6.40 (5H, m), 4.45 (1H, s, br), 3.90 (3H, s), 3.08 (3H, s), 1.75 (3H, s).

Example 23 **2-(2-Furan-2-yl-vinyl)-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one.**
(enantiomer 1)

25 Racemic Example 22 (40mg) was separated using CHIRALPAK AD 250*4.6mm 10μm column eluting with ethanol + 0.1% DEA to afford enantiomer 1 as an off-white solid (17mg). LCMS 366 [M+H]⁺, RT 3.05 mins. ¹H NMR 400MHz (CDCl₃) 8.35 (1H, s), 7.85 (1H, s), 7.30 (1H, s), 7.28(1H, s), 6.30-6.40 (2H, m), 6.25 (1 H, d), 6.10-6.20(2H, m), 4.75 (1H, s, br), 3.90 (3H, s), 3.05 (3H, s), 1.75 (3H, s).
30

Example 24 **2-(2-Furan-2-yl-vinyl)-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one.**
(enantiomer 2)

Racemic Example 22 (40mg) was separated using CHIRALPAK AD 250*4.6mm 10 μ m column eluting with ethanol + 0.1% DEA to afford enantiomer 2 as an off-white solid (19mg). LCMS 366 [M+H]⁺, RT 3.05 mins. ¹H NMR 400MHz (CDCl₃) 8.35 (1H, s), 7.85 (1H, s), 7.30 (1H, s), 7.28 (1H, s), 6.30-6.40 (2H, m), 6.25 (1 H, d), 6.10-6.20(2H, m), 4.65 (1H, s, br), 3.92 (3H, s), 3.10 (3H, s), 1.75 (3H, s).

Example 25 **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-2-styryl-2,3-dihydro-1H-quinazolin-4-one**

A solution of Intermediate 2 (50mg), *trans*-4-phenyl-3-buten-2-one (100mg) and PTSA (1mg) in DMF (2ml) was heated in a sealed tube in a microwave reactor to 170°C for 30 mins. After cooling, the mixture was concentrated *in vacuo* and the residue purified by preparative HPLC (Method A) to yield the title compound as an off-white solid (19mg, 25%). LCMS 376 [M+H]⁺, RT 3.32 mins. ¹H NMR 300MHz (CDCl₃) 8.35 (1H, s), 7.85 (1H, s), 7.2-7.4 (6H, m), 6.60 (1H, d), 6.30 (1H, d), 6.15 (1H, s), 4.51 (1H, s), 3.93 (3H, s), 3.09 (3H, s), 2.81 (3H, s).

The following examples 26 – 28 were prepared in a similar manner to the method in Example 25:-

Example 26 **4-(7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)butyronitrile**

From Intermediate 2 (50mg) and 5-oxohexanenitrile (100mg). Purification by preparative HPLC (Method A) gave the title compound as an off-white solid (25mg, 37%). LCMS 341 [M+H]⁺, RT 2.50 mins. ¹H NMR 300MHz (CDCl₃) 8.30 (1H, s), 7.87 (1H, s), 7.36 (1H, s), 6.14 (1H, s), 4.25 (1H, brs), 3.95 (3H, s), 3.05 (3H, s), 2.3-2.5 (2H, m), 1.55-2.2 (7H, m).

Example 27. **But-2-enoic acid 2-[2-(7-methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)acetoxylethyl ester**

From Intermediate 2 (50mg) and 2-acetoxyethyl methylacrylate (47mg). Purification by column chromatography on silica eluting with 50-100% EtOAc/heptane provided the title compound as a glassy solid (13mg, 15%). TLC R_f 0.69 (EtOAc). LCMS 444 [M+H]⁺, RT 2.99 mins. ¹H NMR 300MHz

(d₄-MeOH) 8.19 (1H, s), 8.13 (1H, s), 7.35 (1H, s), 7.00 (1H, s), 6.39 (1H, s), 6.05 (1H, s), 5.60 (1H, s), 4.2-4.3 (4H, m), 4.00 (3H, s), 3.10 (3H, s), 3.00 (1H, d), 2.75 (1H, d), 1.90 (3H, s), 1.75 (3H, s).

Example 28. **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-2-**

5 **phenylethynyl-2,3-dihydro-1H-quinazolin-4-one**

From Intermediate 2 (65mg) and 4-phenyl-3-butyne-2-one (77μl). Purification by column chromatography on silica eluting with 5% MeOH/DCM, followed by preparative HPLC (Method A), yielded the title compound as a cream solid (28mg, 29%). TLC R_f 0.35 (5% MeOH/DCM). LCMS 374 [M+H]⁺, RT 3.38 mins. ¹H NMR 300MHz (d₄-MeOH) 8.27 (1H, s), 8.25 (1H, s), 7.42 (1H, s), 7.3-7.4 (5H, m), 6.52 (1H, s), 4.07 (3H, s), 3.23 (3H, s), 2.05 (3H, s).

Example 29. **[2-(7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)ethyl]carbamic acid tert-butyl ester**

15 A solution of Intermediate 2 (100mg) and *tert*-butyl 3-oxobutylcarbamic acid (340mg) in DMF (3ml) was heated in a sealed tube in a microwave reactor to 140°C for 30 mins. After cooling, the solvent was evaporated under vacuum, and the residue purified by preparative HPLC (Method A) to yield the title compound as a beige solid (9mg, 5%). LCMS 417 [M+H]⁺, RT 2.96 mins. ¹H NMR 400MHz (d₆-DMSO) 8.30 (1H, s), 7.91 (1H, s), 7.38 (1H, s), 7.15 (1H, s), 6.83 (1H, t), 6.31 (1H, s), 3.90 (3H, s), 3.05-3.15 (1H, m), 2.85-2.95 (4H, m), 2.0-2.1 (1H, m), 2.7-2.8 (1H, m), 1.44 (3H, s), 1.35 (9H, s).

Example 30. **2-(3-Hydroxypropyl)-7-methoxy-2-methyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one**

25 To a suspension of Intermediate 2 (50mg) in anhydrous DCE (10ml) was added 3-acetyl-1-propanol (43μl) followed by PTSA (catalytic). The reaction mixture was heated to reflux under a nitrogen atmosphere for 18 hours and then cooled and concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting with 5-10% MeOH/DCM to give the title compound as a yellow solid (59 mg, 89%). TLC R_f 0.21 (8% MeOH/DCM). LCMS 318 [M+H]⁺, RT 1.91 mins. ¹H NMR 300MHz (d₄-MeOH/CDCl₃) 8.20 (1H, s), 7.92 (1H, s), 7.32 (1H, s), 6.22 (1H, s), 3.95 (3H, s), 3.6 (2H, m), 1.65-1.90 (4H, m), 1.53 (3H, s).

Example 31. **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-2-trifluoromethyl-2,3-dihydro-1H-quinazolin-4-one**

Intermediate 2 (100mg), 1,1,1-trifluoroacetone (40 μ l), MgSO₄ (250mg) and PTSA (catalytic) were combined in 10% anhydrous DMF/anhydrous DCE
5 (3ml) and heated in a sealed tube in a microwave reactor to 130°C for 30 mins. After cooling, boron trifluoride diethyl etherate (41 μ l) was added and the reaction mixture heated in a sealed tube in a microwave reactor to 130°C for a further 30 mins. The reaction was then cooled, concentrated *in vacuo* and the residue purified by preparative HPLC (Method A) to furnish the title
10 compound (17mg, 12%). TLC R_f 0.74 (EtOAc). LCMS 342 [M+H]⁺, RT 2.95 mins. ¹H NMR 300MHz (d₄-MeOH) 8.20 (1H, s), 8.16 (1H, s), 7.37 (1H, s), 6.42 (1H, s), 4.00 (3H, s), 3.18 (3H, s), 1.88 (3H, s).

