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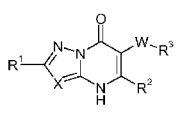
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(54) Title: 4H- [1, 2, 4] TRIAZOLO [5, 1 -B] PYRIMIDIN-7 -ONE DERIVATIVES AS CCR2B RECEPTOR ANTAGONISTS



(57) Abstract: The present invention relates to novel compounds for use in the compositions, to processes for their preparation, to intermediates useful in their preparation and to their use as therapeutic agents. The present invention also relates to pharmaceutical compositions, which comprise compounds that act via antagonism of the CCR2b receptor for which MCP-1 is one of the known ligands and so may be used to treat inflammatory disease, atherosclerosis, diabetes, obesity, cancer, chronic obstructive pulmonary disease (COPD) rheumatoid arthritis and/or neuropathic pain, which is mediated by these receptors.

4H-[1,2,4]TRIAZOLO[5,1-B]PYRIMIDIN-7-ONE DERIVATIVES AS CCR2B RECEPTOR ANTAGONISTS

Technical field of invention

The present invention relates to novel compounds for use in the compositions, to processes for their preparation, to intermediates useful in their preparation and to their use as therapeutic agents. The present invention also relates to pharmaceutical compositions, which comprise compounds that act via antagonism of the CCR2b receptor for which MCP-1 is one of the known ligands and so may be used to treat inflammatory disease, atherosclerosis, diabetes, obesity , cancer, chronic obstructive pulmonary disease (COPD) rheumatoid arthritis and/or neuropathic pain, which is mediated by these receptors.

Background of the invention

Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including rheumatoid arthritis, chronic obstructive pulmonary disease, atherosclerosis and other autoimmune pathologies such as inflammatory bowel disease, diabetes, asthma and allergic diseases. Chemokines also have a role in neuropathic pain, angiogenesis and modulation of chemokines may be beneficial in the treatment of cancer. Chemokines are small secreted molecules belonging to a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C) and Cys-Cys (C-C) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

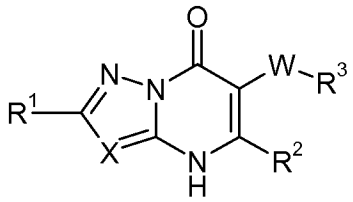
The C-C chemokines include potent chemoattractants of monocytes and lymphocytes such as monocyte chemoattractant proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on activation, Normal T expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2). Studies have demonstrated that the actions of chemokines are mediated by subfamilies of G-protein coupled receptors, among which there are the receptors designated CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5 and CX3CR1. These receptors represent good targets for drug

development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above. WO-2006/067401 discloses piperazine urea compounds useful as modulators of the CCR2b receptor. WO-02/069973 discloses piperidine-piperazine compounds useful as ligands of neurotransmitter receptors. Purandare et al in Bioorganic & Medicinal Chemistry Letters, 2005, 16, 204-207 disclose substituted piperazine compounds useful as CCR4 antagonists. The most preferred compound 8c showed >1000-fold selectivity against *inter alia* the CCR2 chemokine receptor.

Outline of the present invention

The present invention relates to a compound of formula (I)



(I)

wherein

X is NH;

W is-C_{1-4}alkyl-,-C_{1-4}alkyl-O-, -OC_{1-4}alkyl-, -O- or -S- or -S(O)-, wherein said -C_{1-4}alkyl- is optionally substituted with C_{1-2}alkyl or OH;

R^1 is selected from hydrogen, methyl or NH_2;

R^2 is selected from CF_3, halogen, NR^5R^6, SC_{1-6}alkyl, OC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkoxy, aryl, carbocyclyl, heterocyclyl, heteroaryl, C_{1-6}alkyl, carbocyclyl and C_{1-6}alkylheterocyclyl wherein said C_{1-6}alkyl, aryl, carbocyclyl, heterocyclyl or heteroaryl is optionally substituted with one or more groups selected from C_{1-4}alkoxy, C_{1-4}alkyl, OH, heterocyclyl and halogen;

R^3 is phenyl or heteroaryl, wherein said phenyl or heteroaryl is optionally substituted with one or more groups selected from halogen, CF_3, C_{1-4}alkyl, carbocyclyl and C_{1-4}alkoxy;

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

or R^5 and R^6 are joined together to form a heterocyclyl ring containing up to 7 ring atoms, wherein said ring optionally is containing up to 3 atoms selected from nitrogen, oxygen and sulphur, and wherein said heterocyclyl ring is optionally substituted with C_{1-2}alkyl or hydroxyl;

with the proviso that if R^3 is pyridyl then said pyridyl has at least one substituent;
as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.
In another aspect the invention relates to a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

According to one embodiment of the present invention, W is -C_{1-4}alkyl-.

According to another embodiment of the present invention, W is -C_{1-2}alkyl-.

According to another embodiment of the present invention, W is -C_1-alkyl-.

According to one embodiment of the present invention, R^2 is carbocyclyl, C_{1-6}alkyl or heterocyclyl, wherein said carbocyclyl, C_{1-6}alkyl or heterocyclyl is optionally substituted with one or more groups selected from C_{1-4}alkoxy, C_{1-4}alkyl, OH, heterocyclyl and halogen.

According to one embodiment of the present invention, R^2 is carbocyclyl, optionally substituted with one or more groups selected from C_{1-4}alkoxy, C_{1-4}alkyl, OH and halogen.

According to one embodiment of the present invention, said carbocyclyl is not substitituted.

According to one embodiment of the present invention, said carbocyclyl is substituted with OH.

According to one embodiment of the present invention, said carbocyclyl is selected from cyclopropyl, cyclobutyl and cyclopentyl.

According to one embodiment of the present invention, R^2 is C_{1-6}alkyl optionally substituted with one or more groups selected from C_{1-4}alkoxy, C_{1-4}alkyl, heterocyclyl, OH and halogen.

According to another embodiment of the present invention, R^2 is not substituted.

According to another embodiment of the present invention, said C_{1-6}alkyl is substituted with heterocyclyl, C_{1-4}alkoxy, C_{1-4}alkyl or OH.

According to another embodiment of the present invention, R^2 is C_5alkyl.

According to another embodiment of the present invention, R^2 is C_4alkyl.

According to another embodiment of the present invention, R^2 is C_3alkyl.

According to another embodiment of the present invention, R^2 is C_2alkyl.

According to another embodiment of the present invention, R^2 is C_1alkyl.

According to one embodiment of the present invention, said R^2 is heterocyclyl, optionally substituted with one or more groups selected from C_{1-4}alkoxy, C_{1-4}alkyl, OH and halogen.

According to another embodiment of the present invention, said heterocyclyl is not substituted.

According to another embodiment of the present invention, said heterocyclyl is substituted with C_{1-4}alkyl or OH.

According to one embodiment of the present invention, R^3 is phenyl substituted with one or more groups selected from halogen, CF_3, C_{1-4}alkyl and carbocyclyl

According to another embodiment of the present invention, said halogen is fluoro, bromo or chloro.

According to another embodiment of the present invention, said carbocyclyl is cyclopropyl.

According to one embodiment of the present invention, R^3 is heteroaryl.

According to another embodiment of the present invention, said heteroaryl is selected from pyridyl or thiazolyl.

According to another embodiment of the present invention, said heteroaryl is substituted with one or more groups selected from halogen, CF_3, C_{1-4}alkyl and C_{1-4}alkoxy.

The present invention also relates to a compound selected from:

2-Amino-6-[(3-chlorophenyl)methyl]-5-cyclopropyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-Chlorophenyl)methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

5-Cyclobutyl-6-[(3,4-dichlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

5-Cyclobutyl-6-[(3,4-difluorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-Chloro-4-fluoro-phenyl)methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(4-Chloro-3-fluoro-phenyl)methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

5-Cyclobutyl-6-[(5-methyl-3-pyridyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[[4-Chloro-3-(trifluoromethyl)phenyl]methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

5-Cyclobutyl-6-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-Chlorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-Chlorophenyl)methyl]-5-pyrrolidin-1-yl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-Chlorophenyl)methyl]-5-methoxy-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

5-Chloro-6-[(3-chlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-Amino-5-cyclopropyl-6-[(3,4-dichlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-5-ethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-(3-chlorophenoxy)-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-chlorophenyl)methyl]-5-[(2S)-pyrrolidin-2-yl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-(3-chlorophenyl)sulfanyl-5-ethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-chlorophenyl)methyl]-5-(trifluoromethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-chlorophenyl)methyl]-5-methylsulfanyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

5-butoxy-6-[(3-chlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-(3-chlorophenyl)sulfinyl-5-ethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-5-(2-hydroxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-5-(2-hydroxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(6-chloro-2-pyridyl)methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-5-(2-hydroxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(5-chloro-3-pyridyl)methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-chloro-4-fluoro-phenyl)methyl]-5-pyrrolidin-1-yl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-benzyl-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(2,6-dichlorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(4-fluorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3-chlorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-6-[[3,5-bis(trifluoromethyl)phenyl]methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-5-methyl-6-(3-phenylpropyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-benzyl-2,5-dimethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-5-methyl-6-phenethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-5-methyl-6-[[3-(trifluoromethyl)phenyl]methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-6-[(4-bromophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-5-methyl-6-[(5-methylisoxazol-3-yl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-6-[(3,4-dichlorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-6-[(3-chloro-5-fluoro-phenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-6-[(4-chlorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-6-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-6-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-6-[(5-tert-butyl-1,2,4-oxadiazol-3-yl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-5-methyl-6-(m-tolylmethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-6-[[4-methoxy-3-(trifluoromethyl)phenyl]methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-5-methyl-6-[[4-methyl-3-(trifluoromethyl)phenyl]methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-5-methyl-6-[[5-(trifluoromethyl)-2-furyl]methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-6-[(5-chloro-2-thienyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(4-methoxyphenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-5-methyl-6-(2-pyridylmethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one ;

2-amino-6-[(3-chlorophenyl)methyl]-5-propyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3-chlorophenyl)methyl]-5-isopropyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3-methoxyphenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-5-methyl-6-(3-pyridylmethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-5-methyl-6-(4-pyridylmethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3-chlorophenyl)methyl]-5-ethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3-fluorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3-bromophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3-chlorophenyl)methyl]-5-isopentyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3-chlorophenyl)methyl]-5-(methoxymethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-chlorophenyl)methyl]-5-(methoxymethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

2-amino-6-[(3-chlorophenyl)methyl]-5-(hydroxymethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-chlorophenyl)methyl]-5-(hydroxymethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-5-butyl-6-[(3-chlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-chlorophenyl)methyl]-5-tetrahydropyran-4-yl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-chlorophenyl)methyl]-5-isopropyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-chlorophenyl)methyl]-5-cyclopentyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-chlorophenyl)methyl]-5-cyclopropyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-chlorophenyl)methyl]-5-(2-methoxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3-chloro-2-fluoro-phenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(2-fluorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-6-[(2-chlorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-6-[(2-methoxyphenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
5-cyclobutyl-6-[(5,6-dichloro-3-pyridyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
5-cyclobutyl-6-[(3-fluorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
5-cyclobutyl-6-[(3,5-difluorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chlorophenyl)methyl]-5-cyclobutyl-2-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
5-tert-butyl-6-[(3-chlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chlorophenyl)methyl]-5-morpholino-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chlorophenyl)methyl]-5-(4-methylpiperazin-1-yl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chlorophenyl)methyl]-5-(3-hydroxypyrrolidin-1-yl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chlorophenyl)methyl]-5-(1-piperidyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3,4-dichlorophenyl)methyl]-5-ethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
5-cyclobutyl-6-[[3-fluoro-4-(trifluoromethyl)phenyl]methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-bromophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
5-cyclobutyl-6-[[4-methyl-3-(trifluoromethyl)phenyl]methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
5-cyclobutyl-6-[(3-isopropylphenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chlorophenyl)methyl]-5-(cyclopropylmethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-6-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-5-(2-hydroxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-5-(2-methoxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one
6-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-5-(2-methoxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-chloro-4-fluoro-phenyl)methyl]-5-(ethyl-methyl-amino)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-bromophenyl)methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[2-(3-chlorophenyl)ethyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[2-(4-chlorophenoxy)ethyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one; and
5-cyclobutyl-6-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-2-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

In another aspect the invention relates to the above individually named compound or a pharmaceutically-acceptable salt thereof.

Compounds of formula (I) can be used in the treatment of diseases in which the chemokine receptor belongs to the C-C receptor subfamily, more preferably the target chemokine receptor is the CCR2 receptor.

CCR2 is a receptor for the Monocyte chemoattractant protein-1 (MCP-1). MCP-1 is a member of the chemokine family of pro-inflammatory proteins which mediate leukocyte chemotaxis and activation. MCP-1 is a C-C chemokine which is potent T-cell and monocyte chemoattractant. MCP-1 has been implicated in the pathophysiology of a large number of inflammatory diseases including rheumatoid arthritis, chronic obstructive pulmonary disease, atherosclerosis, inflammatory bowel disease and neuropathic pain. In addition, MCP-1 has been implicated in the pathogenesis of insulin resistance associated with obesity and in the progression of several tumours. .

MCP-1 acts through the CCR2 receptor. MCP-2, MCP-3 and MCP-4 may also act, at least in part, through this receptor. Therefore in this specification, when reference is made to “inhibition or antagonism of MCP-1” or “MCP-1 mediated effects” this includes inhibition or antagonism of MCP-2 and/or MCP-3 and/or MCP-4 mediated effects when MCP-2 and/or MCP-3 and/or MCP-4 are acting through the CCR2 receptor.

The term "C_{m-n}" or "C_{m-n} group" refers to any group having m to n carbon atoms. As used herein, "alkyl", used alone or as a suffix or prefix, is intended to include both branched and straight chain saturated aliphatic hydrocarbon groups having from 1 to 12 carbon atoms or if a specified number of carbon atoms is provided then that specific number would be intended. For example "C_{1-6} alkyl" denotes alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-

propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, and hexyl. In the case where a subscript is the integer 0 (zero) the group to which the subscript refers to indicates that the group may be absent, i.e. there is a direct bond between the groups.

The term "alkoxy", unless stated otherwise, refers to radicals of the general formula –O-R, wherein R is selected from a hydrocarbon radical. For example "C_{1-6} alkoxy" denotes alkoxy having 1, 2, 3, 4, 5 or 6 carbon atoms. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy and isobutoxy.

The term "halo" includes fluoro, chloro, bromo and iodo. References to aryl groups include aromatic carbocylic groups such as phenyl and naphthyl.

A "heterocyclyl" is a saturated monocyclic ring containing 4-7 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH_2- group can optionally be replaced by a -C(O)-, or a ring nitrogen and/or sulphur atom may be optionally oxidized to form the *N*-oxide and/or the S-oxides. In one aspect of the invention, "heterocyclyl" is a saturated monocyclic ring containing 5 or 6 atoms. Examples of, but not limited to, the term "heterocyclyl" are morpholino, piperidyl, tetrahydropyranyl, 1,4-dioxanyl, 1,3-dioxolanyl, 1,2-oxathiolanyl, piperazinyl, pyrrolidinyl, tetrahydrofuranyl, thiomorpholino, homopiperazinyl and hexahydropyrimidyl.

A "heteroaryl" is a partially saturated or unsaturated, mono or bicyclic ring containing 5-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH_2- group can optionally be replaced by a -C(O)-, or a ring nitrogen and/or sulphur atom may be optionally oxidized to form the *N*-oxide and/or the S-oxides. Examples of, but not limited to, the term "heteroaryl" are pyridyl, isothiazolyl, indolyl, quinolyl, thienyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzodioxolyl, 1,3-dioxoisoindolin-2-yl, thiadiazolyl, thiazolidinyl, imidazolyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, isoxazolyl, pyrrolyl, 4-pyridone, 1-isoquinolone, 2-pyrrolidone, 4-thiazolidone, pyridine-*N*-oxide, quinoline-*N*-oxide, oxadiazolyl, imidazopyridyl, pyrazolopyrimidiyl, thieno(3,2-d)pyrazolyl, benzo[1,2,3]thiadiazolyl, dihydro-1H-indolyl, thiazolyl, pyrazolopyridinyl, dihydro-1H-benzotriazolyl, benzofuryl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzopyrrolyl, quinazolyl and quinoxalyl. In one aspect of the invention a "heteroaryl" is a unsaturated monocyclic ring containing 5 or 6 atoms of which at least one atom is chosen

from nitrogen, sulphur or oxygen, it may, unless otherwise specified, be carbon or nitrogen linked.

A "carbocyclyl" is a saturated or partially unsaturated monocyclic carbon ring that contains 3-12 atoms, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-. In one aspect of the invention, "carbocyclyl" is a monocyclic ring containing 3 to 6 atoms. Examples of, but not limited to, the term"carbocyclyl" are cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, and cyclopentenyl, cyclohexyl and cyclohexenyl.