Example 32. **2-Furan-2-yl-7-methoxy-3-methyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one**

15 Intermediate 2 (100mg), 2-furaldehyde (39mg), MgSO₄ (250mg) and PTSA (catalytic) were combined in anhydrous DCE (5ml) and heated to reflux under a nitrogen atmosphere for 1.5 hours. After cooling, borontrifluoride diethyletherate (41 μ l) was added and the reaction mixture heated to reflux for a further 18 hours. After cooling once more, the reaction mixture was diluted
20 with EtAOc (20ml) and washed with NaHCO₃ solution (20ml). The organic layer was separated, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC (Method A) to yield the title compound as an off-white solid (12 mg, 9%). TLC R_f 0.66 (EtOAc). LCMS 326 [M+H]⁺, RT 2.62 mins. ¹H NMR 300MHz (d₄-MeOH) 8.23 (1H, s), 8.20 (1H, s), 7.50 (1H, m), 7.47 (1H, s), 6.45 (1H, s), 6.39 (1H, m), 6.34 (1H, m),
25 5.94 (1H, s), 4.00 (3H, s), 3.14 (3H, s).

Example 33. **2-[2-(2,2-Dimethyl-5-oxo-tetrahydro-furan-3-yl)-ethyl]-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one**

30 To a solution of Intermediate 2 (50mg) in acetic acid (3ml) was added 4-hydroxy-4-methyl-3-(3-oxobutyl)valeric acid gamma lactone (111mg). The reaction mixture was heated to 120°C for 30mins in a sealed tube using microwaves. The solvent was removed *in vacuo* and the residue purified by

column chromatography on silica eluting with EtOAc to afford the title compound as a white solid (19.3mg, 23%). LCMS 414 [M+H]⁺, RT 2.64 mins. ¹H NMR 300MHz (d₄-MeOH) 8.20 (1H, s), 8.15 (1H, s), 7.35 (1H, s), 6.35 (1H, s), 4.0 (3H, s), 3.05 (3H, s), 2.75-1.2 (7H, m), 1.55 (3H, s), 1.45 (3H, s), 1.25 (3H, s).

Examples 34-35 were prepared in a similar manner to the method in Example 33:-

Example 34. **2-(4-Chloro-phenylsulfanylmethyl)-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one**

From Intermediate 2 (50mg) and (4-chlorophenylthio)propan-2-one (2ml). Purification by preparative HPLC (Method A) afforded the title compound as an off-white solid (7mg, 8%). LCMS 430 [M+H]⁺, RT 3.41 mins. ¹H NMR 300MHz (CDCl₃) 8.35 (1H, s), 7.95 (1H, s), 7.4 (1H, s), 7.3 (4H, s), 5.6 (1H, s), 4.55 (1H, br s), 3.85 (3H, s), 3.6-3.10 (2H, m), 3.1 (3H, s), 1.75 (3H, s).

Example 35. **N-[2-(7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydro-quinazolin-2-ylmethoxy)-phenyl]-acetamide**

From Intermediate 2 (50mg) and α-acetyl-ortho-acetamideside (124mg). Purification by column chromatography on silica eluting with 50-100% EtOAc/heptane rising to 5% MeOH/DCM afforded the title compound as an off-white solid (22mg, 25%). LCMS 437 [M+H]⁺, RT 2.62 mins. ¹H NMR 300MHz (d₄-MeOH) 8.2 (2H, m), 7.8 (1H, m), 7.35 (1H, s), 7.15-6.95 (3H, m), 6.35 (1H, s), 4.45-4.1 (2H, m), 4.0 (3H, s), 3.2 (3H, s), 2.1 (3H, s), 1.8 (3H, s).

Example 36. **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydro-quinazoline-2-carboxylic acid**

To a solution / suspension of Intermediate 2 (150mg) in DCM (12ml) under nitrogen was added MgSO₄ (300mg), pyruvic acid (0.05ml) and PTSA (catalytic). The reaction mixture was heated at reflux for 75 mins. After cooling to room temperature boron trifluoride diethyl etherate (0.11ml) was added dropwise and the reaction heated at reflux for 10 hours. The DCM was removed *in vacuo* and EtOAc (200ml) was added to the residue. Saturated

NaHCO₃ solution was added to the mixture until all the solid had dissolved. The aqueous layer was acidified to pH2 using 2M HCl and extracted with EtOAc (3 x 200ml). The organic layers were combined, dried over MgSO₄, filtered and concentrated *in vacuo* to give a yellow solid. A portion of this was purified by HPLC (Method A) to afford the title compound as a white solid (5mg). TLC R_f 0.15 (10% MeOH/DCM). LCMS 318 [M+H]⁺, RT 2.21 mins. ¹H NMR 300MHz (d₆-DMSO) 8.46 (1H, s), 8.37 (1H, s), 7.63 (1H, s), 7.22 (1H, s), 4.08 (3H, s), 3.54 (3H, s), 2.59 (3H, s).

Example 37. 7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-2-phenethyl-2,3-dihydro-1H-quinazolin-4-one

A solution of Example 25 (10mg) in EtOH (10ml) was treated with 10% palladium on carbon (catalytic) and stirred under an atmosphere of hydrogen gas at atmospheric pressure for 3 hours. The catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The residue was purified by preparative TLC eluting with 75% EtOAc/hexane to furnish the title compound as a white solid (7mg, 70%). LCMS 378 [M+H]⁺, RT 3.33 mins. ¹H NMR 300MHz (CDCl₃) 8.31 (1H, s), 7.85 (1H, s), 7.1-7.4 (6H, m), 5.91 (1H, s), 4.15 (1H, s), 3.93 (3H, s), 3.12 (3H, s), 2.85 (1H, m), 2.65 (1H, m), 2.45 (1H, m), 1.95 (1H, m), 1.60 (3H, s).

Example 38 was prepared in a similar manner to the method in Example 37:-

Example 38. 7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-2-tetrahydrofuranylethyl-2,3-dihydro-1H-quinazolin-4-one

From Example 22 (50mg). Purification by preparative HPLC (Method A) afforded the title compound as an off-white solid (13mg, 25%). LCMS 372 [M+H]⁺, RT 2.70mins. ¹H NMR 300MHz (CDCl₃) 8.30 (1H, s), 7.85 (1H, s), 7.35 (1H, s), 6.10 (1H, d), 4.40 and 5.00 (1H, 2xs), 3.95 (3H, s), 3.70-3.95 (3H, m), 3.05 (3H, d), 3.40-2.20 (8H, m), 1.55 (3H, d).

Example 39. 7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydro-quinazoline-2-carboxylic acid (2,2-dimethyl-propyl)-amide

Example 36 (35.7mg), HBTU (49.3mg), neopentylamine (22.7mg) and DIPEA (0.12ml) were combined in DMF (5ml) and stirred for 5 days at room

temperature under an atmosphere of nitrogen. The solvents were then removed *in vacuo* and the reaction mixture taken up in EtOAc (50ml) and washed with 2N HCl (3x30ml). The organic layer was separated, dried over MgSO₄, filtered and concentrated *in vacuo* to give a yellow oil. Purification by preparative HPLC (Method A) afforded the title compound as an off-white solid (3.1mg, 7%). TLC R_f 0.44 (10% MeOH/DCM). LCMS 387 [M+H]⁺, RT 2.70mins. ¹H NMR 300MHz (d₄-MeOH) 8.25 (1H, s), 8.20 (1H, s), 7.4 (1H, s), 6.55 (1H, s), 4.05 (3H, s), 3.25 (3H, s), 3.15-2.8 (2H, m), 1.85 (3H, s), 0.75 (9H, s).