An "aryl" is a partially unsaturated or unsaturated, mono or bicyclic ring containing 5-12 atoms, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-. In one aspect of the invention, "aryl" is a monocyclic ring containing 5 to 6 carbon atoms. In another aspect of the invention, "aryl" is a bicyclic ring containing 10 atoms. In such bicyclic rings one of the rings is aromatic, while the other ring may be aromatic or partially hydrogenated. Examples and suitable values are phenyl, naphtyl, tetralinyl and indenyl.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric acid.

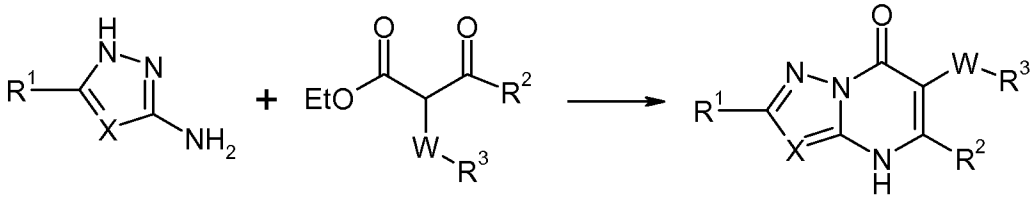
The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like diethyl ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used.

Methods of preparation

Route A

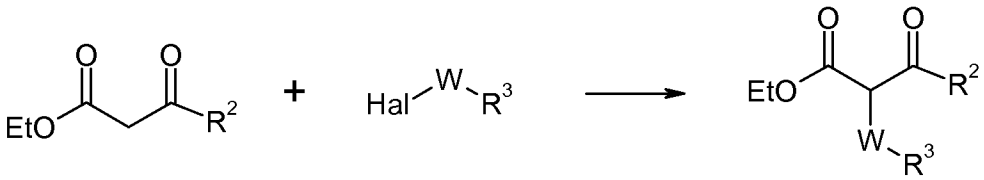
The compounds of formula (I), wherein R^2 is C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl, or C-linked heterocyclyl and R^1, R^2, X and W are as defined for formula (I) above may be prepared as follows:

By reaction of a compound of Formula (II) with a compound of Formula (III):



II III I

Compounds of formula (III) may be prepared by reaction of a beta-keto ester compound of formula (IV) with an alkyl halo compound of formula V (wherein W and R^3 are as defined as for formula (I) above)

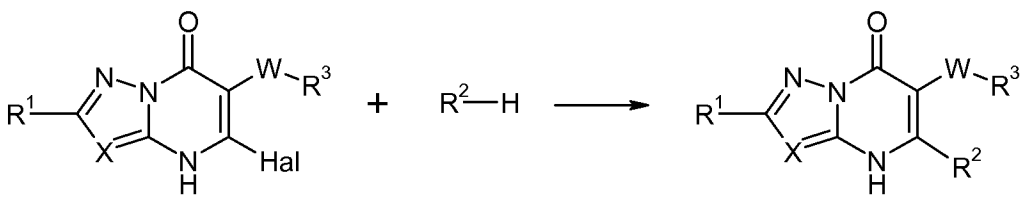


IV V III

Route B

The compounds of Formula (I) wherein R^2 is C_{1-4}alkoxy, C_{1-4}thioalkyl, NR^5R^6, or N-linked heterocyclyl and R^1, R^2, R^5, R^6, X and W are as defined for formula (I) above, may be prepared as follows:

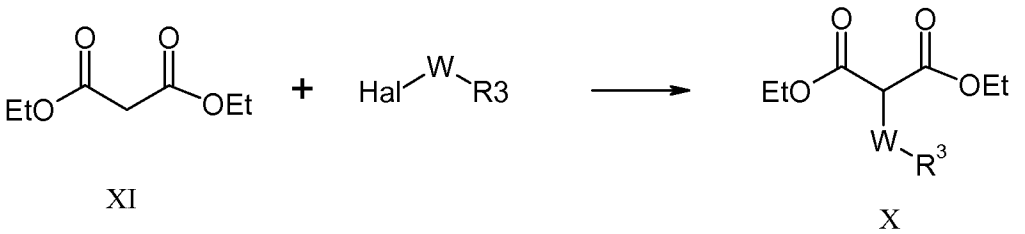
By reaction of an amine, alcohol or thio compound of formula VII with a halo compound of Formula VI:



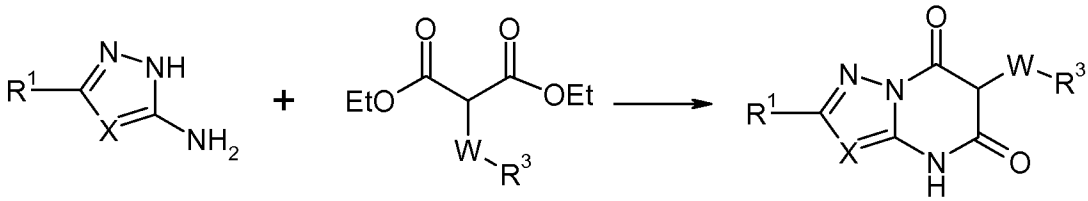
VI VII I

Compounds of formula VI (wherein R^1, R^3, X and W are as defined for formula (I) above) may be prepared by reaction of di-halo compounds of formula VIII (wherein R^1, R^3, X and

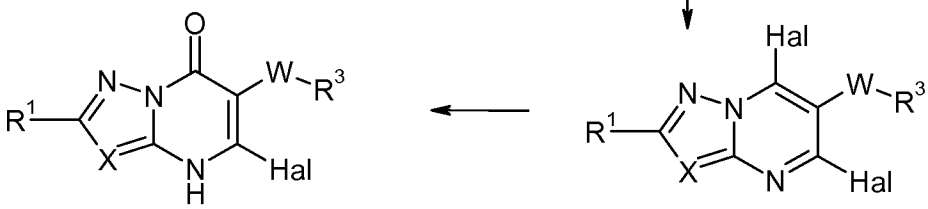
W are as defined for formula (I) above) with, for example, potassium trimethylsilanolate. Compounds of formula VIII may be prepared by reaction of a compound of formula (I)X (wherein R^1, R^3, X and W are as defined for formula (I) above) with, for example, phosphorous oxychloride. Compounds of formula (IX) may be prepared by reacting a compound of Formula (II) (wherein $R^1$and X are as defined for formula (I)) above with a compound of formula X (wherein $R^3$and W are as defined for formula (I) above) Compounds of formula X may be prepared by reaction of di ethyl malonate compound of formula XI with an alkyl halo compound of formula V (wherein W and R^3 are as defined as for formula (I) above).



XI X



II X IX

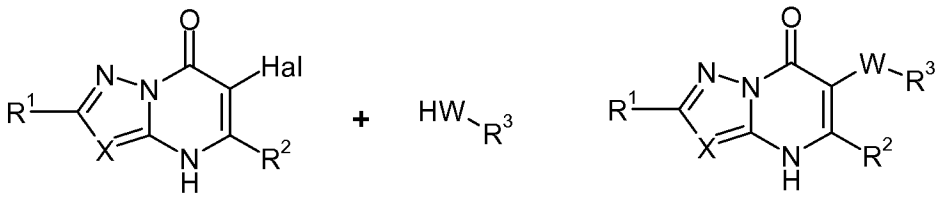


VI VIII

Route C

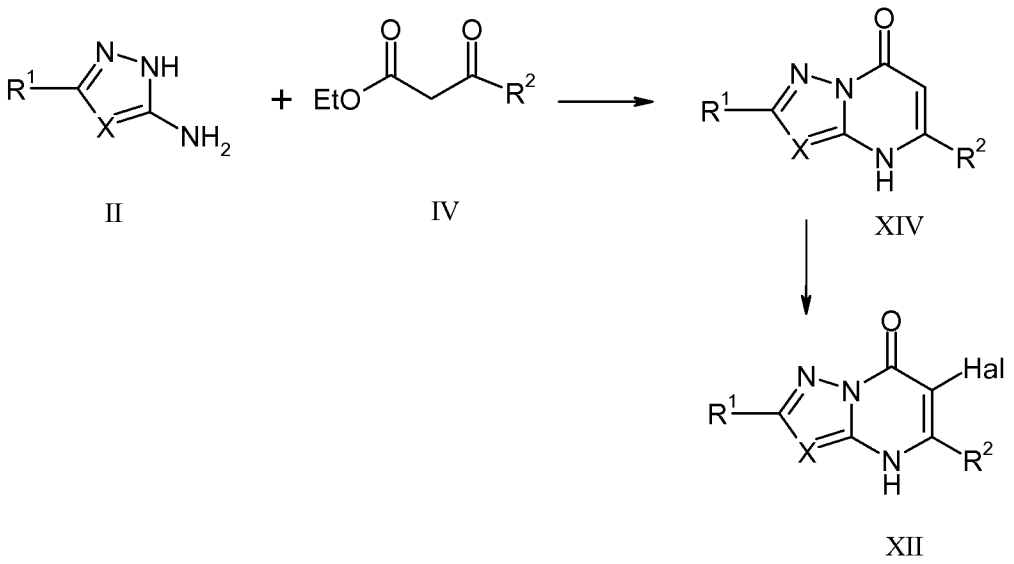
The compounds of formula (I) wherein R^2 is C_{1-4}alkoxy, C_{1-4}thioalkyl, NR^5R^6, or N-linked heterocyclyl and wherein R^1, R^3 and W are as defined for formula (I) above may be prepared as follows:

By reaction of an amine, alcohol or thio compound XIII with a halo compound of Formula XII:



XII XIII I

Compounds of formula XII may be prepared by reacting compounds of formula XIV with, for example, bromine. Compounds of formula XIV may be prepared by reacting a compound of Formula (I)I with a compound of formula (I)V.



II IV XIV XII

A compound of formula (I), or a pharmaceutically acceptable salt thereof, may be used in the treatment of:

Respiratory tract: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of

chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus.

A compound of formula (I), or a pharmaceutically acceptable salt thereof, may be used in the treatment of:

Bone and joints: arthritides associated with or including osteoarthritis/osteoarthrosis, both primary and secondary to, for example, congenital hip dysplasia; cervical and lumbar spondylitis, and low back and neck pain; rheumatoid arthritis and Still's disease; seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated spondarthropathy; septic arthritis and other infection-related arthopathies and bone disorders such as tuberculosis, including Potts' disease and Poncet's syndrome; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and synovial inflammation; Behcet's disease; primary and secondary Sjogren's syndrome; systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositits and polymyositis; polymalgia rheumatica; juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever and its systemic complications; vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, and vasculitides associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins; low back pain; Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; drug-induced arthalgias, tendonititides, and myopathies.

A compound of formula (I), or a pharmaceutically acceptable salt thereof, may be used in the treatment of:

Pain and connective tissue remodelling of musculoskeletal disorders due to injury [for example sports injury] or disease: arthitides (for example rheumatoid arthritis, osteoarthritis, gout or crystal arthropathy), other joint disease (such as intervertebral disc degeneration or temporomandibular joint degeneration), bone remodelling disease (such as

osteoporosis, Paget's disease or osteonecrosis), polychondritits, scleroderma, mixed connective tissue disorder, spondyloarthropathies or periodontal disease (such as periodontitis).

A compound of formula (I), or a pharmaceutically acceptable salt thereof, may be used in the treatment of:

Skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis;cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions.

A compound of formula (I), or a pharmaceutically acceptable salt thereof, may be used in the treatment of:

Eyes: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune; degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral , fungal, and bacterial.

A compound of formula (I), or a pharmaceutically acceptable salt thereof, may be used in the treatment of:

Gastrointestinal tract: glossitis, gingivitis, periodontitis; oesophagitis, including reflux; eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, colitis including ulcerative colitis, proctitis, pruritis ani; coeliac disease, irritable bowel syndrome, and food-related allergies which may have effects remote from the gut (for example migraine, rhinitis or eczema).

A compound of formula (I), or a pharmaceutically acceptable salt thereof, may be used in the treatment of:

Abdominal: hepatitis, including autoimmune, alcoholic and viral; fibrosis and cirrhosis of the liver; cholecystitis; pancreatitis, both acute and chronic.

A compound of formula (I), or a pharmaceutically acceptable salt thereof, may be used in the treatment of:

Genitourinary: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female).

A compound of formula (I), or a pharmaceutically acceptable salt thereof, may be used in the treatment of:

Allograft rejection: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease.

A compound of formula (I), or a pharmaceutically acceptable salt thereof, may be used in the treatment of:

CNS: Alzheimer's disease and other dementing disorders including CJD and nvCJD; amyloidosis; multiple sclerosis and other demyelinating syndromes; cerebral atherosclerosis and vasculitis; temporal arteritis; myasthenia gravis; acute and chronic pain (acute, intermittent or persistent, whether of central or peripheral origin) including visceral pain, headache, migraine, trigeminal neuralgia, atypical facial pain, joint and bone pain, pain arising from cancer and tumor invasion, neuropathic pain syndromes including diabetic, post-herpetic, and HIV-associated neuropathies; neurosarcoidosis; central and peripheral nervous system complications of malignant, infectious or autoimmune processes.

A compound of formula (I), or a pharmaceutically acceptable salt thereof, may be used in the treatment of:

Other auto-immune and allergic disorders including Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome.

A compound of formula (I), or a pharmaceutically acceptable salt thereof, may be used in the treatment of:

Other disorders with an inflammatory or immunological component; including HIV infection and acquired immune deficiency syndrome (AIDS), leprosy, Sezary syndrome, and paraneoplastic syndromes.

A compound of formula (I), or a pharmaceutically acceptable salt thereof, may be used in the treatment of:

Cardiovascular: atherosclerosis, affecting the coronary and peripheral circulation; pericarditis; myocarditis , inflammatory and auto-immune cardiomyopathies including myocardial sarcoid; ischaemic reperfusion injuries; endocarditis, valvulitis, and aortitis including infective (for example syphilitic); vasculitides; disorders of the proximal and peripheral veins including phlebitis and thrombosis, including deep vein thrombosis and complications of varicose veins.

A compound of formula (I), or a pharmaceutically acceptable salt thereof, may be used in the treatment of:

Oncology: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes.

A compound of formula (I), or a pharmaceutically acceptable salt thereof, may be used in the treatment of:

Gastrointestinal tract: Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, microscopic colitis, indeterminant colitis, irritable bowel disorder, irritable bowel syndrome, non-inflammatory diarrhea, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema.

The invention further provides a compound of Formula (I) as defined above for use in the treatment of C-C-chemokine mediated disease such as inflammatory disease. When used in this way, the compounds are suitably formulated into pharmaceutical compositions which further contain a pharmaceutically acceptable carrier and these form a further aspect of the invention. The compound is conveniently used for the treatment of CCR2b mediated inflammatory diseases, atherosclerosis, diabetes, obesity , cancer, chronic obstructive pulmonary disease (COPD) and/or neuropathic pain.

The compounds of the present invention may be used in the treatment of neuropathic pain associated with a C-C chemokine mediated disease, condition or disorder such as those listed hereinbefore. In particular compounds of the invention may be used in

the treatment of neuropathic pain associated with a CCR2b chemokine mediated disease, condition or disorder.

Convenient examples include neuropathic pain associated with inflammatory diseases such as rheumatoid arthritis, osteoarthritis, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), psoriasis and inflammatory bowel disease.

In particular compounds of the invention may be used to treat neuropathic pain associated with arthtritis and in particular osteoarthritis.

Furthermore, the invention provides the use of a compound of Formula (I) as defined above in the preparation of a medicament for treating C-C chemokine mediated disease, and in particular for the treatment of CCR2b mediated inflammatory diseases.

The invention further relates to combination therapies wherein a compound of the invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or formulation comprising a compound of the invention, is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents, for the treatment of one or more of the conditions listed.

In particular, for the treatment of the inflammatory diseases such as (but not restricted to) rheumatoid arthritis, osteoarthritis, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), psoriasis neuropathic pain and inflammatory bowel disease, the compounds of the invention may be combined with agents listed below.

Non-steroidal anti-inflammatory agents (hereinafter NSAIDs) including non-selective cyclo-oxygenase COX-1 / COX-2 inhibitors whether applied topically or systemically (such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin); selective COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumarocoxib, parecoxib and etoricoxib); cyclo-oxygenase inhibiting nitric oxide donors (CINODs); glucocorticosteroids (whether administered by topical, oral, intramuscular, intravenous, or intra-articular routes); methotrexate; leflunomide; hydroxychloroquine; d-penicillamine; auranofin or other parenteral or oral gold preparations; analgesics; diacerein; intra-articular therapies such as hyaluronic acid derivatives; and nutritional supplements such as glucosamine.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a cytokine or agonist or antagonist of cytokine function, (including agents which act on cytokine signalling pathways such as modulators of the SOCS system) including alpha-, beta-, and gamma-interferons; insulin-like growth factor type I (IGF-1); interleukins (IL) including IL1 to 17, and interleukin antagonists or inhibitors such as anakinra; tumour necrosis factor alpha (TNF-α) inhibitors such as anti-TNF monoclonal antibodies (for example infliximab; adalimumab, and CDP-870) and TNF receptor antagonists including immunoglobulin molecules (such as etanercept) and low-molecular-weight agents such as pentoxyfylline.