10 **Example 40.** **7-Methoxy-2,2,3-trimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazoline-4-thione**

A solution of Example 2 (50mg), and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (70mg) in toluene (1ml) was heated to reflux for 2 hours under nitrogen. The reaction mixture was purified by column chromatography on silica eluting with 50% EtOAc/hexane to yield the title compound as a yellow solid (21.1mg, 40%). TLC R_f 0.56 (EtOAc). LCMS 304 [M+H]⁺, RT 2.93 mins. ¹H NMR 300MHz (d₄-MeOH) 8.98 (1H, s), 8.40 (1H, s), 7.54 (1H, s), 6.55 (1H, s), 4.20 (3H, s), 3.83 (3H, s), 1.80 (6H, s).

20 **Example 41.** **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-(2-quinolin-2-yl-vinyl)-2,3-dihydro-1H-quinazoline-4-one**

A solution of Intermediate 2 (100mg), and 4-quinolin-2-yl-but-3-en-2-one (80mg) in a mixture of DMF (5ml) and toluene (5ml), was heated at 70°C under vacuum for 2 hours. The reaction mixture was evaporated *in vacuo* and purified by preparative HPLC (Method A) to yield the title compound as an off-white solid (53 mg, 62%). LCMS 427 [M+H]⁺, RT 2.72 mins. ¹H NMR 300MHz (CDCl₃) 8.35 (1H, s), 8.10 (1H, d), 8.00 (1H, d), 7.85 (1H, s), 7.65-7.80 (2H, m), 7.45 (2H, m), 7.30 (1H, s), 6.90 (2H, m), 6.20 (1H, s), 4.90 (1H, br s), 3.90 (3H, s), 3.25 (3H, s), 1.85 (3H, s).

30 Examples 42-52 were prepared in a similar manner to the method in Example 41:-

Example 42. **2-(2-Cyclohexyl-vinyl)-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazoline-4-one**

From Intermediate 2 (50mg), and 4-cyclohexyl-but-3-en-one (CAS 7152-32-1) (31mg). The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC (Method A) to yield the title compound as an off-white solid (8 mg, 10%). LCMS 381[M+H]⁺, RT 4.17 mins. ¹H NMR 300MHz (CDCl₃) 8.30 (1H, s), 7.85 (1H, s), 7.35 (1H, s), 6.10 (1H, s), 5.50-5.80 (2H, m), 4.30 (1H, br s), 3.90 (3H, s), 3.00 (3H, s), 2.00 (1H, m) 1.65-1.80 (5H, m), 1.65 (3H, s), 1.00-1.35 (5H, m).

Example 43. **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-(2-pyridin-3-yl-vinyl)-2,3-dihydro-1H-quinazoline-4-one**

10 From Intermediate 2 (100mg), and 4-pyridin-3-yl-but-3-en-2-one (CAS 28447-16-7) (100mg). The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC (Method B) to yield the title compound as an off-white solid (37 mg, 25%). LCMS 377 [M+H]⁺, RT 1.84 mins. ¹H NMR 300MHz (CDCl₃) 8.55 (1H, s), 8.50 (1H, d), 8.35 (1H, s), 7.85 (1H, s), 7.65 (2H, d),
15 7.35 (1H, s), 7.25 (1H, m), 6.65 (1H, d), 6.30 (1H, d), 6.20 (1H, s), 4.85 (1H, br s), 3.90 (3H, s), 3.10 (3H, s), 1.80 (3H, s).

Example 44. **N-{4-[2-(7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydro-quinazolin-2-yl)-vinyl]phenyl}-acetamide**

20 From Intermediate 2 (60mg), and 4-(4-acetylamino-phenyl)-but-3-en-2-one (CAS 27861-32-1) (100mg). The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC (Method B) to yield the title compound as a yellow solid (7 mg, 7%). LCMS 433 [M+H]⁺, RT 2.74 mins. ¹H NMR 300MHz (CDCl₃) 8.25 (1H, s), 7.95 (1H, s), 7.50 (2H, d), 7.30 (3H, m), 6.55 (1H, d),
25 6.25 (1H, br s), 6.20 (1H, d), 3.95 (3H, s), 3.05 (3H, s), 2.15 (3H, s), 1.75 (3H, s).

Example 45. **2-Benzyloxymethyl-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazoline-4-one**

30 From Intermediate 2 (100mg), and benzyloxy acetone (128μL). The reaction mixture was evaporated *in vacuo* and purified by column chromatography on silica eluting with 2-3% MeOH/DCM to yield the title compound as an off-white solid (84 mg, 53%). LCMS 394 [M+H]⁺, RT 3.25 mins. ¹H NMR 300MHz (d₄-MeOH) 8.15 (1H, s), 8.10 (1H, d), 7.30 (1H, s), 7.25 (5H, m), 6.30 (1H, s),

4.50 (2H, m), 3.95 (3H, s), 3.65 (1H, d), 3.55 (1H, d), 3.05 (3H, s), 1.65 (3H, s).

Example 46. **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-2-quinolin-2-yl-2,3-dihydro-1H-quinazolin-4-one**

5 From Intermediate 2 (100mg) and 1-quinolin-2-yl-ethanone (CAS 1011-47-8) (200mg). Purification by column chromatography on silica eluting with 0-3% MeOH/DCM gave a solid which was washed sparingly with ether to yield the title compound as a solid (112mg, 69%). TLC R_f 0.46 (5% MeOH/DCM). LCMS 401 [M+H]⁺, RT 3.24 mins. ¹H NMR 300MHz (MeOH) 8.35 (1H, d),
10 8.21 (1H, s), 8.20 (1H, s), 8.09 (1H, dd), 7.92 (1H, dd), 7.78 (1H, td), 7.73 (1H, d), 7.61 (1H,td), 7.31 (1H, s), 6.40 (1H, s) 3.77 (3H, s), 3.17 (3H, s), 2.15 (3H s).

Example 47. **7-Methoxy-2,3-dimethyl-2-[2-(1-methyl-1H-imidazol-2-yl-vinyl)-6-oxazol-5-yl-2,3-dihydro-1H-quinazoline-4-one**

15 From Intermediate 2 (100mg), and Intermediate 13 (50mg). The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC (Method A) to yield the title compound as an off-white solid (12 mg, 15%). LCMS 380 [M+H]⁺, RT 1.54 mins. ¹H NMR 300MHz (CDCl₃) 8.35 (1H, s), 7.85 (1H, s),
20 7.35 (1H, s), 7.05 (1H, s), 6.85 (1H, s), 6.65 (1H, d), 6.25 (1H, d), 5.30 (1H, br s), 3.85 (3H, s), 3.70 (3H, s), 3.10(3H, s), 1.75 (3H, s).