In addition the invention relates to a combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, HuMax Il-15).

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a modulator of chemokine receptor function such as an antagonist of CCR1, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX_3CR1 for the $C\text{-}X_3\text{-}C$ family.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with an inhibitor of matrix metalloprotease (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-9 and MMP-12, including agents such as doxycycline.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrazones; a methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2-

cyanoquinoline compound such as L-746,530; or an indole or quinoline compound such as MK-591, MK-886, and BAY x 1005.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a receptor antagonist for leukotrienes (LT) B4, LTC4, LTD4, and LTE4. selected from the group consisting of the phenothiazin-3-1s such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a phosphodiesterase (PDE) inhibitor such as a methylxanthanine including theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE4 inhibitor an inhibitor of the isoform PDE4D, or an inhibitor of PDE5.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine; applied orally, topically or parenterally.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a proton pump inhibitor (such as omeprazole) or a gastroprotective histamine type 2 receptor antagonist.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an antagonist of the histamine type 4 receptor.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an anticholinergic agents including muscarinic receptor (M1, M2, and M3) antagonist such as atropine, hyoscine, glycopyrrrolate, ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine or telenzepine.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a beta-adrenoceptor agonist (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, or pirbuterol, or a chiral enantiomer thereof.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a chromone, such as sodium cromoglycate or nedocromil sodium.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide or mometasone furoate.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with an agent that modulates a nuclear hormone receptor such as PPARs, for example rosiglitazone.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with an immunoglobulin (Ig) or Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (for example omalizumab).

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and another systemic or topically-applied anti-inflammatory agent, such as thalidomide or a derivative thereof, a retinoid, dithranol or calcipotriol.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and combinations of aminosalicylates and sulfapyridine such as sulfasalazine, mesalazine, balsalazide, and

olsalazine; and immunomodulatory agents such as the thiopurines, and corticosteroids such as budesonide.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with an antibacterial agent such as a penicillin derivative, a tetracycline, a macrolide, a beta-lactam, a fluoroquinolone, metronidazole, an inhaled aminoglycoside; an antiviral agent including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir, amantadine, rimantadine, ribavirin, zanamavir and oseltamavir; a protease inhibitor such as indinavir, nelfinavir, ritonavir, and saquinavir; a nucleoside reverse transcriptase inhibitor such as didanosine, lamivudine, stavudine, zalcitabine or zidovudine; or a non-nucleoside reverse transcriptase inhibitor such as nevirapine or efavirenz.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a cardiovascular agent such as a calcium channel blocker, a beta-adrenoceptor blocker, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-2 receptor antagonist; a lipid lowering agent such as a statin or a fibrate; a modulator of blood cell morphology such as pentoxyfylline; thrombolytic, or an anticoagulant such as a platelet aggregation inhibitor.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a CNS agent such as an antidepressant (such as sertraline), an anti-Parkinsonian drug (such as deprenyl, L-dopa, ropinirole, pramipexole, a MAOB inhibitor such as selegine and rasagiline, a comP inhibitor such as tasmar, an A-2 inhibitor, a dopamine reuptake inhibitor, an NMDA antagonist, a nicotine agonist, a dopamine agonist or an inhibitor of neuronal nitric oxide synthase), or an anti-Alzheimer's drug such as donepezil, rivastigmine, tacrine, a COX-2 inhibitor, propentofylline or metrifonate.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an agent for the treatment of acute or chronic pain, such as a centrally or peripherally-acting analgesic (for example an opioid or derivative thereof), carbamazepine, gabapentin, pregabalin, phenytoin, sodium valproate, amitryptiline or other anti-depressant agent-s, paracetamol, CB1 agonist, muscarinic agonist, TRPV-1 antagonist, mGluR5 agonist or a non-steroidal anti-inflammatory agent.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a parenterally or topically-applied (including inhaled) local anaesthetic agent such as lignocaine or a derivative thereof.

A compound of the present invention, or a pharmaceutically acceptable salt thereof, can also be used in combination with an anti-osteoporosis agent including a hormonal agent such as raloxifene, or a biphosphonate such as alendronate.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a: (i) tryptase inhibitor; (ii) platelet activating factor (PAF) antagonist; (iii) interleukin converting enzyme (ICE) inhibitor; (iv) IMPDH inhibitor; (v) adhesion molecule inhibitors including VLA-4 antagonist; (vi) cathepsin; (vii) kinase inhibitor such as an inhibitor of tyrosine kinase (such as Btk, Itk, Jak3 or MAP, for example Gefitinib or Imatinib mesylate), a serine / threonine kinase (such as an inhibitor of a MAP kinase such as p38, JNK, protein kinase A, B or C, or IKK), or a kinase involved in cell cycle regulation (such as a cylin dependent kinase); (viii) glucose-6 phosphate dehydrogenase inhibitor; (ix) kinin-B.sub1. - or B.sub2. -receptor antagonist; (x) anti-gout agent, for example colchicine; (xi) xanthine oxidase inhibitor, for example allopurinol; (xii) uricosuric agent, for example probenecid, sulfinpyrazone or benzbromarone; (xiii) growth hormone secretagogue; (xiv) transforming growth factor (TGFβ); (xv) platelet-derived growth factor (PDGF); (xvi) fibroblast growth factor for example basic fibroblast growth factor (bFGF); (xvii) granulocyte macrophage colony stimulating factor (GM-CSF); (xviii) capsaicin cream; (xix) tachykinin NK.sub1. or NK.sub3. receptor antagonist such as NKP-608C, SB-233412 (talnetant) or D-4418; (xx) elastase inhibitor such as UT-77 or ZD-0892; (xxi) TNF-alpha converting enzyme inhibitor (TACE); (xxii) induced nitric oxide synthase (iNOS) inhibitor; (xxiii) chemoattractant receptor-homologous molecule expressed on TH2 cells, (such as a CRTH2 antagonist); (xxiv) inhibitor of P38; (xxv) agent modulating the function of Toll-like receptors (TLR), (xxvi) agent modulating the activity of purinergic receptors such as P2X7 or P2X3; or (xxvii) inhibitor of transcription factor activation such as NFkB, API, or STATS.

A compound of the invention, or a pharmaceutically acceptable salt thereof, can also be used in combination with an existing therapeutic agent for the treatment of cancer, for example suitable agents include:

(i) an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin);

(ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5α-reductase such as finasteride;

(iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function);

(iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbb2 antibody trastuzumab, or the anti-erbb1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family;

(v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody

bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin αvβ3 function or an angiostatin);

(vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213;

(vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense;

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

(ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Some compounds of formula (I) may possess chiral centres. It is to be understood that the invention encompasses the use of all such optical isomers and diasteroisomers as well as compounds of formula (I) in any of these forms, and pharmaceutical compositions containing compounds of formula (I).

The invention further relates to all tautomeric forms of the compounds of formula (I) and pharmaceutical compositions containing these.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms and pharmaceutical compositions containing these.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by

inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intermuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives

(such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile

injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30μ or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For

further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the formula (I) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the formula (I) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

In a further aspect, the invention provides a method of treating inflammatory disease by administering a compound of Formula (I) as described above, or a pharmaceutical composition as described above.

In a further aspect the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; or COPD.

In a still further aspect a compound of formula (I), or a pharmaceutically acceptable salt thereof, is useful in the treatment of COPD.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; or COPD.

In another particular aspect, the compounds of the present invention may be used to treat rheumatoid arthritis.

In use for therapy in a warm-blooded animal such as a human, the compound of the present invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, transdermally, intracerebroventricularly and by injection into the joints.

Within the scope of the invention is the use of any compound of formula (I) as defined above for the manufacture of a medicament.

Also within the scope of the invention is the use of any compound of formula (I) for the manufacture of a medicament for the therapy of pain.

A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the Formula (I) above, is administered to a patient in need of such therapy.

In a further aspect, the invention provides a method of treating inflammatory disease by administering a compound of Formula (I) as described above, or a pharmaceutical composition as described above.

Examples

The invention will now be illustrated by the following non-limiting Examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25 °C;

(ii) organic solutions were dried over anhydrous magnesium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) chromatography unless otherwise stated means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields, when given, are for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) when given, ^{1}H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 400 MHz using perdeuterio DMSO (CD_3SOCD_3) as the solvent unless otherwise stated; coupling constants (J) are given in Hz;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) solvent ratios are given in percentage by volume;

(ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (APCI) mode using a direct exposure probe; where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(x) LCMS characterisation was performed using a pair of Gilson 306 pumps with Gilson 233 XL sampler and Waters Micromass ZQ mass spectrometer. The LC comprised water symmetry 2x50 column C18 with 5 micron particle size. The eluents were: A, water with 0.1% formic acid and B, acetonitrile with 0.1% formic acid. The eluent gradient went from 95% A to 95% B in 5 minutes. Where indicated ionisation was effected by electrospray (ES); where values for m/z are given. Or the following method was used for LC/MS analysis: Instrument Agilent 1100; Column Waters Symmetry 2.1 x 30 mm; Mass APCI; Flow rate 0.7 mL/min; Wavelength 254 nm; Solvent A: water + 0.1% TFA; Solvent B: acetonitrile + 0.1% TFA ; Gradient 15-95%/B 2.7 min, 95% B 0.3 min, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$ and

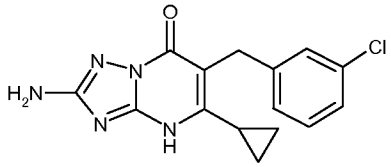
(xi) the following abbreviations are used:

$CDCl_3$	chloroform-d;
DIPEA	diisopropylethylamine;
DMSO	dimethyl sulfoxide;
DMF	*N,N*-dimethylformamide;
DCM	dichloromethane;
EtOH	ethanol;
EtOAc	ethyl acetate;
Equ.	Equivalent;
Et_2O	diethyl ether;

g	gram;
^{1}H NMR	proton nuclear magnetic resonance;
HATU	*O*-(7-azabenzotriazol-1yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate;
HCl	hydrochloric acid;
hrs	hours;
$LiAlH_4$	lithium aluminium hydride;
m	multiplet;
M	molar;
min	minutes;
mL	milliliter ;
mg	milligram;
MHz	megahertz;
MeCN	Acetonitrile;
MeOH	methanol;
$MgSO_4$	magnesium sulfate;
$NaHCO_3$	sodium hydrogencarbonate;
NH_3	ammonia;
NMP	N-methylpyrrolidine;
RT	retention time (HPLC) ;
s	singlet;
SCX	Strong Cation Exchange
t	triplet;
t-BuOH	tert-butanol;
THF	tetrahydrofuran;
TFA	trifluoroacetic acid;
µ	micro;
µL	microliter;
µM	micromolar;

Example 1

2-Amino-6-[(3-chlorophenyl)methyl]-5-cyclopropyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

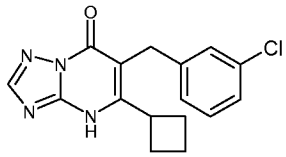


3,5-Diamino-1,2,4-triazole (141 mg, 1.42 mmol) was added to ethyl 2-[(3-chlorophenyl)methyl]-3-cyclopropyl-3-oxo-propanoate (200 mg, 0.71 mmol) and 1-butyl-3-methylimidazolium hexafluorophosphate (1 mL, 4.25 mmol) in a microwave tube at room temperature. The open tube was then placed in a fitted aluminium block preheated to 200 °C and magnetically stirred for 20 minutes with the formation of a white precipitate. After cooling the mixture was added to DCM (30 mL), water (10 mL) and citric acid (10% aqueous solution, 1 mL) and stirred for 20 minutes. The layers were separated using a hydrophobic membrane filter and the organic layer was evaporated. The remaining aqueous layer was filtered and the solid collected. The crude product was dissolved and purified by preparative HPLC (Waters XTerra C18 column, 5µ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (110 mg, 48.9 %) as a white solid.

^{1}H NMR (700.03 MHz, DMSO-d6) δ 0.85-0.90 (2H, m), 0.93-0.98 (2H, m), 2.06-2.10 (1H, m), 3.98 (2H, s), 6.16 (2H, br s), 7.15-7.21 (2H, m), 7.27-7.29 (2H, m), 12.17 (1H, br s) m/z (ES) $(M+H)^+$ = 316.

Example 2

6-[(3-Chlorophenyl)methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



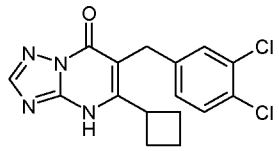
1H-1,2,4-Triazol-3-amine (84 mg, 1.00 mmol) was added to ethyl 2-[(3-chlorophenyl)methyl]-3-cyclobutyl-3-oxo-propanoate (295 mg, 1.00 mmol), in toluene (2 mL) at 20 °C under air. The resulting mixture was stirred at 110 °C for 18 hours during

which time the toluene boiled off to leave an orange gum. The crude product was purified by preparative HPLC Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length, using decreasingly polar mixtures of water (containing 0.1% NH_3) and MeCN as eluents. Fractions containing the desired compound were lyophilised to dryness to afford the title compound (101 mg, 32.1 %).

^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.72-1.83 (1H, m), 1.90-1.99 (1H, m), 2.01-2.10 (2H, m), 2.43 (2H, t), 3.87 (1H, t), 3.91 (2H, s), 7.17 (1H, d), 7.21-7.32 (3H, m), 8.29 (1H, s), 13.02 (1H, br s); m/z (ES) $(M+H)^+$ = 315.

Example 3

5-Cyclobutyl-6-[(3,4-dichlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

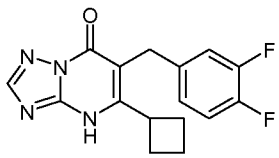


1H-1,2,4-Triazol-3-amine (0.084 g, 1 mmol) was added to ethyl 3-cyclobutyl-2-[(3,4-dichlorophenyl)methyl]-3-oxo-propanoate (0.329 g, 1 mmol) and 4-methylbenzenesulfonic acid hydrate (0.190 g, 1.00 mmol). The resulting mixture was stirred at 160 °C for 18 hours (as a melt reaction). The crude product was purified by preparative HPLC Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length, using decreasingly polar mixtures of water (containing 0.1% NH_3) and MeCN as eluents. Fractions containing the desired compound were lyophilised to dryness to afford the title compound (0.159 g, 45.5 %) as a white solid.

^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.70-1.82 (1H, m), 1.89-2.00 (1H, m), 2.05-2.07 (2H, m), 2.31-2.43 (2H, m), 3.80-3.90 (1H, m), 3.90 (2H, s), 7.19-7.21 (1H, m), 7.47-7.49 (1H, m), 7.49 (1H, s), 8.30 (1H, s); m/z (ES) $(M+H)^+$ = 349.

Example 4

5-Cyclobutyl-6-[(3,4-difluorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

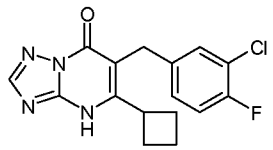


1H-1,2,4-Triazol-3-amine (0.346 g, 4.12 mmol) was added to ethyl 3-cyclobutyl-2-[(3,4-difluorophenyl)methyl]-3-oxo-propanoate (1.22 g, 4.12 mmol), and 4-methylbenzenesulfonic acid hydrate (0.783 g, 4.12 mmol) under air. The resulting mixture was stirred at 150 °C for 18 hours (as a melt reaction). The crude product was purified by preparative HPLC Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length, using decreasingly polar mixtures of water (containing 0.1% NH_3) and MeCN as eluents. Fractions containing the desired compound were lyophilised to dryness to afford the title compound (0.188 g, 14.44 %) as a white solid.

^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.76-1.81 (1H, m), 1.92 (1H, t), 2.02-2.07 (2H, m), 2.37 (1H, d), 2.41-2.46 (1H, m), 3.81 (1H, q), 3.89 (2H, s), 7.02-7.06 (1H, m), 7.22-7.33 (1H, m), 7.25-7.31 (1H, m), 8.27 (1H, s); m/z (ES) $(M+H)^+$ = 317.

Example 5

6-[(3-Chloro-4-fluoro-phenyl)methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

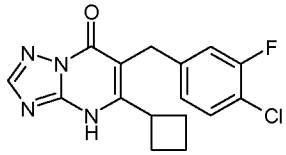


1H-1,2,4-Triazol-3-amine (0.084 g, 1 mmol) was added to ethyl 2-[(3-chloro-4-fluoro-phenyl)methyl]-3-cyclobutyl-3-oxo-propanoate (0.313 g, 1.00 mmol) and 4-methylbenzenesulfonic acid hydrate (0.190 g, 1.00 mmol). The resulting mixture was stirred at 160 °C for 18 hours (as a melt reaction). The crude product was purified by preparative HPLC Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length, using decreasingly polar mixtures of water (containing 0.1% NH_3) and MeCN as eluents. Fractions containing the desired compound were lyophilised to dryness to give the title compound (0.079 g, 23.74 %) as an off-white foam.