Example 48. **7-Methoxy-2-(7-methoxybenzofuran-2-yl)-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one**

25 From Intermediate 2 (100mg) and 2-acetyl-7-methoxybenzofuran (228mg). Purification column chromatography on silica eluting with 50-100% EtOAc/heptane yielded the title compound as a solid (10 mg, 6%). TLC R_f 0.66 (10% MeOH/DCM). LCMS 420 [M+H]⁺, RT 3.29 mins. ¹H NMR 400MHz (d₄-MeOH) 8.14-8.16 (2H, 2 x s), 7.30 (1H, s), 7.08 (2H, m), 6.82 (1H, dd),
30 6.60 (1H, s), 6.39 (1H, s), 3.94 (3H, s), 3.92 (3H, s), 3.15 (3H s), 2.08 (3H, s).

Example 49. **2-[2-Phenylvinyl]-7-methoxy-3-methyl-2-trifluoromethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one.**

From Intermediate 2 (100mg) and trans-1,1,1-trifluoro-4-phenyl-3-buten-2-one (160mg). Purification by preparative HPLC (method A) yielded the title compound as a solid (11.7mg, 7%). TLC R_f 0.32 (5% MeOH/DCM). LCMS 430 [M+H]⁺, RT 3.84 mins. ¹H NMR 300MHz (d₄-MeOH) 8.25 (1H, s), 8.24 (1H, s), 7.64-7.67 (2H, m), 7.34-7.52 (5H, m), 6.75 (1H, d), 6.57 (1H, s), 4.05 (3H, s), 3.18 (3H s).

Example 50. 2-(5-Chloro-benzofuran-2-yl)-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one

From Intermediate 2 (64mg) and 2-acetyl-5-chlorobenzofuran (100mg). Purification by column chromatography on silica eluting with 50-100% EtOAc/heptane, followed by trituration of the residue with diethyl ether, gave the title compound as a yellow solid (7.6mg, 7%). TLC R_f 0.72 (10% MeOH/DCM). LCMS 424 [M+H]⁺, RT 3.56 mins. ¹H NMR 300MHz (d₄-MeOH) 8.18 (2H, s), 8.24 (1H, s), 7.55 (1H, d), 7.43 (1H, d), 7.32 (1H, s), 7.26 (1H, dd), 6.65 (1H, s), 6.40 (1H, s), 3.95 (3H, s), 3.15 (3H s), 2.08 (3H, s).

Example 51. 5-[2-(7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)vinyl]thiophene-3-carboxylic acid methyl ester

From Intermediate 2 (74mg) and Intermediate 10 (60mg). A crude product precipitated from the reaction, which was purified by preparative HPLC (method C) to provide the title compound as a solid (12 mg, 9%). LCMS 440 [M+H]⁺, RT 3.15 mins. ¹H NMR 400MHz (d₆-DMSO) 8.31 (1H, s), 8.20 (1H, s), 7.95 (1H, s), 7.51 (1H, s), 7.47 (1H, s), 6.68 (1H, d), 6.38 (1H, s), 6.18 (1H, d), 3.91 (3H, s), 3.86 (3H s), 2.95 (3H, s), 1.70 (3H, s).

Example 52. 2-(2-Furan-2-yl-vinyl)-7-methoxy-2-methyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one.

From Intermediate 6 (100mg) and 4-(2-furyl)-3-buten-2-one (117mg). Purification by preparative HPLC (method A) yielded the title compound as a solid (38mg, 25%). LCMS 352 [M+H]⁺, RT 2.76 mins. ¹H NMR 300MHz (d₆-DMSO) 8.35(1H, s), 8.24 (1H, s), 7.96 (1H, s), 7.53 (1H, s), 7.34 (1H, s), 6.52 (1H, s), 6.42 (1H, s), 6.36 (1H, d), 6.15 (1H, d), 3.97 (3H, s), 1.63 (3H, s).

Example 53. 2-(2-(4-Fluorophenyl)-vinyl)-2-yl-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one

A solution of Intermediate 2 (75mg), 4-(4-fluorophenyl)but-3-en-2-one (100mg) and cerium (III) chloride heptahydrate (226mg) was stirred with 4A molecular sieves (300mg) in ethanol at 55°C for 2 hours. The reaction mixture was filtered and concentrated *in vacuo* and the residue was taken up in DCM (300ml) and washed with 1N HCl. The organic layer was separated, dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by preparative HPLC (method A) gave the title compound as a solid (1.6mg, 1.3%). TLC R_f 0.48 (5% MeOH/DCM). LCMS 394 [M+H]⁺, RT 3.37 mins. ¹H NMR 300MHz (d₄-MeOH) 8.20 (1H, s), 8.19 (1H, s), 7.45 (2H, m), 7.36 (1H, s), 7.05 (2H, t), 6.61 (1H, d), 6.43 (1H, s), 6.33 (1H, d), 4.02 (3H, s), 3.13 (3H, s) 1.84 (3H, s).

Example 54 was prepared in a similar manner to the method in Example 53:-

Example 54. 2-(2-(4-methoxyphenyl)-vinyl)-2-yl-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one

From Intermediate 2 (100mg) and 4-(4-methoxyphenyl)but-3-en-2-one (143mg). Purification by column chromatography eluting with 0-3% MeOH/DCM yielded the title compound as a solid (13.5mg, 8%). TLC R_f 0.56 (5% MeOH/DCM). LCMS 406 [M+H]⁺, RT 3.30 mins. ¹H NMR 300MHz (d₄-MeOH) 8.19 (1H, s), 8.18 (1H, s), 7.36 (1H, d), 7.34 (1H, s), 6.88 (1H, d), 6.58 (1H, d), 6.42 (1H, s), 6.22 (1H, d), 4.00 (3H, s), 3.80 (3H, s), 3.20 (3H,s), 1.82 (3H,s).

Example 55. 7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydroquinazoline-2-carboxylic acid ethyl ester

Ethyl pyruvate (0.52 ml) and Intermediate 2 (1.10 g) were dissolved in ethanol (40 ml), treated with concentrated hydrochloric acid (5 drops) and heated to reflux under a calcium chloride guard tube. After 90 hours, the reaction was cooled and concentrated *in vacuo*. The residue was dissolved in EtOAc (50ml) and washed with 50% saturated NaHCO₃/water (30ml), water (20ml) and saturated brine (20ml). The organic layer was separated, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Trituration of the residue with DCM (5ml, then 3 x 2ml) followed by drying *in vacuo* afforded the title compound as a light beige solid (1.01g, 66%). TLC R_f 0.28 (5% MeOH/DCM). LCMS 346 [M+H]⁺, RT 2.66 mins. ¹H NMR 300MHz (CDCl₃)

8.33 (1H, s), 7.88 (1H, s), 7.39 (1H, s), 6.25 (1H, s), 4.96 (1H, s), 4.13 (2H, m), 3.95 (3H, s), 3.21 (3H, s), 1.81 (3H, s), 1.20 (3H, m).

Example 56. **(E)-3-(7-methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydro-quinazolin-2-yl)-acrylic acid methyl ester**

5 A mixture of Intermediate 2 (304mg), methyl-trans-4-oxo-2-pentanoate (157mg) and PTSA (catalytic) in isopropyl acetate (60ml) was heated to 95°C using Dean-Stark apparatus for 24 hours. The solvent was removed *in vacuo* and the residue was taken up in EtOAc (150ml) and washed with water (100ml).
10 The organic layer was separated, dried over MgSO₄, filtered and concentrated *in vacuo* to give the title compound as a yellow solid (350mg, 80%) LCMS 358 [M+H]⁺, RT 2.61 mins. ¹H NMR 300MHz (d₆-DMSO) 8.32 (1H, s), 7.95 (1H, s), 7.60 (1H, s), 7.32 (1H, s), 7.76 (1H, d), 6.38 (1H, s), 5.75 (1H, d), 3.92 (3H, s), 3.60 (3H, s), 2.95 (3H, s), 1.70 (3H, s).