^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.77 (1H, q), 1.92 (1H, t), 2.01-2.06 (2H, m), 2.31-2.48 (2H, m), 3.80 (1H, t), 3.88 (2H, s), 7.21-7.22 (1H, m), 7.28 (1H, t), 7.38-7.41 (1H, m), 8.24 (1H, s); m/z (ES) $(M+H)^+$ = 333.

Example 6

6-[(4-Chloro-3-fluoro-phenyl)methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

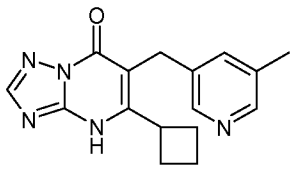


1H-1,2,4-Triazol-3-amine (0.084 g, 1 mmol) was added to ethyl 2-[(4-chloro-3-fluoro-phenyl)methyl]-3-cyclobutyl-3-oxo-propanoate (0.313 g, 1.00 mmol) and 4-methylbenzenesulfonic acid hydrate (0.190 g, 1.00 mmol). The resulting mixture was stirred at 160 °C for 18 hours (as a melt reaction). The crude product was purified by preparative HPLC Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length, using decreasingly polar mixtures of water (containing 0.1% NH_3) and MeCN as eluents. Fractions containing the desired compound were lyophilised to dryness to give the title compound (0.059 g, 17.7 %) as a white solid.

^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.76-1.78 (1H, m), 1.90-1.94 (1H, m), 2.05 (2H, q), 2.40 (1H, d), 2.44 (1H, s), 3.84 (1H, q), 3.91 (2H, s), 7.08 (1H, d), 7.23-7.27 (1H, m), 7.46 (1H, t), 8.30 (1H, s); m/z (ES) $(M+H)^+$ = 333.

Example 7

5-Cyclobutyl-6-[(5-methyl-3-pyridyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



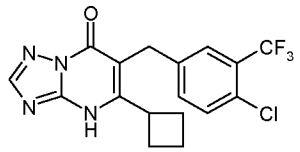
4-Methylbenzenesulfonic acid (84 µL, 0.52 mmol) was added in one portion to ethyl 3-cyclobutyl-2-((5-methylpyridin-3-yl)methyl)-3-oxopropanoate (144 mg, 0.52 mmol) over a period of 1 minute under argon. The resulting mixture was stirred at 150 °C for 16 hours. The crude product was purified by preparative HPLC Waters XBridge Prep C18 OBD column, 10µ silica, 50 mm diameter, 150 mm length, using decreasingly polar mixtures of water (containing 0.2% NH_3) and MeCN as eluents. Fractions containing the desired

compound were evaporated to dryness to give the title compound (94 mg, 60.9 %) as a solid.

^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.75 (1H, d), 1.89 (1H, t), 1.97-2.04 (2H, m), 2.21 (3H, s), 2.33-2.39 (2H, m), 3.69 (1H, t), 3.82 (2H, s), 7.32 (1H, s), 8.02 (1H, s), 8.17 (1H, d), 8.25 (1H, d); m/z (ES) $(M+H)^+$ = 296.

Example 8

6-[[4-Chloro-3-(trifluoromethyl)phenyl]methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

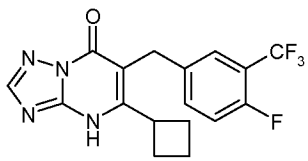


1H-1,2,4-Triazol-3-amine (0.084 g, 1 mmol) was added to ethyl 2-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-3-cyclobutyl-3-oxo-propanoate (0.363 g, 1.00 mmol) and 4-methylbenzenesulfonic acid hydrate (0.190 g, 1.00 mmol). The resulting mixture was stirred at 160 °C for 18 hours (as a melt reaction). The crude product was purified by preparative HPLC Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length, using decreasingly polar mixtures of water (containing 0.1% NH_3) and MeCN as eluents. Fractions containing the desired compound were lyophilised to dryness to give the title compound (0.075 g, 19.59 %) as an off-white foam.

^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.79 (1H, q), 1.93-1.96 (1H, m), 2.06 (2H, q), 2.40 (1H, t), 2.46 (1H, d), 3.91 (1H, q), 3.98 (2H, s), 7.48-7.51 (1H, m), 7.60 (1H, d), 7.72 (1H, d), 8.31 (1H, s); m/z (ES) $(M+H)^+$ = 383.

Example 9

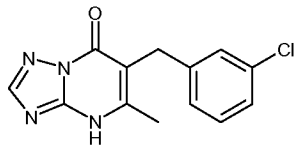
5-Cyclobutyl-6-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



1H-1,2,4-Triazol-3-amine (0.084 g, 1 mmol) was added to ethyl 3-cyclobutyl-2-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-3-oxo-propanoate (0.346 g, 1.00 mmol) and 4-methylbenzenesulfonic acid hydrate (0.190 g, 1.00 mmol). The resulting mixture was stirred at 160 °C for 18 hours (as a melt reaction). The crude product was purified by preparative HPLC Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length, using decreasingly polar mixtures of water (containing 0.1% NH_3) and MeCN as eluents. Fractions containing the desired compound were lyophilised to dryness to give the title compound (0.070 g, 19.1 %) as an off-white foam;
^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.75-1.82 (1H, m), 1.93-1.96 (1H, m), 2.03-2.08 (2H, m), 2.40-2.47 (2H, m), 3.87-3.98 (1H, m), 3.95 (2H, s), 7.36-7.41 (1H, m), 7.53-7.57 (1H, m), 7.61-7.63 (1H, m), 8.29 (1H, s), 13.11 (1H, s); m/z (ES) $(M+H)^+$ = 367.

Example 10

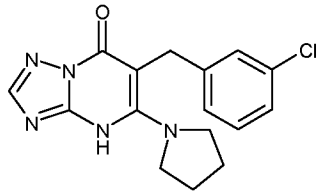
6-[(3-Chlorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



3-Amino-1H-1,2,4-triazole (330 mg, 3.93 mmol) was added to ethyl 2-[(3-chlorophenyl)methyl]-3-oxo-butanoate (500 mg, 1.96 mmol) in glacial acetic acid (3 mL) and the mixture heated to 120 °C for 1 hour with the formation of a white precipitate. After cooling diethyl ether (20mL) was added and the precipitate produced filtered and dried in vacuo at 50°C overnight to give the crude title compound (529 mg, 1.58 mmol, 81 %) as a white powder. A portion of this (100 mg) was further purified by dissolving in NMP (3mL) and purified by preparative HPLC (Phenomenex Luna C18 100A column, 5µ silica, 21 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents. The fraction containing the desired compound was diluted with distilled water (30mL) to produce a white precipitate which was filtered and evaporated to dryness to give the title compound (53 mg, 99%) as a fluffy white solid.
^{1}H NMR (400.13 MHz, DMSO-d6) δ 2.35 (3H, s), 3.88 (2H, s), 7.20-7.31 (4H, m), 8.19 (1H, s), 13.15 (1H, s); m/z (ES) $(M+H)^+$ = 275.

Example 11

6-[(3-Chlorophenyl)methyl]-5-pyrrolidin-1-yl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

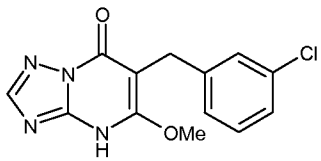


Pyrrolidine (25.0 mL, 300 mmol) was added in one portion to 5-chloro-6-[(3-chlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one (250 mg, 0.85 mmol, Example 13). The resulting mixture was stirred at 120 °C for 4 days. The reaction mixture was evaporated. The crude product was purified by preparative HPLC (Waters XTerra C18 column, 5µ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (219 mg, 78 %) as a white solid.

^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.70-1.87 (m, 4H), 2.85-3.06 (m, 2H), 3.30-3.45 (m, 2H), 4.0 (s, 2H), 7.21-7.35 (m, 4H), 8.55 (s, 1H), 13.25 (s, 1H); m/z (ES) $(M+H)^+$ = 330.

Example 12

6-[(3-Chlorophenyl)methyl]-5-methoxy-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

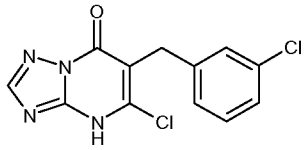


To a mixture of 5-chloro-6-[(3-chlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one (200 mg, 0.68 mmol, Example 22) in MeOH (6.78 mL) was added sodium methoxide (110 mg, 2.03 mmol). The resulting mixture was stirred at 115 °C for 16 hours then transferred to a microwave vial and heated at 140 °C for a further 12hrs at 140 °C. The mixture was evaporated to dryness and the crude product was purified by preparative HPLC Phenomenex Gemini Prep C18 11A (axia) column, 5µ silica, 21 mm diameter, 100 mm length, using decreasingly polar mixtures of water (0.1% NH_3) and MeCN as eluents. Fractions containing the desired compound were lyophilised to dryness to give the title compound as a solid (122 mg, 61.9 %).

^{1}H NMR (400.13 MHz, DMSO-d6) δ 3.69 (2H, s), 3.79 (3H, s), 7.13-7.27 (4H, m), 7.90 (1H, s); m/z (ES) $(M+H)^+$ = 291.

Example 13

5-Chloro-6-[(3-chlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

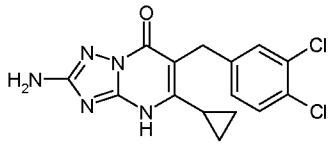


Potassium trimethylsilanolate (3.07 g, 23.92 mmol) was added to 5,7-dichloro-6-[(3-chlorophenyl)methyl]-[1,2,4]triazolo[1,5-a]pyrimidine (2.50 g, 7.97 mmol) in THF (100 mL). The resulting suspension was stirred at room temperature for 18 hours. The solvent was removed in vacuo and the residue suspended in water (80mL) and acidified with 2M HCl. The resulting precipitate was filtered off, washed with water and dried under vacuum. This gave the title compound (2.351 g, 100 %) as a white solid.

^{1}H NMR (400.13 MHz, DMSO-d6) δ 3.95 (s, 2H), 7.20-7.31 (m, 4H), 8.9 (s, 1H); m/z (ES) $(M+H)^+$ = 295.

Example 14

2-Amino-5-cyclopropyl-6-[(3,4-dichlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

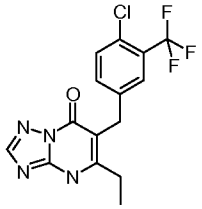


Ethyl 3-cyclopropyl-2-[(3,4-dichlorophenyl)methyl]-3-oxo-propanoate (200 mg, 634.5 mmol, Method II) and 1H-1,2,4-triazole-3,5-diamine (57.2 mg, 577 mmol) were added to tri-n-butylamine (228 µL) and the resulting mixture stirred at 160 °C for 48 h. The mixture was evaporated and the residue recrystallised from isopropanol to give the title compound (43 mg, 21%) as a white solid.

^{1}H NMR (400.13 MHz, DMSO-d6) δ 0.90-1.05 (4H, m), 2.05-2.17 (1H, m), 4.00 (2H, s), 6.25 (2H, br s), 7.28 (1H, d), 7.52 (2H, d), 12.20 (1H, br s); m/z (ES) $(M+H)^+$ = 350.

Example 15

6-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-5-ethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

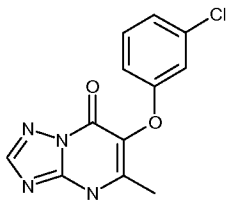


Ethyl 2-(4-chloro-3-(trifluoromethyl)benzyl)-3-oxopentanoate (656 mg, 1.95 mmol) was added to 1H-1,2,4-triazol-3-amine (197 mg, 2.34 mmol) and 4-methylbenzenesulfonic acid hydrate (185 mg, 0.97 mmol). The resulting mixture was stirred at 180 °C for 30 min (as a melt reaction). The crude product was purified by preparative HPLC (Waters X-bridge C18 OBD column, 5µ silica, 30 mm diameter, 150 mm length, using decreasingly polar mixtures of water (containing 0.1% TFA) and acetonitrile as eluents). to give 6-(4-chloro-3-(trifluoromethyl)benzyl)-5-ethyl-[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one (420 mg, 60.4 %) as a solid

^{1}H NMR (399.99 MHz, DMSO-d6) δ 13.18 (1H, s), 8.21 (1H, s), 7.77 (1H, s), 7.59 (1H, d), 7.52 (1H, d), 3.97 (2H, s), 2.68 (2H, q), 1.09 (3H, t); m/z (APCI) $(M+H)^+$ 357

Example 16

6-(3-chlorophenoxy)-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



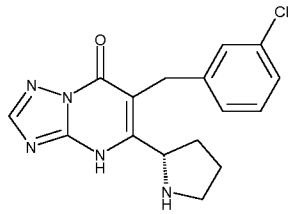
Ethyl 2-(3-chlorophenoxy)-3-oxobutanoate (0.153 g, 0.59 mmol) was added to 1H-1,2,4-triazol-3-amine (0.05 g, 0.59 mmol) in acetic acid (1 mL) . The resulting mixture was stirred at 120 °C for 2 hrs. The mixture was concentrated under reduced pressure and the diluted with acetonitrile/water. Purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 150 mm length, using decreasingly polar mixtures of water (containing 0.1% NH_3) and acetonitrile as eluents). to give 6-(3-

chlorophenoxy)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one (90 mg, 54.7 %) as a solid.

^{1}H NMR (399.99 MHz, DMSO-d6) δ 8.12 (1H, s), 7.31 (1H, t), 7.05 (1H, d), 7.03 (1H, s), 6.96 (1H, d), 2.19 (3H, s); m/z (APCI) $(M+H)^+$ 277

Example 17

6-[(3-chlorophenyl)methyl]-5-[(2S)-pyrrolidin-2-yl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

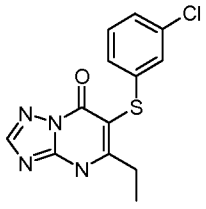


1H-1,2,4-triazol-3-amine (44.7 mg, 0.53 mmol) was added to (2S)-tert-butyl 2-(2-(3-chlorobenzyl)-3-ethoxy-3-oxopropanoyl)pyrrolidine-1-carboxylate (218 mg, 0.53 mmol) and 4-methylbenzenesulfonic acid hydrate (101 mg, 0.53 mmol). The resulting mixture was stirred at 180 °C for 2 hrs (as a melt reaction). The crude product was purified by preparative HPLC (Waters X-bridge C18 OBD column, 5μ silica, 30 mm diameter, 150 mm length, using decreasingly polar mixtures of water (containing 0.1% TFA) and acetonitrile as eluents), the pure fractions were collected and freeze dried to give (S)-6-(3-chlorobenzyl)-5-(pyrrolidin-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one (21.00 mg, 11.97 %) as a solid.