15

Example 57 was prepared in a similar manner to the method in Example 56:-

Example 57. **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydro-quinazolin-2-yl)-acrylonitrile.**

A mixture of Intermediate 2 (390mg), 4-oxo-pent-2-enenitrile (CAS 55728-58-0) (220mg) and PTSA (catalytic) in isopropyl acetate (20ml) was heated to 100°C using Dean-Stark apparatus for 3 hours. The solvent was removed *in vacuo* and the residue purified by preparative HPLC (method A) to give the title compound as an off-white solid (70mg, 9%). LCMS 325 [M+H]⁺, RT 2.53 mins. ¹H NMR 300MHz (CDCl₃) 8.30 (1H, s), 7.95 (1H, s), 7.40 (1H, s), 6.60 (1H, d), 6.20 (1H, s), 5.45 (1H, d), 5.00 (1H, br s), 3.90 (3H, s), 3.05 (3H, s), 1.80 (3H, s).
25

Example 58. **2-[2-(1H-imidazole-4-yl)-vinyl]-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one**

30 A mixture of Intermediate 8 (30mg) in acetic acid was stirred at 50°C for 6 hours. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (Method C) to yield the title compound as a solid (2mg, 11%). TLC R_f 0.1 (10% MeOH/DCM). LCMS 366 [M+H]⁺, RT 1.60 mins. ¹H NMR 300MHz (d₄-MeOH) 8.22 (1H, s), 8.20 (1H, s), 7.75 (1H, d), 7.35 (1H,

s), 7.17 (1H, s), 6.57 (1H, d), 6.45 (1H, s), 6.35 (1H, d), 3.90 (3H, s), 3.13 (3H, s), 1.84 (3H, s).

Example 59. **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-2-[2-(1-oxo-pyridin-3-yl)-vinyl]-2,3-dihydro-1H-quinazolin-4-one**

5 A mixture of Example 43 (60mg) and 3-chloroperoxybenzoic acid (55mg) in DCM (20ml) was stirred at 0°C for 10 hours and then at RT for 16 hours. The mixture was taken up in DCM (150ml) and extracted with 1N HCl (150ml). The acid layer was basified with Na₂CO₃ and re-extracted with DCM (2x150ml). The organic layers were combined, dried over MgSO₄, filtered and
10 concentrated *in vacuo*. The residue was purified by column chromatography eluting with 10-15% MeOH/DCM to give a solid which was dissolved in DCM and filtered. The filtrate was concentrated *in vacuo* to yield the title compound as a solid (18mg, 29%). TLC R_f 0.13 (5% MeOH/DCM). LCMS 393 [M+H]⁺, RT 2.09 mins. ¹H NMR 300MHz (d₄-MeOH) 8.42 (1H, s), 8.23 (1H, d), 8.22
15 (1H, s), 8.21 (1H, s), 7.71 (1H, d), 7.49 (1H, dd), 7.35 (1H, s), 6.64 (1H, d), 6.55 (1H, d), 6.42 (1H, s), 4.02 (3H, s), 3.13 (3H, s), 1.84 (3H, s).

Example 60. **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydroquinazoline-2-carboxylic acid phenylamide**

Aniline (0.011ml) was added to an ice-cold solution of Example 36 (35mg) in
20 anhydrous DMF (5ml) under nitrogen. After 5 minutes, EDC (25mg) was added and the reaction was stirred in the ice-bath, warming to room temperature over 18 hours. The DMF was evaporated *in vacuo* and the residue dissolved in EtOAc (25ml) and washed with 1% citric acid solution (20ml), water (20ml), saturated NaHCO₃ (20ml) and saturated brine (20ml).
25 The organic layer was separated, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue (21mg) was purified by preparative HPLC (method A) to yield the title compound as a white solid (5.3mg, 12%). TLC R_f 0.28 (5% MeOH/DCM). LCMS 393 [M+H]⁺, RT 2.85 mins. ¹H NMR 300MHz (d₄-MeOH) 8.25 (1H, s), 8.23 (1H, d), 7.58 (2H, m), 7.40 (1H, s), 7.35 (2H, m),
30 7.16 (1H, m), 6.52 (1H, s), 4.04 (3H, s), 3.17 (3H, s), 1.85 (3H, s).

Example 61. **2-Ethynyl-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one**

An ice-cold solution of Intermediate 9 (0.983 g) in THF (40 ml) was treated dropwise with a solution of tetrabutylammonium fluoride (1M in THF, 2.79 ml)

and the reaction stirred in the ice-bath for 1 hour. Acetic acid (0.25ml) was added and the mixture stirred in the ice-bath for 15 minutes, then at room temperature for 15 minutes. The mixture was concentrated *in vacuo* and the solid residue triturated with saturated NaHCO₃ and water. After drying *in vacuo*, the solid was recrystallised from boiling EtOAc (100 ml) to furnish the title compound as a crystalline yellow solid (0.566 g, 72%). TLC R_f 0.41 (5% MeOH/DCM). LCMS 298 [M+H]⁺, RT 2.61 mins. ¹H NMR 400MHz (d₄-MeOH) 8.24 (1H, s), 8.22 (1H, s), 7.40 (1H, s), 6.48 (1H, s), 4.04 (3H, s), 3.14 (3H, s), 2.98 (1H, s), 1.93 (3H, s).

10 **Example 62.** **Cyclohexanecarboxylic acid [2-(7-methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydro-quinazolin-2-yl)ethyl]amide**

A crude sample of Intermediate 12 (50 mg) was combined with cyclohexanecarboxylic acid (20 mg), HBTU (60 mg) and TEA (0.1ml) in DMF (2ml), and stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* and the residue purified by preparative HPLC (method A) to yield the title compound as a yellow glass (16mg, 24%). LCMS 427 [M+H]⁺, RT 2.66 mins. ¹H NMR 400MHz (d₄-MeOH) 8.14 (1H, s), 8.09 (1H, s), 7.83 (1H, m), 7.29 (1H, s), 6.32 (1H, s), 3.95 (3H, s), 3.38 (1H, m), 3.15 (1H, m), 3.04 (3H, s), 2.20 (1H, m), 2.10 (1H, m), 1.88 (1H, m), 1.62-1.78 (5H, m), 1.54 (3H, s), 1.20-1.42 (5H, m).

Example 63 was prepared in a similar manner to the method in Example 62:-

25 **Example 63.** **N-[2-(7-methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)ethyl]benzamide**

From Intermediate 12 (50mg) and benzoic acid (19mg). Purification by preparative HPLC (method A) provided the title compound as a yellow glass (18mg, 27%). LCMS 421 [M+H]⁺, RT 2.70 mins. ¹H NMR 400MHz (d₄-MeOH) 8.51 (1H, m), 8.14 (1H, s), 8.10 (1H, s), 7.77 (2H, m), 7.50 (1H, m), 7.42 (2H, m), 7.28 (1H, m), 6.27 (1H, s), 3.84 (3H, s), 3.60 (1H, m), 3.41 (1H, m), 3.09 (3H, s), 2.35 (1H, m), 2.01 (1H, m), 1.60 (3H, s).