^{1}H NMR (399.99 MHz, DMSO-d6) δ 9.77 (1H, s), 8.37 (1H, s), 7.31 - 7.14 (4H, m), 4.83 (1H, m), 3.65 (1H, d), 3.53 (1H, d), 3.40 - 3.20 (1H, m), 3.06 - 2.97 (1H, m), 2.35 - 2.25 (1H, m), 2.07 - 1.97 (1H, m), 1.18 - 1.05 (1H, m); m/z (APCI) $(M+H)^+$ 330

Example 18

6-(3-chlorophenyl)sulfanyl-5-ethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

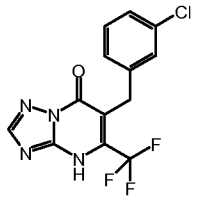


3-chlorobenzenethiol (0.149 g, 1.03 mmol) was added to 6-bromo-5-ethyl-[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one (0.25 g, 1.03 mmol) and cesium carbonate (0.335 g, 1.03 mmol) in ethylene glycol (3 mL). The resulting mixture was stirred at 140-150 °C for 6 hrs. The reaction mixture was diluted with acetonitrile/water (90/10) and purified by preparative HPLC (Waters X-bridge C18 OBD column, 5µ silica, 30 mm diameter, 150 mm length, using decreasingly polar mixtures of water (containing 0.1% TFA) and acetonitrile as eluents), The pure fractions were collected and freeze dried to give 6-(3-chlorophenylthio)-5-ethyl-[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one (34 mg, 10.78 %) as solid

^{1}H NMR (399.99 MHz, DMSO-d6) δ 8.31 (1H, s), 7.28 (1H, d), 7.25 (1H, d), 7.18 (1H, d), 7.16 (1H, d), 2.89 (2H, q), 1.18 (3H, t); m/z (APCI) $(M+H)^+$ 307

Example 19

6-[(3-chlorophenyl)methyl]-5-(trifluoromethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



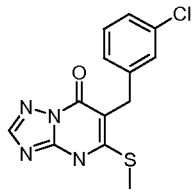
1H-1,2,4-triazol-3-amine (98 mg, 1.17 mmol) was added to ethyl 2-(3-chlorobenzyl)-4,4,4-trifluoro-3-oxobutanoate (300 mg, 0.97 mmol) and 4-methylbenzenesulfonic acid hydrate (92 mg, 0.49 mmol). The resulting mixture was stirred at 180 °C for 25 min (as a melt reaction). The crude product diluted with acetonitrile/dimethylsulfoxide/water. Purified by preparative HPLC (Waters X-bridge C18 OBD column, 5µ silica, 30 mm diameter, 150 mm length, using decreasingly polar mixtures of water (containing 0.1% TFA) and acetonitrile as eluents). The pure fractions were freeze dried to give 6-(3-chlorobenzyl)-5-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one (77 mg, 24.11 %) as a solid

6-(3-chlorobenzyl)-5-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one

^{1}H NMR (499.876 MHz, DMSO-d6) δ 8.95 (1H, s), 7.29 - 7.25 (2H, m), 7.22 (1H, d), 7.13 (1H, d), 4.00 (2H, s); m/z (APCI) $(M+H)^+$ 329

Example 20

6-[(3-chlorophenyl)methyl]-5-methylsulfanyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

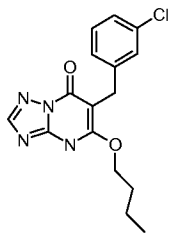


Sodium methanethiolate (119 mg, 1.69 mmol) was added to 5-chloro-6-(3-chlorobenzyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one (100 mg, 0.34 mmol) in dimethoxyethanol (3 mL). The resulting mixture was stirred at 60 °C for 18 hrs. The crude product was purified by preparative HPLC, (Waters X-bridge C18 OBD column, 5µ silica, 30 mm diameter, 150 mm length, using decreasingly polar mixtures of water (containing 0.1% TFA) and acetonitrile as eluents), the pure fractions were collected and freeze dried to give 35 mg of the product. Not pure by HPLC and NMR. The product was purified a second time by preparative HPLC (Waters X-bridge C18 OBD column, 5µ silica, 30 mm diameter, 150 mm length, using decreasingly polar mixtures of water (containing 0.1% TFA) and acetonitrile as eluents), the pure fractions were collected and freeze dried to give 6-(3-chlorobenzyl)-5-(methylthio)-[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one (18.00 mg, 17.32 %) as a solid.

^{1}H NMR (399.99 MHz, DMSO-d6) δ 8.79 (1H, s), 7.31 - 7.18 (4H, m), 3.86 (2H, s), 2.51 (3H, s); m/z (APCI) $(M+H)^+$ 307

Example 21

5-butoxy-6-[(3-chlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



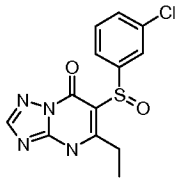
Sodium ethanolate (23.06 mg, 0.34 mmol) was added to 5-chloro-6-(3-chlorobenzyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one (100 mg, 0.34 mmol) in buta-1-ol (3 mL). The resulting mixture was stirred at 120 °C over night. The crude product was purified by

preparative HPLC, (Waters X-bridge C18 OBD column, 5µ silica, 30 mm diameter, 150 mm length, using decreasingly polar mixtures of water (containing 0.1% TFA) and acetonitrile as eluents), the pure fractions were collected and freeze dried to give 5-butoxy-6-(3-chlorobenzyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one (31.0 mg, 27.5 %) as a solid.

^{1}H NMR (299.946 MHz, DMSO-d6) δ 8.74 (1H, s), 7.29 - 7.14 (4H, m), 4.25 (2H, t), 3.71 (2H, s), 1.64 (2H, quintet), 1.33 (2H, sextet), 0.88 (3H, t); m/z (APCI) $(M+H)^+$ 333

Example 22

6-(3-chlorophenyl)sulfinyl-5-ethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

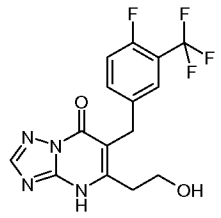


Hydrogen peroxide (0.060 mL, 0.23 mmol) was added to 6-(3-chlorophenylthio)-5-ethyl-[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one (70 mg, 0.23 mmol) in acetic acid (2 mL). The reaction mixure was stirred at 45 °C over night. The crude product was purified by preparative HPLC (Waters X-bridge C18 OBD column, 5µ silica, 30 mm diameter, 150 mm length, using decreasingly polar mixtures of water (containing 0.1% TFA) and acetonitrile as eluents), the pure fractions were collected and freeze dried to give 6-(3-chlorophenylsulfinyl)-5-ethyl-[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one (49.0 mg, 66.5 %) as a solid.

^{1}H NMR (399.99 MHz, DMSO-d6) δ 8.37 (1H, s), 7.68 (1H, s), 7.60 - 7.51 (4H, m), 3.17 - 2.91 (2H, m), 1.27 (3H, t); m/z (APCI) $(M+H)^+$ 323

Example 23

6-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-5-(2-hydroxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

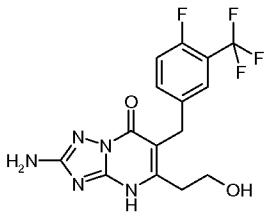


6-(4-fluoro-3-(trifluoromethyl)benzyl)-5-(2-methoxyethyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one (58 mg, 0.16 mmol) was suspended in dichloromethane (3 ml) and cooled to – 40 °C under an inert atmosphere (Argon). A saturated solution of potassium iodide (37.4 µl, 0.70 mmol) and 1,4,7,10,13,16-hexaoxacyclooctadecane (171 µl, 0.70 mmol) in dichloromethane was added slowly. After 10 min tribromoborane (470 µl, 0.47 mmol) was added and the reaction mixture was stirred for 3 hrs at – 30 °C. The reaction mixture was allowed to reach -10 °C, stirred for 1 hour and quenched with saturated sodium hydrogencarbonate (5ml). The phases were separated and the organic phase washed with water. The organic phase was dried (magnesiumsulphate), filtered and evaporated. The crude product was purified with preparative HPLC (Waters X-bridge C18 OBD column, 5µ silica, 30 mm diameter, 150 mm length, using decreasingly polar mixtures of water (containing 0.1% TFA) and acetonitrile as eluents). Fractions containing pure product was lyophilised to give the title compound (5 mg, 9%).

^{1}H NMR (399.99 MHz, DMSO-d6) δ 13.11 (1H, s), 8.21 (1H, s), 7.68 (1H, m), 7.59 (1H, m), 7.38 (1H, m), 3.97 (2H, s), 3.66 (2H, m), 2.84 (2H, t). m/z (APCI) $(M+H)^+$ 357.

Example 24

2-amino-6-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-5-(2-hydroxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



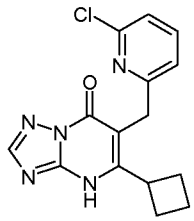
Ethyl 2-(4-fluoro-3-(trifluoromethyl)benzyl)-5-hydroxy-3-oxopentanoate (160 mg, 0.48 mmol), 1H-1,2,4-triazole-3,5-diamine (71 mg, 0.71 mmol) and 4-methylbenzenesulfonic acid (41 mg, 0.24 mmol) in n-butanol (0.5ml) was heated to 160 °C in an open vial. The reaction mixture was heated until the reaction mixture melted and became light brown and was then removed from the heat. The crude product was purified with preparative HPLC (Waters X-bridge C18 OBD column, 5µ silica, 30 mm diameter, 150 mm length, using decreasingly polar mixtures of water (containing 0.1% TFA) and acetonitrile as eluents). Fractions containing pure product was lyophilised to give the title compound (12 mg, 7%).

^{1}H NMR (399.99 MHz, DMSO-d6) δ 12.52 (1H, s), 7.64 (1H, m), 7.57 (1H, m), 7.37 (1H,

m), 5.99 (2H, s), 4.84 (1H, s), 3.89 (2H, s), 3.62 (2H, t), 2.76 (2H, t). m/z (APCI) $(M+H)^+$ 372.

Example 25

6-[(6-chloro-2-pyridyl)methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

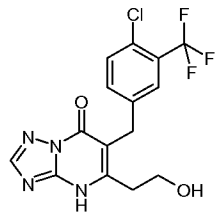


Ethyl 2-((6-chloropyridin-2-yl)methyl)-3-cyclobutyl-3-oxopropanoate (450 mg, 1.52 mmol), 4-methylbenzenesulfonic acid hydrate (289 mg, 1.52 mmol) and 1H-1,2,4-triazol-3-amine (128 mg, 1.52 mmol) was stirred in n- butanol at 150 °C in an open vial until all n-butanol was boiled away. The procedure was repeated three additional times. The crude product was purified with preparative HPLC (Waters X-bridge C18 OBD column, 5µ silica, 30 mm diameter, 150 mm length, using decreasingly polar mixtures of water (containing 0.1% TFA) and acetonitrile as eluents). Fractions containing pure product was lyophilised to give the title compound (25 mg, 5%).

^{1}H NMR (399.99 MHz, DMSO-d6) δ 13.06 (1H, bs), 8.27 (1H, bs), 7.73 (1H, t), 7.31 (1H, d), 7.23 (1H, d), 4.02 (2H, s), 2.10 (2H, m), 1.93 (1H, m), 1.78 (1H, m). m/z (APCI) $(M+H)^+$ 316.

Example 26

6-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-5-(2-hydroxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



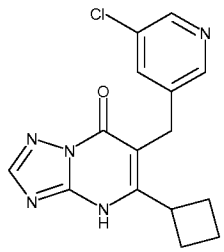
Ethyl 2-(4-chloro-3-(trifluoromethyl)benzyl)-5-hydroxy-3-oxopentanoate (175 mg, 0.50 mmol), 4-methylbenzenesulfonic acid hydrate (47 mg, 0.25 mmol) and 1H-1,2,4-triazol-3-amine (63 mg, 0.74 mmol) was heated with stirring to 180 °C, neat in open vial. The

reaction mixture was heated for 30 min, cooled to room temperature, dissolved in 2M acetic acid in methanol and run through an ion-exchange column (MEGA Bond Elute SCX , 10 g) and the eluate was evaporated. The product was purified with preparative HPLC (Waters X-bridge C18 OBD column, 5µ silica, 30 mm diameter, 150 mm length, using decreasingly polar mixtures of water (containing 0.1% TFA) and acetonitrile as eluents). Fractions containing pure product was lyophilised to give the title compound. (10 mg, 6%).

^{1}H NMR (399.99 MHz, DMSO-d6) δ 8.20 (1H, s), 7.77 (1H, s), 7.60 - 7.52 (2H, m), 3.98 (2H, s), 3.66 (2H, t), 2.84 (2H, t). m/z (APCI) $(M+H)^+$ 373.

Example 27

6-[(5-chloro-3-pyridyl)methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

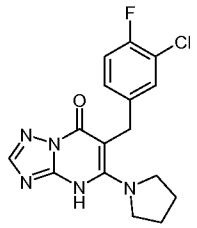


Ethyl 2-((5-chloropyridin-3-yl)methyl)-3-cyclobutyl-3-oxopropanoate (180 mg, 0.61 mmol) and 4-methylbenzenesulfonic acid (52 mg, 0.30 mmol) was heated to 180 °C for 1 hour. The product was dissolved in dichloromethane and the organic phase was washed with water. The organic phase was dried (magnesiumsulphate), filtered and evaporated. The crude product was purified with preparative HPLC (Waters X-bridge C18 OBD column, 5µ silica, 30 mm diameter, 150 mm length, using decreasingly polar mixtures of water (containing 0.1% TFA) and acetonitrile as eluents). Fractions containing pure product was lyophilised to give the title compound. (30 mg, 16%).

^{1}H NMR (399.99 MHz, Acetone-d6) δ 8.51(1H, bs), 8.40 (1H, d), 8.05 (1H, s), 7.75 (1H, m), 4.10 (1H, m), 4.05 (2H, s), 2.57 (2H, m), 2.30 (2H, m), 2.08 (1H, m), 1.90 (1H, m). m/z (APCI) $(M+H)^+$ 316.

Example 28

6-[(3-chloro-4-fluoro-phenyl)methyl]-5-pyrrolidin-1-yl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

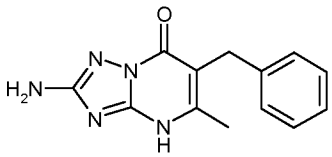


5-chloro-6-(3-chloro-4-fluorobenzyl)[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one (70 mg, 0.22 mmol) and pyrrolidine (850mg, 12 mmol) was run in a microwave oven at 150 °C for 2 hrs. The crude product was purified with preparative HPLC (Waters X-bridge C18 OBD column, 5µ silica, 30 mm diameter, 150 mm length, using decreasingly polar mixtures of water (containing 0.1% TFA) and acetonitrile as eluents). Fractions containing pure product was lyophilised to give the title compound. (10 mg, 10%).

^{1}H NMR (399.99 MHz, DMSO-d6) δ 8.50 (1H, bs), 7.31-7.25 (2H, m), 7.15 (1H, m), 3.94 (2H, s), 3.41 (4H, m), 1.74 (4H, m). m/z (APCI) $(M+H)^+$ 348.

Example 29

2-amino-6-benzyl-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



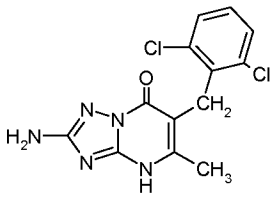
The title compound was prepared according to the procedure described in Example 19.

m/z: 256

^{1}H NMR (400 MHz, DMSO-d6) 2.28 (3H, s), 3.82 (2H, s), 6.00 (2H, s), 7.17-7.47 (5H, m), 12.60 (1H, br s)

Example 30

2-amino-6-[(2,6-dichlorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



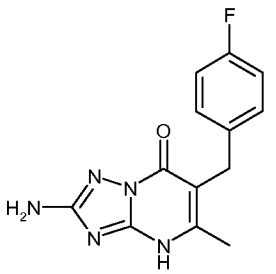
The title compound was prepared according to the procedure described in Example 10.

m/z: 324

^{1}H NMR (400 MHz, DMSO-d6) 2.20 (3H, s), 4.07 (2H, s), 5.95 (2H, s), 7.26 (1H, t), 7.42 (2H, d)

Example 31

2-amino-6-[(4-fluorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

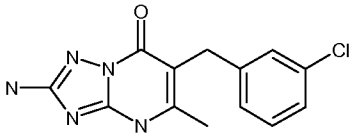


Ethyl 2-[(4-flourophenyl)methyl]-3-methyl-3-oxo-propanoate (314 mg , 1.32 mmol was added to 3-amino-5-amino-triazole (100 mg, 1.2 mmol) followed by glacial acetic acid (2.0 mL) and the reaction was heated at 120 °C under microwave irradiation for 15 minutes The solvent was evaporated and then basified with sodium hydrogencarbonate. The formed precipitate was filtered and washed with water, dichloromethane and MeCN to give the title compound (160 mg 49%)

^{1}H NMR (400 MHz, DMSO-d6) 2.27 (3H, s), 3.77 (2H, s), 5.95 (2H, s), 7.06 (2H, d), 7.23-7.25 (2H, m). m/z (ES) $(M+H)^+$ 274.