30 **Example 64.** **Piperidine-1-carboxylic acid [2-(7-methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-1,2,3,4-tetrahydro-quinazolin-2-yl)ethyl]amide**

A solution of Intermediate 12 (50 mg) and TEA (0.1 ml) in DMF (2 ml) was treated with 1-piperidinecarbonyl chloride (0.02 ml), and stirred at room temperature for 20 hours. The mixture was concentrated *in vacuo* and the residue purified by preparative HPLC (method A) to furnish the title compound as a pale yellow glass (16 mg, 24%). LCMS 428 [M+H]⁺, RT 2.65 mins.
¹H NMR 400MHz (d₄-MeOH) 8.15 (1H, s), 8.10 (1H, s), 7.29 (1H, s), 6.31 (1H, s), 3.95 (3H, s), 3.27-3.41 (5H, m), 3.15 (1H, m), 3.05 (3H, s), 2.21 (1H, m), 1.90 (1H, m), 1.46-1.62 (9H, m).

Example 65. **2-(2-Benzofuran-2-yl-vinyl)-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one**

A solution of Intermediate 7 (50mg) in EtOH (10ml) was treated with a solution of KOH (6.5mg) in ethanol (1ml) at 0°C. After 10 minutes the reaction was treated with 2-benzofuran benzaldehyde [CAS 95353-39-2](23mg). The mixture was stirred at room temperature for 2 hours and then heated at reflux for 1 hour. The solvent was removed *in vacuo* and the residue purified by column chromatography eluting with 20-75% EtOAc/heptane the title compound as an off-white solid (42 mg, 84%). LCMS 416 [M+H]⁺, RT 3.59 mins. ¹H NMR 300MHz (CDCl₃) 8.35(1H, s), 7.85 (1H, s), 7.50 (1H, d), 7.40 (2H, m), 7.20 (2H, m), 6.60 (1H, s), 6.45 (2H, d), 6.15 (1H, s), 4.65 (1H, br s), 3.90 (3H, s), 3.15 (3H, d), 1.80 (3H, s).

Examples 66-67 were prepared in a similar manner to the method in Example 65:-

Example 66. **2-(4,4-Dimethyl-pent-1-enyl)-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one**

From Intermediate 7 (60mg) and dimethylbutyraldehyde (15mg). Purification by preparative HPLC (method C) yielded the title compound as a solid (3.2mg, 6%). TLC R_f 0.36 (5% MeOH/DCM). LCMS 370 [M+H]⁺, RT 3.72 mins. ¹H NMR 300MHz (d₄-MeOH) 8.22 (1H, s), 8.17 (1H, s), 7.35 (1H, s), 6.42 (1H, s), 5.68 (1H, d), 5.50 (1H, d), 4.00 (3H, s), 3.08 (3H, d), 1.72 (3H, s), 0.78 (9H, s).

Example 67. **2-(2-Benzo[1,3]dioxol-4-yl-vinyl)-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-one**

From Intermediate 7 (60mg) and 2,3-methylene dioxybenzaldehyde (22mg). Purification by preparative HPLC (method C) yielded the title compound as a solid (3.2mg, 6%). TLC R_f 0.33 (5% MeOH/DCM). LCMS 420 $[M+H]^+$, RT 3.30 mins. ^1H NMR 300MHz (d_4 -MeOH) 8.22 (1H, s), 8.20 (1H, s), 7.37 (1H, s), 6.88-6.73 (3H, m), 6.55 (2H, s), 6.43 (1H, s), 6.00 (2H, s), 4.00 (3H, s), 3.12 (3H, s), 1.83 (3H, s).

Example 68. **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-2-[(E)-2-pyridin-2-yl-vinyl]-2,3-dihydro-1H-quinazolin-4-one**

From Intermediate 7 (120mg) and 2-pyridine carboxaldehyde (33mg). Purification by preparative HPLC (Method C) yielded the title compound as a solid (3.4mg, 3%). LCMS 377 $[M+H]^+$, RT 1.97 mins. ^1H NMR 300MHz (d_4 -MeOH) 8.59 (1H, m), 8.20 (2H, s), 7.80 (1H, td), 7.52 (1H, d), 7.36 (1H, s), 7.29 (1H, td), 6.82 (2H, d), 6.65 (2H, d); 6.45 (2H, s); 4.04 (3H, s), 3.19 (3H, s), 1.88 (3H, s).

Example 69. **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-2-[(E)-(5-phenyl-furan-2-yl)-vinyl]-2,3-dihydro-1H-quinazolin-4-one**

A solution of Intermediate 7 (137mg) in THF (10ml) was treated with *n*-butyl lithium (0.2ml, 2.5M) at 0°C. After 3 minutes, the reaction was treated with 5-phenyl-2-furalanaldehyde (60mg) and the mixture was allowed to warm to room temperature and stirred for 3 hours. The solvent was removed *in vacuo* and the residue purified by preparative HPLC (Method C) to yield the title compound as an off-white solid (11.5 mg, 7.4%). LCMS 442 $[M+H]^+$, RT 3.66 mins. ^1H NMR 300MHz (d_4 -MeOH) 8.20 (2H, s), 7.70 (2H, dd), 7.43-7.22 (4H, m), 6.77 (1H, d), 6.46 (1H, d), 6.44 (1H, d), 6.41 (1H, d), 6.31 (1H, d), 4.00 (3H, s), 3.10 (3H, d), 1.81 (3H, s).

Example 70 was prepared in a similar manner to the method in Example 69:-

Example 70. **7-Methoxy-2,3-dimethyl-2-[(E)-2-(1-methyl-1H-indol-3-yl)-vinyl]-6-oxazol-5-yl]-2,3-dihydro-1H-quinazolin-4-one**

From Intermediate 7 (100mg) and 1-methylindole-2-carboxaldehyde (53mg). Purification by preparative HPLC (Method C) yielded the title compound as a solid (12.3mg, 8.7%). LCMS 429 $[M+H]^+$, RT 3.48 mins. ^1H NMR 300MHz (d_4 -MeOH) 8.26 (1H, s), 8.24 (1H, s), 7.52 (1H, d), 7.40 (1H, s), 7.37 (1H, d),

7.18 (1H, t), 7.04 (1H, t), 6.77 (1H, d); 6.69 (1H, s); 6.47 (1H, s); 6.39 (1H, d)
4.04 (3H, s), 3.72 (3H, s), 3.18 (3H, s), 1.90 (3H, s).

**Example 71. 7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-2-[(E)-2-(1-oxy-
pyridin-2-yl)-vinyl]-2,3-dihydro-1H-quinazolin-4-one**

5 To a stirred solution of Example 68 (40mg) in DCM (20ml) at 0°C was added
3-chloroperoxybenzoic acid (134mg) and the mixture was allowed to warm to
room temperature and stirred for 24 hours. The reaction mixture was diluted
with DCM (50ml) and washed with saturated aqueous Na₂CO₃ (25ml). The
organic layer was separated, dried over MgSO₄, filtered and the solvent
10 removed *in vacuo*. The residue was purified by preparative HPLC (method C)
to yield the title compound as an off-white solid (0.6 mg, 1.4%). LCMS 393
[M+H]⁺, RT 2.10 mins. ¹H NMR 300MHz (d₄-MeOH) 8.33 (1H, d), 8.21 (1H,
s), 8.20 (1H, s); 7.83 (1H, dd), 7.53 (1H, t), 7.41 (1H, td), 7.37 (1H, s); 7.26
(1H, d), 6.93 (1H, d), 6.46 (1H, s), 4.02 (3H, s), 3.17 (3H, d), 1.75 (3H, s).