Example 32

2-amino-6-[(3-chlorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



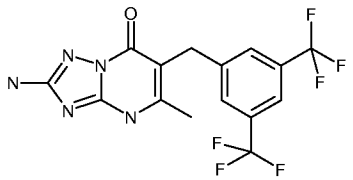
The title compound was prepared according to the procedure described in Example 31.

m/z: 290

^{1}H NMR (400 MHz, DMSO-d6) 2.30 (3H, s), 3.83 (2H, s), 6.02 (2H, s), 7.21-7.25 (1H, m), 7.27-7.42 (3H, m), 12.30 (1H, br s)

Example 33

2-amino-6-[[3,5-bis(trifluoromethyl)phenyl]methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



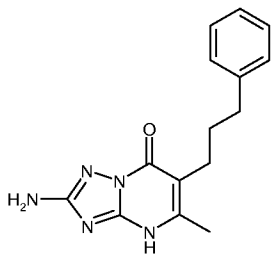
The title compound was prepared according to the procedure described in Example 10.

m/z: 284

^{1}H NMR (400 MHz, DMSO-d6) 2.33 (3H, s), 4.02 (2H, s), 6.02 (2H, br s), 7.95 (3H, s)

Example 34

2-amino-5-methyl-6-(3-phenylpropyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



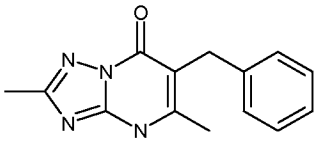
The title compound was prepared according to the procedure described in Example 10.

m/z: 284

^{1}H NMR (400 MHz, DMSO-d6) 1.70-1.77 (2H, m), 2.24 (3H, s), 2.46 (2H, t), 2.65 (2H, t), 5.89 (2H, s), 7.17-7.32 (5H, m)

Example 35

6-benzyl-2,5-dimethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



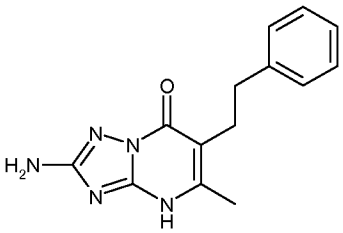
The title compound was prepared according to the procedure described in Example 10.

m/z: 255

^{1}H NMR (400 MHz, DMSO-d6) 2.32 (3H, s), 2.37 (3H, s), 3.96 (2H, s), 7.17-7.31 (5H, m), 13.02 (1H, br s)

Example 36

2-amino-5-methyl-6-phenethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



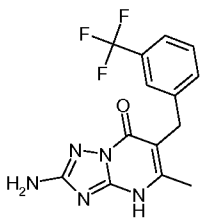
The title compound was prepared according to the procedure described in Example 10.

m/z: 270

^{1}H NMR (400 MHz, DMSO-d6) 2.07 (3H, s), 2.69-2.73 (4H, m), 5.98 (2H, s), 7.21-7.24 (3H, m), 7.29-7.33 (2H, m), 12.35 (1H, br s)

Example 37

2-amino-5-methyl-6-[[3-(trifluoromethyl)phenyl]methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



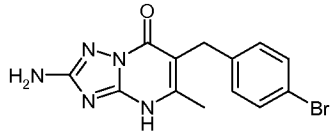
The title compound was prepared according to the procedure described in Example 10.

m/z: 322 $(M-H)^-$

^{1}H NMR (400 MHz, DMSO-d6) 2.31 (3H, s), 2.92 (2H, s), 6.03 (2H, br s), 7.54-7.56 (3H, m), 7.62 (1H, s)

Example 38

2-amino-6-[(4-bromophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



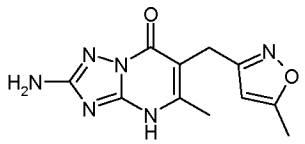
The title compound was prepared according to the procedure described in Example 31.

m/z: 334, 336 (Br isotopes)

^{1}H NMR (400 MHz, DMSO-d6) 2.26 (3H, s), 3.80(2H, s), 6.01 (2H, s), 7.22 (2H, d), 7.47 (2H, d), 12.60 (1H, br s)

Example 39

2-amino-5-methyl-6-[(5-methylisoxazol-3-yl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



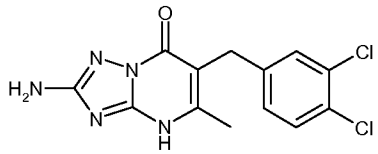
The title compound was prepared according to the procedure described in Example 31.

m/z: 261

^{1}H NMR (400 MHz, DMSO-d6) 2.28 (3H, s), 2.37 (3H, s), 3.78 (2H, s), 6.00 (2H, s), 6.08 (1H, s), 12.70 (1H, br s)

Example 40

2-amino-6-[(3,4-dichlorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



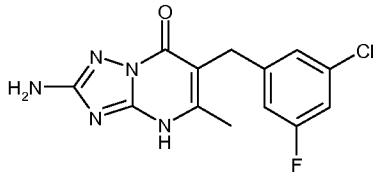
The title compound was prepared according to the procedure described in Example 10.

m/z: 324

^{1}H NMR (400 MHz, DMSO-d6) 2.30 (3H, s), 3.82 (2H, s), 6.00 (2H, s), 7.25 (1H, d), 7.50-7.54 (2H, m), 12.50 (1H, br s)

Example 41

2-amino-6-[(3-chloro-5-fluoro-phenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



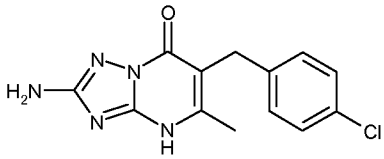
The title compound was prepared according to the procedure described in Example 10.

m/z: 308

^{1}H NMR (400 MHz, DMSO-d6) 2.30 (3H, s), 3.84 (2H, s), 6.01 (2H, s), 7.09 (1H, d), 7.19 (1H, s), 7.25 (1H, d), 12.40 (1H, br s)

Example 42

2-amino-6-[(4-chlorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



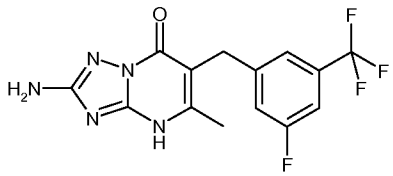
The title compound was prepared according to the procedure described in Example 31.

m/z: 290

^{1}H NMR (400 MHz, DMSO-d6) 2.28 (3H, s), 3.80 (2H, s), 5.98 (2H, s), 7.25 (2H, d), 7.32 (2H, d)

Example 43

2-amino-6-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



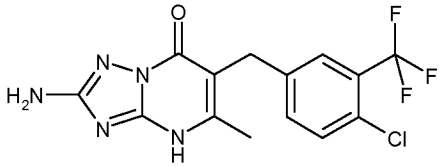
The title compound was prepared according to the procedure described in Example 31.

m/z: 342

^{1}H NMR (400 MHz, DMSO-d6) 2.31 (3H, s), 3.92 (2H, s), 6.00 (2H, s), 7.90 (1H, d), 7.50 (2H, m), 12.60 (1H, br s)

Example 44

2-amino-6-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



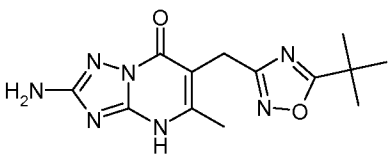
The title compound was prepared according to the procedure described in Example 31.

m/z: 358

^{1}H NMR (400 MHz, DMSO-d6) 2.31 (3H, s), 3.90 (2H, s), 5.98 (2H, s), 7.53 (1H, d), 7.61 (1H, d), 7.76 (1H, s), 12.50 (1H, br s)

Example 45

2-amino-6-[(5-tert-butyl-1,2,4-oxadiazol-3-yl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



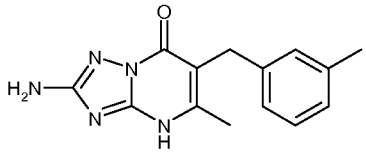
The title compound was prepared according to the procedure described in Example 31.

m/z: 304

^{1}H NMR (400 MHz, DMSO-d6) 1.40 (9H, s), 2.35 (3H, s), 3.95 (2H, s), 6.00 (2H, s), 12.57 (1H, br s)

Example 46

2-amino-5-methyl-6-(m-tolylmethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



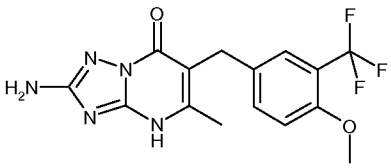
The title compound was prepared according to the procedure described in Example 31.

m/z: 270

^{1}H NMR (400 MHz, DMSO-d6) 2.3 (6H, s), 3.8 (2H, s), 6.0 (2H, s), 7.0 (3H, m), 7.2 (1H, m), 12.6 (1H, br s)

Example 47

2-amino-6-[[4-methoxy-3-(trifluoromethyl)phenyl]methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



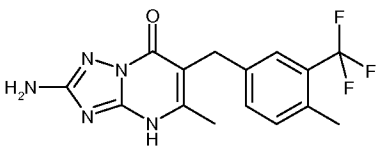
The title compound was prepared according to the procedure described in Example 31.

m/z: 354

^{1}H NMR (400 MHz, DMSO-d6) 2.31 (3H, s), 3.80 (3H, s), 3.88 (3H, s), 6.00 (2H, br s), 7.15 (1H, d), 7.49 (2H, m)

Example 48

2-amino-5-methyl-6-[[4-methyl-3-(trifluoromethyl)phenyl]methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



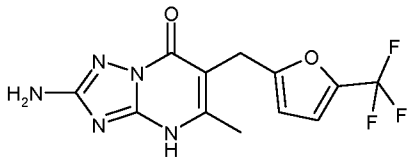
The title compound was prepared according to the procedure described in Example 31.

m/z: 338

^{1}H NMR (400 MHz, DMSO-d6) 2.26 (3H, s), 2.37 (3H, s), 3.82 (2H, s), 5.96 (2H, br s), 7.31 (1H, d), 7.35 (1H, d), 7.52 (1H, s), 12.54 (1H, br s)

Example 49

2-amino-5-methyl-6-[[5-(trifluoromethyl)-2-furyl]methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



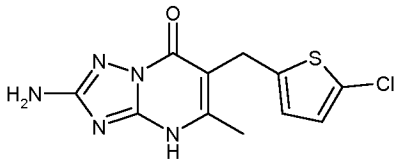
The title compound was prepared according to the procedure described in Example 31.

m/z: 314

^{1}H NMR (400 MHz, DMSO-d6) 2.32 (3H, s), 3.91 (2H, s), 6.05 (2H, s), 6.31 (1H, d), 7.12 (1H, d), 12.7 (1H, br s)

Example 50

2-amino-6-[(5-chloro-2-thienyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



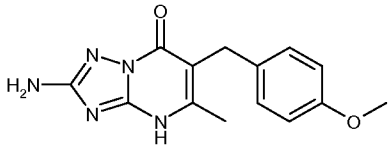
The title compound was prepared according to the procedure described in Example 31.

m/z: 296

^{1}H NMR (400 MHz, DMSO-d6) 2.35 (3H, s), 3.90 (2H, s), 6.02 (2H, s), 6.7 (1H, d), 6.92 (1H, d), 12.7 (1H, br s)

Example 51

2-amino-6-[(4-methoxyphenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



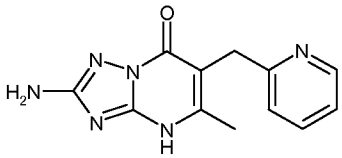
The title compound was prepared according to the procedure described in Example 1.

m/z: 286

^{1}H NMR (400 MHz, DMSO-d6) 2.28 (3H, s), 3.74 (5H, m), 5.99 (2H, br s), 6.85 (2H, m), 7.16 (2H, m), 12.55 (1H, br s)

Example 52

2-amino-5-methyl-6-(2-pyridylmethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



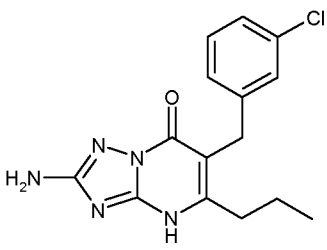
The title compound was prepared according to the procedure described in Example 10.

m/z: 257

^{1}H NMR (400 MHz, DMSO-d6) 2.34 (3H, s), 3.95 (2H, s), 5.98 (2H, s), 7.21 (1H, dd), 7.25 (1H, d), 7.68 (1H, dd), 8.94 (1H, d)

Example 53

2-amino-6-[(3-chlorophenyl)methyl]-5-propyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



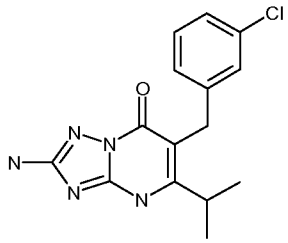
The title compound was prepared according to the procedure described in Example 31.

m/z: 318

^{1}H NMR (400 MHz, DMSO-d6) 0.86 (3H, t), 1.50 (2H, m), 2.55 (2H, m), 3.82 (2H, s), 5.98 (2H, br s), 7.15 (1H, m), 7.25 (3H, m), 12.50 (1H, br s)

Example 54

2-amino-6-[(3-chlorophenyl)methyl]-5-isopropyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



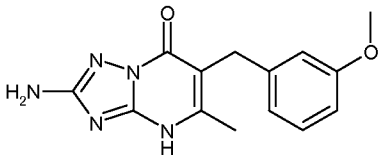
The title compound was prepared according to the procedure described in Example 10.

m/z: 318

^{1}H NMR (400 MHz, DMSO-d6) 1.12-1.13 (6H, m), 3.20 (1H, q), 3.89 (2H, s), 6.05 (2H, s), 7.16 (1H, d), 7.22-7.31 (3H, m), 12.34 (1H, s)

Example 55

2-amino-6-[(3-methoxyphenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



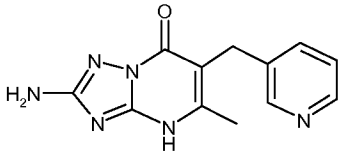
The title compound was prepared according to the procedure described in Example 31.

m/z: 286

^{1}H NMR (400 MHz, DMSO-d6) 2.28 (3H, s), 3.75 (3H, s), 3.79 (2H, s), 5.99 (2H, br s), 6.75 (3H, m), 7.21 (1H, m)

Example 56

2-amino-5-methyl-6-(3-pyridylmethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



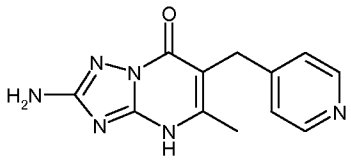
The title compound was prepared according to the procedure described in Example 10.

m/z: 257

^{1}H NMR (400 MHz, DMSO-d6) 2.33 (3H, s), 3.83 (2H, s), 6.00 (2H, s), 7.29 (1H, dd), 7.60 (1H, d), 8.40 (1H, d), 8.50 (1H, s), 12.55 (1H, br s)

Example 57

2-amino-5-methyl-6-(4-pyridylmethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



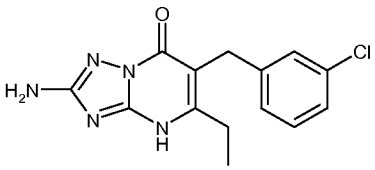
The title compound was prepared according to the procedure described in Example 10.

m/z: 257

^{1}H NMR (400 MHz, DMSO-d6) 2.28 (3H, s), 3.84 (2H, s), 6.01 (2H, s), 7.25 (2H, d), 8.45 (2H, d), 12.60 (1H, br s)

Example 58

2-amino-6-[(3-chlorophenyl)methyl]-5-ethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



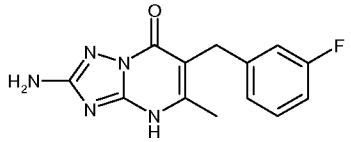
The title compound was prepared according to the procedure described in Example 31.

m/z: 304

^{1}H NMR (400 MHz, DMSO-d6) 1.09 (3H, t), 2.60 (2H, m), 3.86 (2H, s), 7.15-7.32 (4H, m), 12.60 (1H, br s)

Example 59

2-amino-6-[(3-fluorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



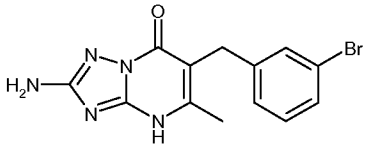
The title compound was prepared according to the procedure described in Example 31.

m/z: 274

^{1}H NMR (400 MHz, DMSO-d6) 2.29 (3H, s), 3.84 (2H, s), 6.01 (2H, s), 6.99-7.10 (3H, m), 7.30-7.35 (1H, m)

Example 60

2-amino-6-[(3-bromophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



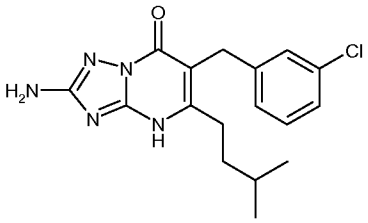
The title compound was prepared according to the procedure described in Example 10.

m/z: 334, 336

^{1}H NMR (400 MHz, DMSO-d6) 2.27 (3H, s), 3.80 (2H, s), 5.95 (2H, s), 7.22 (2H, d), 7.35-7.38 (1H, m), 7.42 (1H, s), 12.52 (1H, s)

Example 61

2-amino-6-[(3-chlorophenyl)methyl]-5-isopentyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



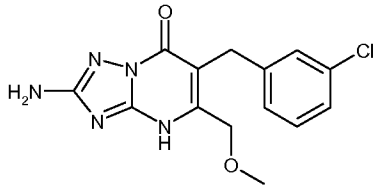
The title compound was prepared according to the procedure described in Example 10.

m/z: 346

^{1}H NMR (400 MHz, DMSO-d6) 0.82 (6H, d), 1.18-1.26 (2H, m), 1.45-1.55 (1H, m), 2.55 (2H, m), 3.81 (2H, s), 6.00 (2H, br s), 7.15 (1H, d), 7.18-7.30 (3H, m), 12.55 (1H, br s)

Example 62

2-amino-6-[(3-chlorophenyl)methyl]-5-(methoxymethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



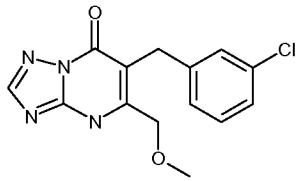
The title compound was prepared according to the procedure described in Example 10.

m/z: 320

^{1}H NMR (400 MHz, DMSO-d6) 3.29 (3H, s), 3.84 (2H, s), 4.41 (2H, s), 6.12 (2H, s), 7.17 - 7.31 (4H, m), 12.71 (1H, s)

Example 63

6-[(3-chlorophenyl)methyl]-5-(methoxymethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



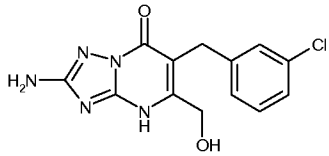
The title compound was prepared according to the procedure described in Example 31.

m/z: 305

^{1}H NMR (400 MHz, DMSO-d6) 3.21 (3H, s), 3.89 (2H, s), 4.25 (2H, s), 7.10-7.23 (4H, m), 7.89 (1H, s)

Example 64

2-amino-6-[(3-chlorophenyl)methyl]-5-(hydroxymethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



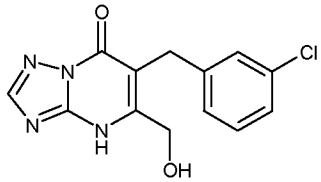
Boron tribromide (8.7 mL 1M solution in DCM, 8.7 mmol) was added to 6-[(3-chlorophenyl)methyl]-5-(2-methoxymethyl)-4H-triazolo[5,1-b]pyrimidin-7-one (464 mg,

1.45 mmol) in DCM (20 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 2 hours. Sodium hydrogencarbonate (saturated aqueous solution, 2 mL) was added and the mixture stirred at room temperature for 1 hour. The solid was collected and washed successively with water and Et_2O to give the title compound (215 mg, 49%). .