15 **Example 72. (E)-3-(7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-
1,2,3,4-tetrahydro-quinazolin-2-yl)-acrylic acid**

Example 56 (100mg), LiOH.H₂O (17.6mg), THF (10ml) and H₂O (2ml) were
combined and stirred at room temperature for 1 hour. All solvents were
removed *in vacuo* and the resulting residue triturated with 1N HCl to give a
20 yellow solid, 20mg of which was purified by preparative HPLC (Method A) to
give the title compound as a white glass (2.1mg). LCMS 344 [M+H]⁺, RT 2.21
mins. ¹H NMR 300MHz (d₄-MeOH) 8.15 (1H, s), 8.1 (1H, s), 7.3 (1H, s), 6.7
(1H, d), 6.35 (1H, s), 5.85 (1H, d), 3.95 (3H, s), 3.05 (3H, s), 1.75 (3H, s).

25 **Example 73. (E)-3-(7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-4-oxo-
1,2,3,4-tetrahydro-quinazolin-2-yl)-N-methyl-N-
phenyl-acrylamide**

Example 72 (20mg), HBTU (21mg), Et₃N (0.1ml), DMF (2ml) and *N*-methyl
aniline (2 drops) were combined and stirred at room temperature for 48 hrs.
The reaction was concentrated *in vacuo* and the resulting residue purified by
30 preparative HPLC (Method A) to give the title compound as a tan glass
(2.4mg, 10%). LCMS 433 [M+H]⁺, RT 2.65 mins. ¹H NMR 300MHz (d₄-
MeOH) 8.5 (1H, s), 8.25 (1H, s), 8.05 (1H, s), 7.4 (1H, s), 7.3-7.15 (3H, m),
7.0-6.9 (2H, m), 6.65 (1H, d) 6.1 (1H, s), 5.75 (1H, d), 3.9 (3H, s), 3.2 (3H, s),
2.95 (3H, s), 1.65 (3H, s).

Example 74. **7-Methoxy-2,3-dimethyl-6-oxazol-5-yl-2-((E)-3-oxo-3-piperidin-1-yl-propenyl)-2,3-dihydro-1H-quinazolin-4-one**

Example 72 (20mg), HBTU (21mg), DMF (2ml) and piperidine (3 drops) were
5 combined and stirred at room temperature for 24 hours. The reaction was
concentrated *in vacuo* and the resulting residue purified by preparative HPLC
(Method A) to give the title compound as a tan glass (3.5mg, 15%). LCMS
411 [M+H]⁺, RT 2.52 mins. ¹H NMR 300MHz (d₄-MeOH) 8.15 (1H, s), 8.1
(1H, s), 7.3 (1H, s), 6.45 (1H, d) 6.4 (1H, s), 6.3 (1H, d), 3.95 (3H, s), 3.6-3.2
10 (4H, m), 3.05 (3H, s), 1.75 (3H, s), 1.6-1.25 (6H, m).

Example 75. **2-[(E)-2-(6-Chloro-pyridin-3-yl)-vinyl]-7-methoxy-2,3-dimethyl-6-oxazol-5-yl-2,3,4a,8a-tetrahydro-1H-quinazolin-4-one**

A solution of 2-chloropyridine-5-carboxaldehyde (CAS 23100-12-1) (0.2g) and
15 1-triphenylphosphoranylidene-2-propanone (0.45g) in THF (15ml) were stirred
at room temperature for 18 hours. The solvent was removed *in vacuo* and the
residue purified by column chromatography on silica eluting with 25-100%
EtOAc/heptane to yield the desired product as an off-white solid. This was
dissolved in DMF/toluene (10ml/10ml) and treated with Intermediate 2 (0.31g)
20 and PTSA (2mg). The reaction mixture was heated at 150°C under Dean-
Stark conditions for 90 mins. The solvent was removed *in vacuo* and the
residue purified by column chromatography on silica eluting with 2-10%
MeOH/DCM to afford the title compound as a yellow solid (0.42g, 75%). A
sample of this was further purified by preparative HPLC (Method C) to afford
25 the title compound. TLC R_f 0.20 (10% MeOH/DCM). LCMS 411 [M+H]⁺, RT
2.97 mins. ¹H NMR 300MHz (CDCl₃) 8.34 (1H, s), 8.33-8.32 (1H, d), 7.85
(1H, s), 7.74-7.70 (1H, dd), 7.36 (1H, s), 7.28-7.25 (1H, d), 7.39 (1H, s), 6.53-
6.47 (1H, d), 6.33-6.27 (1H, d), 6.17 (1H, s), 4.50 (1H, s), 3.94 (3H, s), 3.11
(3H, s), 1.83 (3H, s).

30 **Example 76.** **2-Benzofuran-2-yl-7-methoxy-3-methyl-6-oxazol-5-yl-2-trifluoromethyl-2,3,4a,8a-tetrahydro-1H-quinazolin-4-one**

A solution of Intermediate 2 (100mg), 1-benzofuran-2-yl-2,2,2-trifluoro-ethanone (CAS 75277-96-2) (171mg) and PTSA (5mg) in toluene/DMF (10ml/5ml) was heated to 80°C and the toluene removed under reduced pressure. More toluene was added to the reaction mixture (3 x 10ml) and the
5 procedure repeated three times. The DMF was removed *in vacuo* and the residue purified by preparative HPLC (Method C) to afford the title compound as a pale yellow solid (19.6mg, 11%). TLC R_f 0.41 (10% MeOH/DCM). LCMS 444 [M+H]⁺, RT 3.78 mins. ¹H NMR 300MHz (CDCl₃) 8.39 (1H, s), 7.88 (1H, s), 7.67-7.65 (1H, d), 7.56-7.54 (1H, d), 7.44-7.39 (1H, m); 7.39 (1H, s), 7.35-
10 7.30 (1H, m), 7.11 (1H, s), 6.24 (1H, s), 5.07 (1H, s), 3.95 (3H, s), 3.03 (3H, s).

The ability of the compounds of the invention to inhibit the IMPDH enzymes may be determined using the following assays:

15 Abbreviations used:

IMPDH Inosine 5'-monophosphate dehydrogenase

IMP Inosine 5'-monophosphate XMP Xanthosine 5'-monophosphate

NAD β- Nicotinamide adenine dinucleotide

NADH β- Nicotinamide adenine dinucleotide, reduced form

20 MTT 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

Assay Protocol 1

IMPDH catalyses the NAD dependent oxidation of IMP to XMP with concomitant reduction of the coenzyme. IMPDH activity was determined by monitoring the production of the fluorescent product, NADH. Assays were
25 performed in a final volume of 200μl containing IMPDH (2μg), NAD (100μM), IMP (100μM), 1% DMSO, 30mM KCl and 100mM Tris/HCl, pH7.5. Fluorescence (excitation 340nm / emission 465nm) was read continuously at 25°C for 30 minutes. From this data, initial rates (i.e. change in fluorescence intensity per minute) were calculated. To determine the IC₅₀ values, test
30 compounds were prepared at an initial concentration of 1.0mM in 100% DMSO, then diluted in assay buffer to 0.2mM. Further dilutions were made in assay buffer containing 20% DMSO, prior to diluting 20-fold into the assay, to allow testing across the range 0.3nM to 10μM.

The functional effect of the compounds of the invention may be demonstrated using the following assay:

PBMC Proliferation Assay

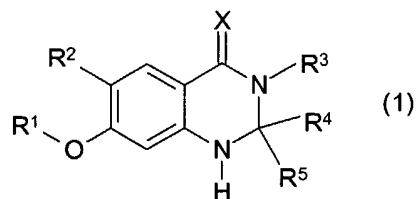
- 5 Peripheral blood mononuclear cells were isolated from freshly taken human blood using standard procedures. Cells were plated out in RPMI medium containing 5% human serum in the presence and absence of inhibitor. PHA (25 μ l of 30 μ g/ml solution to each well) was added and the plates were incubated at 37°C in an atmosphere of 95% air/5% CO₂ for 48 hours. 0.5 μ Ci
- 10 of tritiated thymidine was added to each well and the plates were incubated for a further 18 hours. The contents of the plate were transferred to a filter plate and the cells washed with saline. The plates were dried, microscintillation fluid was added to each well and the plate was counted on a scintillation counter. IC₅₀ values were calculated by plotting inhibitor
- 15 concentration versus %inhibition.

The assay described above can be carried out using anti-CD3 (40 μ l of 3750ng/ml concentration to each well) stimulation instead of PHA.

- 20 Compounds of the invention such as compounds of the Examples generally inhibit IMPDH enzymes with IC₅₀ values of 5 μ M or below.

CLAIMS

1. A compound of formula (1):



5 wherein:

X is an oxygen or sulfur atom;

R¹ is an aliphatic, cycloaliphatic or cycloalkyl-alkyl- group;

R² is an optionally substituted heteroaromatic group or a –CN group;

R³ is a group $-(Alk^1)_m L^1 (Alk^2)_n R^6$ in which m and n, which may be the same or different, is each zero or the integer 1, Alk¹ and Alk², which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain, L¹ is a covalent bond or a linker atom or group and R⁶ is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;

15 R⁴ is a group $-(Alk^3)_p L^2 (Alk^4)_q R^7$ in which p and q, which may be the same or different, is each zero or the integer 1, Alk³ and Alk⁴, which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain, L² is a covalent bond or a linker atom or group and R⁷ is a hydrogen or halogen atom or a –CN group or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;

R⁵ is a hydrogen atom or an optionally substituted aliphatic group;

and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

2. A compound according to Claim 1 in which Alk¹, Alk², Alk³ or Alk⁴, when present in compounds of formula (1), which may be the same or different, is each an optionally substituted C₁₋₆alkylene chain.

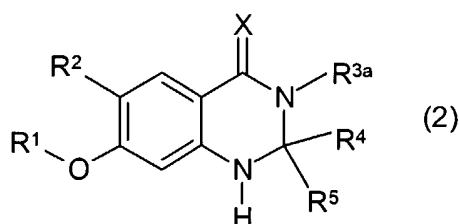
3. A compound according to Claim 2 in which Alk¹, Alk², Alk³ or Alk⁴, which may be the same or different, is each a –CH₂–, –(CH₂)₂– or –(CH₂)₃– chain.

4. A compound according to Claim 1 wherein Alk³ is an optionally substituted C₂₋₆alkenylene chain or C₂₋₆alkynylene chain.

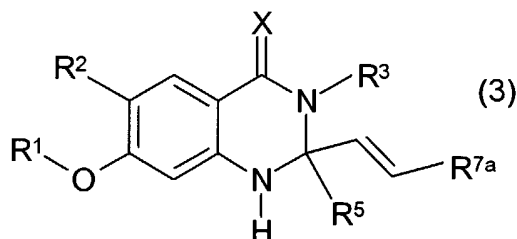
5. A compound according to Claim 4 in which Alk³ is a –CHCH– chain.

6. A compound according to Claim 1 wherein n is zero.
7. A compound according to Claim 1 wherein m is the integer 1.
8. A compound according to any one of Claims 1-7 wherein R^3 is a group $-(Alk^1)_m L^1 (Alk^2)_n R^6$ and R^4 is a group $-(Alk^3)_p L^2 (Alk^4)_q R^7$ in which L^1 or L^2 ,
 5 which may be the same or different, is each a covalent bond or an atom or group selected from $-O-$ or $-S-$ atoms or $-C(O)-$, $-C(S)-$, $-S(O)-$, $-S(O)_2-$, $-C(O)O-$, $-OC(O)-$, $-N(R^8)-$ [where R^8 is a hydrogen atom or a straight or branched C_{1-6} alkyl group], $-CON(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$ or $-N(R^8)S(O)_2-$ groups.
- 10 9. A compound according to Claim 8 wherein L^1 is a covalent bond.
10. A compound according to Claim 8 wherein L^2 is a covalent bond or an $-O-$ or $-S-$ atom or a $-CO-$, $-C(O)O-$, $-CON(R^8)-$ or $-N(R^8)CO-$ group.
11. A compound according to any one of Claims 1 – 10 in which R^7 is an optionally substituted 3-10 membered saturated monocyclic
 15 heterocycloaliphatic, phenyl or heteroaromatic group.
12. A compound according to any of Claims 1-10 wherein R^7 is an optionally substituted C_{3-6} cycloalkyl, 3-7 membered saturated monocyclic heterocycloalkyl, phenyl or heteroaromatic group.
13. A compound according to any one of Claims 1 – 12 in which R^6 is a
 20 hydrogen atom or a morpholin-1-yl, pyrid-4-yl or imidazol-1-yl group.
14. A compound according to any one of Claims 1 - 13 in which R^4 is the group $-Alk^3-L^2-R^7$.
15. A compound according to any one of Claims 1 - 14 in which R^4 is a C_{1-6} alkyl group.
- 25 16. A compound according to any one of Claims 1 - 15 in which R^5 is a hydrogen atom or a C_{1-3} alkyl group.
17. A compound according to any one of Claims 1 – 16 in which X is an O atom.
18. A compound according to any one of Claims 1 – 17 wherein R^1 is a C_{1-6}
 30 alkyl group.
19. A compound according to Claim 18 wherein R^1 is a methyl group.
20. A compound according to any one of Claims 1 – 19 wherein R^2 is a five-membered heteroaromatic group containing one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen.

21. A compound according to Claim 20 wherein R^2 is an oxazolyl group.
22. A compound according to any one of Claims 1-21, which has the formula (2):



- 5 wherein R^1 , R^2 , R^4 , R^5 and X are as defined;
 R^{3a} is a hydrogen atom or a C_{1-6} alkyl group;
 and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.
23. A compound according to any one of Claims 1- 21, which has the formula (3):



- 10 wherein R^1 , R^2 , R^3 , R^5 and X are as defined herein;
 R^{7a} is an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;
 and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.
- 15 24. A pharmaceutical composition comprising a compound according to any of Claims 1 to 23 together with one or more pharmaceutically acceptable carriers, excipients or diluents.
25. A compound according to any of Claims 1 to 23 for use in the treatment of cancer, inflammatory disorders, autoimmune disorders, psoriatic disorders
- 20 and viral disorders.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/03600

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D413/04 C07D413/14 A61K31/517

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 81340 A (IWANOWICZ EDWIN J ;SQUIBB BRISTOL MYERS CO (US); WATTERSON SCOTT H) 1 November 2001 (2001-11-01) the whole document ----	1-25
Y	WO 00 26197 A (SQUIBB BRISTOL MYERS CO) 11 May 2000 (2000-05-11) the whole document -----	1-25



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Fink, D

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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