^{1}H NMR (400 MHz, DMSO-d6) 3.80 (2H, s), 4.41 (2H, s), 5.55 (1H, br m), 5.87 (2H, s), 7.17-7.28 (4H, m). m/z (ES) $(M+H)^+$ 306.

Example 65

6-[(3-chlorophenyl)methyl]-5-(hydroxymethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



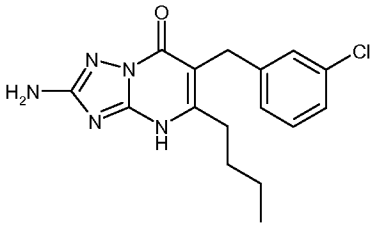
The title compound was prepared according to the procedure described in Example 64.

m/z: 291

^{1}H NMR (400 MHz, DMSO-d6) 3.80 (2H, s), 4.32 (2H, d), 4.81 (1H, t), 7.13-7.25 (4H, m), 7.89 (1H, s).

Example 66

2-amino-5-butyl-6-[(3-chlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



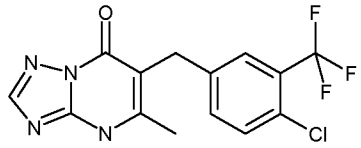
The title compound was prepared according to the procedure described in Example 10.

m/z: 332

^{1}H NMR (400 MHz, DMSO-d6) 0.85 (3H, t), 1.25-1.39 (2H, m), 1.40-1.48 (2H, m), 2.55 (2H, m), 3.86 (2H, s), 5.99 (2H, br s), 7.21 (1H, d), 7.27-7.31 (3H, m), 12.55 (1H, br s).

Example 67

6-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



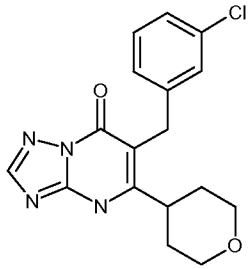
The title compound was prepared according to the procedure described in Example 31.

m/z: 343

^{1}H NMR (400 MHz, DMSO-d6) 2.46 (3H, s), 4.04 (2H, s), 7.49 (2H, m), 7.73 (1H, s), 8.15 (1H, s).

Example 68

6-[(3-chlorophenyl)methyl]-5-tetrahydropyran-4-yl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



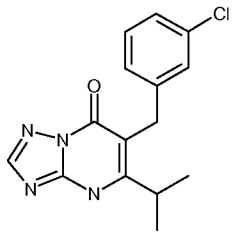
The title compound was prepared according to the procedure described in Example 31.

m/z: 345

^{1}H NMR (400 MHz, DMSO-d6) 1.32 (2H, m), 1.96 (2H, m), 3.22 (1H, m), 3.37 (2H, m), 3.89 (2H, m), 4.03 (2H, s), 7.19-7.35 (4H, m), 8.29 (1H, s).

Example 69

6-[(3-chlorophenyl)methyl]-5-isopropyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



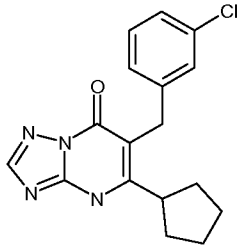
The title compound was prepared according to the procedure described in Example 31.

m/z: 303

^{1}H NMR (400 MHz, DMSO-d6) 1.18 (6H, d), 3.28 (1H, m), 3.99 (2H, s), 7.20 (2H, m), 7.26 (1H, m), 7.31 (1H, m), 8.27 (1H, s).

Example 70

6-[(3-chlorophenyl)methyl]-5-cyclopentyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



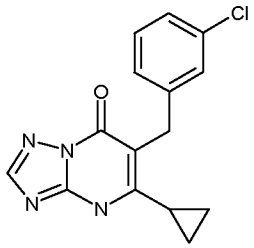
The title compound was prepared according to the procedure described in Example 31.

m/z: 329

^{1}H NMR (400 MHz, DMSO-d6) 1.59 (2H, m), 1.74-1.82 (6H, m), 3.30 (1H, m), 4.00 (2H, s), 7.18-7.32 (4H, m), 8.26 (1H, s).

Example 71

6-[(3-chlorophenyl)methyl]-5-cyclopropyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



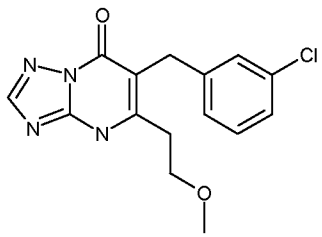
The title compound was prepared according to the procedure described in Example 31.

m/z: 301

^{1}H NMR (400 MHz, DMSO-d6) 1.02 (4H, m), 2.15 (1H, m), 4.04 (2H, s), 7.22 (2H, m), 7.32 (2H, m), 8.30 (1H, s).

Example 72

6-[(3-chlorophenyl)methyl]-5-(2-methoxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



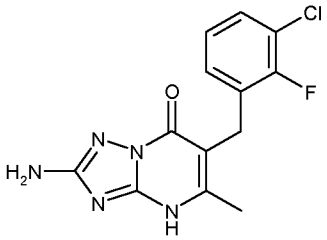
The title compound was prepared according to the procedure described in Example 10.

m/z: 319

^{1}H NMR (400 MHz, DMSO-d6) 2.99 (2H, t), 3.70 (3H, s), 3.74 (2H, s), 4.12 (2H, t), 7.18 (1H, d), 7.25-7.28 (2H, m), 7.33 (1H, dd), 8.25 (1H, s), 11.50 (1H, s).

Example 73

2-amino-6-[(3-chloro-2-fluoro-phenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



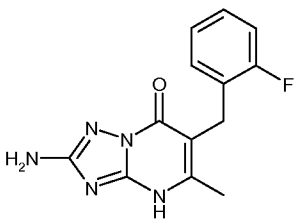
The title compound was prepared according to the procedure described in Example 10.

m/z: 308

^{1}H NMR (400 MHz, DMSO-d6) 2.29 (3H, s), 3.90 (2H, s), 6.07 (2H, s), 7.01-7.16 (2H, m), 7.34-7.50 (1H, m), 13.25 (1H, s).

Example 74

2-amino-6-[(2-fluorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



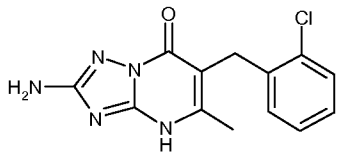
The title compound was prepared according to the procedure described in Example 10.

m/z: 274

^{1}H NMR (400 MHz, DMSO-d6) 2.26 (3H, s), 3.79 (2H, s), 6.02 (2H, s), 7.13 (4H, m), 12.64 (1H, s).

Example 75

2-amino-6-[(2-chlorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



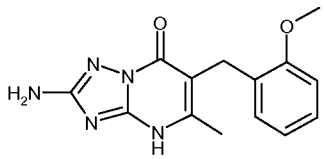
The title compound was prepared according to the procedure described in Example 10.

m/z: 290

^{1}H NMR (400 MHz, DMSO-d6) 2.20 (3H, s), 3.84 (2H, s), 6.03 (2H, s), 7.01 (1H, d), 7.22 (2H, m), 7.45 (1H, d), 12.69 (1H, s).

Example 76

2-amino-6-[(2-methoxyphenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



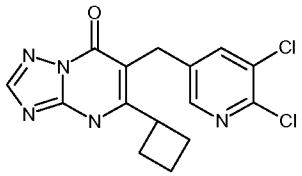
The title compound was prepared according to the procedure described in Example 10.

m/z: 286

^{1}H NMR (400 MHz, DMSO-d6) 2.32 (3H, s), 3.82 (2H, s), 3.95 (3H, s), 6.04 (2H, s), 6.91 (1H, t), 7.06 (2H, m), 7.29 (1H, t), 12.60 (1H, s).

Example 77

5-cyclobutyl-6-[(5,6-dichloro-3-pyridyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



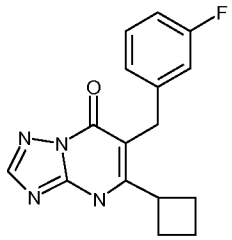
The title compound was prepared according to the procedure described in Example 2.

m/z: 350

^{1}H NMR (400 MHz, DMSO-d6) 1.76-1.78 (1H, m), 1.91 (1H, t), 2.04 (2H, q), 2.33-2.36 (2H, m), 3.70 (1H, t), 3.86 (2H, s), 7.85 (1H, d), 7.98 (1H, s), 8.27 (1H, d).

Example 78

5-cyclobutyl-6-[(3-fluorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



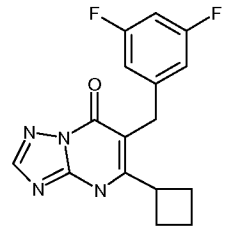
The title compound was prepared according to the procedure described in Example 4:

m/z: 299

^{1}H NMR (400 MHz, DMSO-d6) 1.77 (1H, t), 1.88 (1H, t), 1.95-2.05 (2H, m), 2.32-2.35 (1H, m), 2.37 (1H, d), 3.65-3.74 (1H, m), 3.88 (2H, s), 6.91-6.98 (2H, m), 7.03 (1H, d), 7.24-7.27 (1H, m), 8.05 (1H, s).

Example 79

5-cyclobutyl-6-[(3,5-difluorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



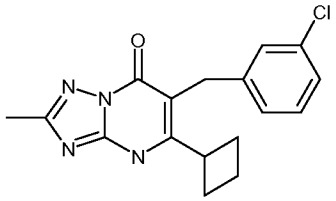
The title compound was prepared according to the procedure described in Example 4.

m/z: 317

^{1}H NMR (400 MHz, DMSO-d6) 1.77-1.80 (1H, m), 1.90 (1H, m), 2.04-2.10 (2H, m), 2.37-2.40 (1H, m), 2.45 (1H, d), 3.82 (1H, t), 3.93 (2H, s), 6.90-6.95 (3H, m), 8.28 (1H, s).

Example 80

6-[(3-chlorophenyl)methyl]-5-cyclobutyl-2-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



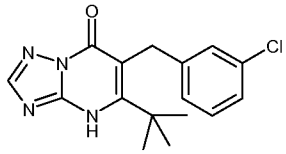
The title compound was prepared according to the procedure described in Example 4.

m/z: 329

^{1}H NMR (400 MHz, DMSO-d6) 1.73-1.75 (1H, m), 1.84 (1H, t), 1.94-1.99 (2H, m), 2.26 (3H, s), 2.31-2.34 (2H, m), 3.55 (1H, dt), 3.81 (2H, s), 7.13 (1H, s), 7.15-7.16 (2H, m), 7.22-7.24 (1H, m).

Example 81

5-tert-butyl-6-[(3-chlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



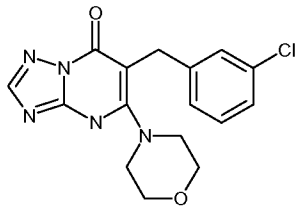
The title compound was prepared according to the procedure described in Example 4.

m/z: 317

^{1}H NMR (400 MHz, DMSO-d6) 1.30 (9H, s), 4.12 (2H, s), 7.05-7.28 (4H, m), 8.07 (1H, s).

Example 82

6-[(3-chlorophenyl)methyl]-5-morpholino-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



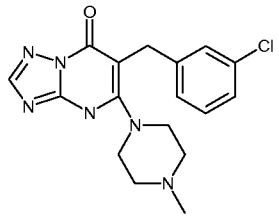
The title compound was prepared according to the procedure described in Example 11.

m/z: 346

^{1}H NMR (400 MHz, DMSO-d6) 3.05 (4H, t), 3.61 (4H, t), 3.84 (2H, s), 7.16-7.31 (4H, m), 8.65 (1H, s).

Example 83

6-[(3-chlorophenyl)methyl]-5-(4-methylpiperazin-1-yl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



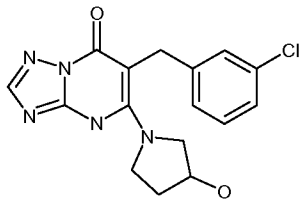
The title compound was prepared according to the procedure described in Example 11.

m/z: 330

^{1}H NMR (400 MHz, DMSO-d6) 2.69 (3H, s), 3.09 (8H, s), 3.79 (2H, s), 7.18-7.30 (4H, m), 7.94 (1H, s).

Example 84

6-[(3-chlorophenyl)methyl]-5-(3-hydroxypyrrolidin-1-yl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



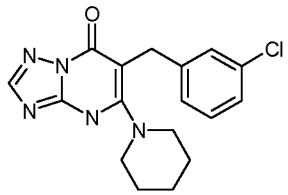
The title compound was prepared according to the procedure described in Example 11.

m/z: 346

^{1}H NMR (400 MHz, DMSO-d6) 1.72 (1H, t), 1.78-1.81 (1H, m), 3.16-3.19 (1H, m), 3.59-3.69 (2H, m), 3.96 (2H, s), 4.19 (1H, s), 7.14 (1H, d), 7.18 (1H, s), 7.21 (1H, s), 7.29 (1H, t), 8.46 (1H, s).

Example 85

6-[(3-chlorophenyl)methyl]-5-(1-piperidyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



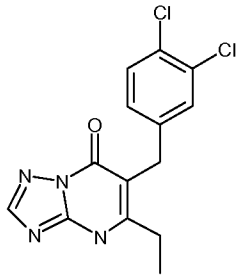
The title compound was prepared according to the procedure described in Example 11.

m/z: 344

^{1}H NMR (400 MHz, DMSO-d6) 1.52 (6H, s), 3.04 (4H, s), 3.79 (2H, s), 7.18-7.24 (2H, m), 7.26-7.28 (2H, m), 8.54 (1H, s).

Example 86

6-[(3,4-dichlorophenyl)methyl]-5-ethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



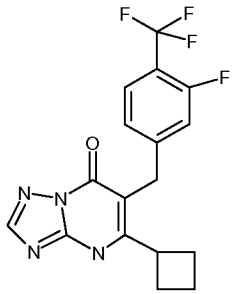
The title compound was prepared according to the procedure described in Example 78.

m/z: 323

^{1}H NMR (400 MHz, DMSO-d6) 1.09 (3H, t), 2.61 (2H, q), 3.88 (2H, s), 7.21-7.24 (1H, m), 7.50 (2H, d), 8.12 (1H, s) .

Example 87

5-cyclobutyl-6-[[3-fluoro-4-(trifluoromethyl)phenyl]methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



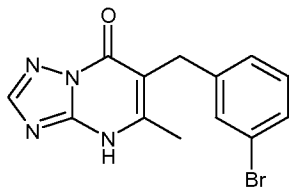
The title compound was prepared according to the procedure described in Example 78.

m/z: 367

^{1}H NMR (400 MHz, DMSO-d6) 1.77 (1H, q), 1.91-1.96 (1H, m), 2.02-2.09 (2H, m), 2.38-2.45 (2H, m), 3.76-3.85 (1H, m), 3.99 (2H, s), 7.24 (1H, d), 7.32-7.35 (1H, m), 7.65 (1H, t), 8.26 (1H, s).

Example 88

6-[(3-bromophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



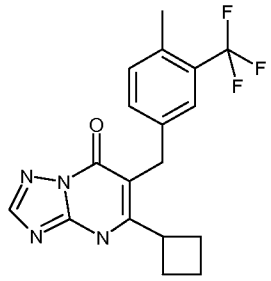
The title compound was prepared according to the procedure described in Example 19.

m/z: 319

^{1}H NMR (400 MHz, DMSO-d6) 2.35 (3H, s), 3.87 (2H, s), 7.21-7.26 (2H, m), 7.36-7.39 (1H, m), 7.45 (1H, s), 8.20 (1H, s), 13.16 (1H, s).

Example 89

5-cyclobutyl-6-[[4-methyl-3-(trifluoromethyl)phenyl]methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



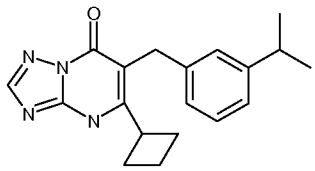
The title compound was prepared according to the procedure described in Example 78.

m/z: 363

^{1}H NMR (400 MHz, DMSO-d6) 1.79 (1H, q), 1.94 (1H, d), 2.00-2.09 (2H, m), 2.38 (3H, s), 2.40-2.48 (2H, m), 3.91-3.95 (3H, m), 7.32-7.35 (1H, m), 7.51 (1H, s), 8.30 (1H, s).

Example 90

5-cyclobutyl-6-[(3-isopropylphenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



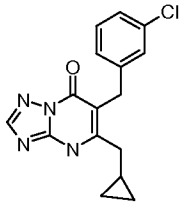
The title compound was prepared according to the procedure described in Example 78.

m/z: 323

^{1}H NMR (400 MHz, DMSO-d6) 1.17 (6H, d), 1.80-1.90 (1H, m), 1.92 (1H, s), 2.03 (2H, d), 2.42 (2H, t), 2.82 (1H, t), 3.89-3.98 (3H, m), 6.96 (1H, d), 7.04 (1H, d), 7.09 (1H, s), 7.16 (1H, t), 8.28 (1H, s).

Example 91

6-[(3-chlorophenyl)methyl]-5-(cyclopropylmethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



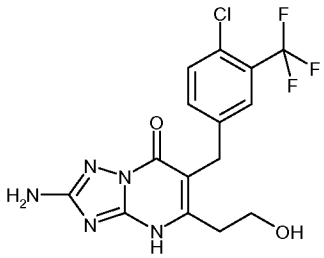
The title compound was prepared according to the procedure described in Example 19.

m/z: 315

^{1}H NMR (400 MHz, DMSO-d6) 13.11 (1H, s), 8.23 (1H, s), 7.32 - 7.15 (4H, m), 3.90 (2H, s), 2.59 (2H, d), 1.03 - 0.94 (1H, m), 0.43 - 0.36 (2H, m), 0.26 - 0.20 (2H, m).

Example 92

2-amino-6-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-5-(2-hydroxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



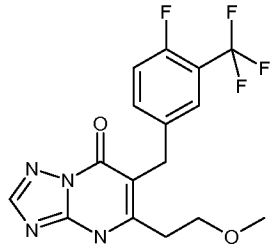
The title compound was prepared according to the procedure described in Example 24.

m/z: 388

^{1}H NMR (399.99 MHz, acetone-d6) δ 7.80 (1H, m), 7.59 (1H, m), 7.52 (1H, m), 4.04 (2H, s), 3.89 (2H, t), 2.98 (2H, t).

Example 93

6-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-5-(2-methoxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



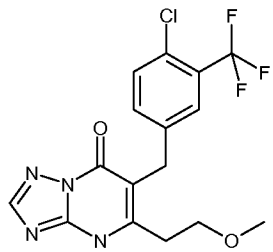
The title compound was prepared according to the procedure described in Example 26.

m/z: 371

^{1}H NMR (399.99 MHz, acetone-d6) δ 8.02 (1H, s), 7.68 (2H, m), 7.28 (1H, m), 4.09 (2H, s), 3.71 (2H, t), 3.28 (3H, s), 3.14 (2H, t)

Example 94

6-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-5-(2-methoxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



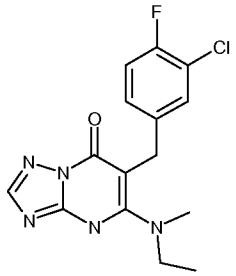
The title compound was prepared according to the procedure described in Example 26.

m/z: 387

^{1}H NMR (399.99 MHz, acetone-d6) δ 8.02 (1H, s), 7.80 (1H, m), 7.61 (1H, m), 7.54 (1H, m), 4.10 (2H, s), 3.71 (2H, t), 3.27 (3H, s), 3.14 (2H, t).

Example 95

6-[(3-chloro-4-fluoro-phenyl)methyl]-5-(ethyl-methyl-amino)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



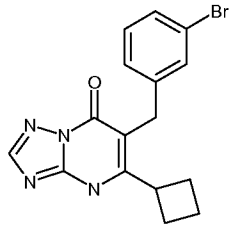
The title compound was prepared according to the procedure described in Example 28.

m/z: 336

^{1}H NMR (399.99 MHz, DMSO-d6) δ 8.62 (1H, bs), 7.35 (1H, m), 7.28 (1H, m), 7.19 (1H, m), 3.81 (2H, s), 3.14 (2H, q), 2.80 (3H, s), 1.02 (3H, t).

Example 96

6-[(3-bromophenyl)methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



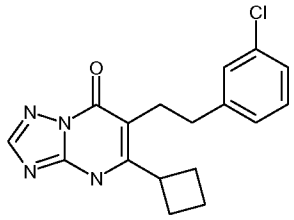
The title compound was prepared according to the procedure described in Example 4.

m/z: 359

^{1}H NMR (399.99 MHz, $CDCl_3$) δ 8.19 (1H, s), 7.35 - 7.32 (2H, m), 7.21 - 7.12 (1H, m), 4.02 (2H, s), 3.93 - 3.81 (1H, m), 2.58 - 2.40 (2H, m), 2.38 - 2.29 (2H, m), 2.26 - 2.11 (1H, m), 2.07 - 1.95 (1H, m).

Example 97

6-[2-(3-chlorophenyl)ethyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



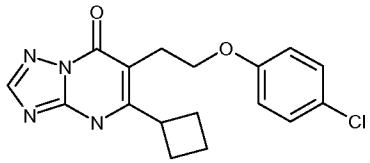
The title compound was prepared according to the procedure described in Example 31.

m/z: 329

^{1}H NMR (399.99 MHz, $CDCl_3$) δ 8.20 (1H, s), 7.25 - 6.88 (4H, m), 3.84 (1H, m), 3.64 (1H, m), 3.00 - 1.96 (10H, m).

Example 98

6-[2-(4-chlorophenoxy)ethyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



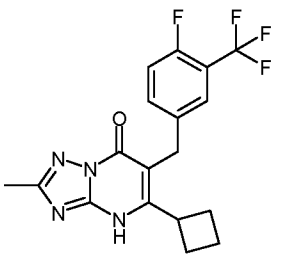
The title compound was prepared according to the procedure described in Example 5.

m/z: 345

^{1}H NMR (399.99 MHz, DMSO-d6) δ 12.88 (1H, s), 12.88 (1H, s), 7.32 - 7.27 (2H, m), 6.98 - 6.89 (2H, m), 4.04 - 3.93 (3H, m), 3.00 - 2.92 (3H, m), 2.21 (2H, t), 1.82 (1H, q), 2.00 (1H, q).

Example 99

5-cyclobutyl-6-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-2-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one



The title compound was prepared according to the procedure described in Example 15.

m/z: 381

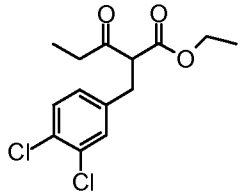
^{1}H NMR (399.99 MHz, DMSO-d6) δ 12.96 (1H, s), 7.61 - 7.49 (2H, m), 7.40 - 7.34 (1H, m), 3.94 (2H, s), 3.86 (1H, t), 2.43 - 2.30 (5H, m), 2.04 (2H, q), 1.98 - 1.89 (1H, m), 1.82 - 1.72 (1H, m).

Preparation of Starting Materials :-

The starting materials for the examples above are either commercially available or are readily prepared by standard methods from known materials. For example, the following reactions are an illustration, but not a limitation, of the preparation of some of the starting materials.

Method I

Ethyl 2-[(3,4-dichlorophenyl)methyl]-3-oxo-pentanoate

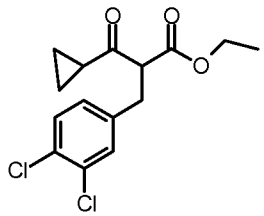


N-Ethyl-*N*-isopropylpropan-2-amine (1.452 mL, 8.34 mmol) was added to lithium chloride (0.177 g, 4.17 mmol), ethyl 3-oxopentanoate (0.594 mL, 4.17 mmol) and 4-(bromomethyl)-1,2-dichlorobenzene (1.00 g, 4.17 mmol) in THF (12 mL) at 20 °C under air. The resulting mixture was stirred at 80 °C for 18 hours. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with water (25 mL) and saturated brine (25 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (1.00 g, 79 %) as a colourless oil.

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.03 (3H, t), 1.22 (3H, t), 2.33-2.43 (1H, m), 2.57-2.67 (1H, m), 3.07-3.13 (2H, m), 3.73 (1H, t), 4.11-4.20 (2H, m), 7.01-7.03 (1H, m), 7.28-7.28 (1H, m), 7.33 (1H, q); m/z (ES) $(M–H)^-$ = 301.

Method II

Ethyl 3-cyclopropyl-2-[(3,4-dichlorophenyl)methyl]-3-oxo-propanoate

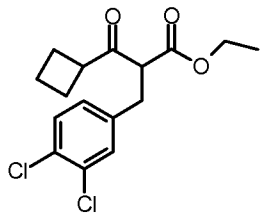


Sodium (184 mg, 8.00 mmol) was added to EtOH (10 mL) at 0 °C. Ethyl 3-cyclopropyl-3-oxopropanoate (1.25 g, 8.00 mmol) was added and the mixture stirred at 0-5 °C for 15 minutes. 4-(Bromomethyl)-1,2-dichlorobenzene (1.92 g, 8.00 mmol) was added and the resulting mixture stirred at room temperature for 30 minutes then heated to 80 °C for 15 hours. The crude mixture was concentrated and purified by silica column chromatography, eluting with EtOAc/isohexane (2.5:97.5) to give the title compound (1.66 g, 66%) as a colourless oil.

^{1}H NMR (400.13 MHz, DMSO-d6) δ 0.87 (2H, m), 0.97 (2H, m), 1.17 (3H, t), 2.21 (1H, m), 2.54 (1H, dd), 2.80 (1H, dd), 4.11 (2H, m), 4.28 (1H, t), 7.27 (1H, dd), 7.58 (2H, m).

Method III

Ethyl 3-cyclobutyl-2-[(3,4-dichlorophenyl)methyl]-3-oxo-propanoate



N-Ethyl-*N*-isopropylpropan-2-amine (2.46 mL, 14.10 mmol) was added to lithium chloride (0.299 g, 7.05 mmol), ethyl 3-cyclobutyl-3-oxopropanoate (1.2 g, 7.05 mmol) and 4-(bromomethyl)-1,2-dichlorobenzene (1.692 g, 7.05 mmol) in THF (12 mL) at 20 °C under air. The resulting mixture was stirred at 80 °C for 18 hours. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with water (25 mL) andsaturated brine (25 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (2.000 g, 86 %) as a colourless oil.

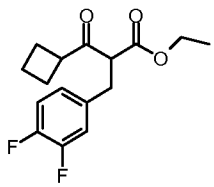
^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.16-1.28 (3H, m), 1.74-1.83 (1H, m), 1.92-1.94 (1H, m), 1.99 (1H, q), 2.03-2.11 (2H, m), 2.23-2.33 (1H, m), 3.04-3.15 (2H, m), 3.33-3.41 (1H, m), 3.69 (1H, t), 4.09-4.19 (2H, m), 6.99-7.02 (1H, m), 7.27 (1H, d), 7.32-7.34 (1H, m); m/z (ES) $(M-H)^-$ = 327.

The ethyl 3-cyclobutyl-3-oxopropanoate used as starting material was prepared as follows: To a suspension of potassium 3-ethoxy-3-oxopropanoate (60.3 g, 354.25 mmol) in acetonitrile (600 mL) under argon at 10 °C was added triethylamine (75 mL, 540 mmol) then magnesium chloride (40.2 g, 421.72 mmol) keeping the temperature below 25 °C. The thick white suspension was stirred for 2.5 hours under argon at room temperature. Cyclobutanecarbonyl chloride (19.25 mL, 167 mmol) was added slowly (over 1 hour) to the re-cooled mixture at 0-5 °C. The reaction was allowed to warm to room temperature and was stirred for 18 hours. The solvent was then evaporated. The white residue was taken up in EtOAc (700 mL) and 2M HCl (about 400 mL) was added until it was all in solution (pH of aqueous = 5). The organic layer was separated then washed with 2M. HCl (200 mL), sat. $NaHCO_3$ (2 x 200 mL, saturated aqueous solution) and the organic layer was dried ($MgSO_4$), filtered and evaporated to afford ethyl 3-cyclobutyl-3-oxopropanoate (28.0 g, 98 %) as pale yellow oil.

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.28 (3H, t), 1.80-1.89 (1H, m), 1.91-2.05 (1H, m), 2.12-2.34 (4H, m), 3.39 (2H, s), 3.34-3.42 (1H, m), 4.19 (2H, q).

Method IV

Ethyl 3-cyclobutyl-2-[(3,4-difluorophenyl)methyl]-3-oxo-propanoate



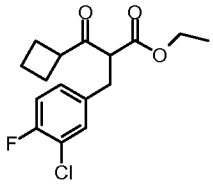
N-Ethyl-*N*-isopropylpropan-2-amine (3.07 mL, 17.63 mmol) was added to lithium chloride (0.374 g, 8.81 mmol), ethyl 3-cyclobutyl-3-oxopropanoate (1.5g, 8.81 mmol) and 4-(bromomethyl)-1,2-difluorobenzene (1.128 mL, 8.81 mmol) in THF (12 mL) at 20°C. The resulting mixture was stirred at 80 °C for 18 hours. The reaction mixture was diluted with EtOAc (25 mL), and washed sequentially with water (20 mL), saturated brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product.

The crude product was purified by flash silica chromatography, elution gradient 0 to 15% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (2.400 g, 92 %) as a colourless oil.

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.15-1.23 (3H, m), 1.74-1.81 (1H, m), 1.87-1.96 (1H, m), 2.01-2.10 (1H, m), 2.02-2.10 (2H, m), 2.23-2.32 (1H, m), 3.01-3.15 (2H, m), 3.36 (1H, t), 3.68 (1H, t), 4.09-4.18 (2H, m), 6.88-6.92 (1H, m), 6.96-6.99 (1H, m), 7.01-7.07 (1H, m); m/z (ES) $(M–H)^-$ = 295.

Method V

Ethyl 2-[(3-chloro-4-fluoro-phenyl)methyl]-3-cyclobutyl-3-oxo-propanoate

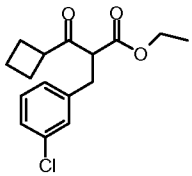


Lithium chloride (139 mg, 3.28 mmol) was added to 4-(bromomethyl)-2-chloro-1-fluorobenzene (733mg, 3.28 mmol), ethyl 3-cyclobutyl-3-oxopropanoate (558 mg, 3.28 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (1.143 mL, 6.56 mmol) in THF (12 mL) at 20 °C under air. The resulting mixture was stirred at 80 °C for 18 hours. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with water (20 mL) andsaturated brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (649 mg, 63.3 %) as a colourless oil.

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.08-1.16 (3H, m), 1.66-1.77 (1H, m), 1.80-1.92 (2H, m), 1.98-2.04 (2H, m), 2.16-2.26 (1H, m), 2.97-3.08 (2H, m), 3.25-3.34 (1H, m), 3.62 (1H, t), 4.04-4.10 (2H, m), 6.96 (2H, d), 7.14 (1H, d); m/z (ES) $(M–H)^-$ = 311.

Method VI

Ethyl 2-[(3-chlorophenyl)methyl]-3-cyclobutyl-3-oxo-propanoate

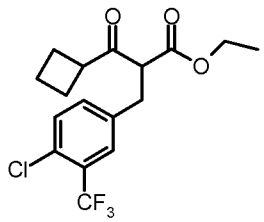


Lithium chloride (0.241 mL, 11.75 mmol) was added in one portion to *N*-ethyl-*N*-diisopropylamine (4.09 mL, 23.50 mmol), 1-(bromomethyl)-3-chlorobenzene (1.541 mL, 11.75 mmol) and ethyl 3-cyclobutyl-3-oxopropanoate (2g, 11.75 mmol) in THF (15mL) at 20 °C over a period of 5 minutes under argon. The resulting mixture was stirred at 70 °C for 16 hours. The reaction mixture was evaporated to dryness and diluted with EtOAc (250 mL), and washed sequentially with 1M Citric acid (50 mL) and saturated $NaHCO_3$ (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the crude product which was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (3.28 g, 95 %) as a colourless liquid.

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.21 (3H, t), 1.71-2.10 (5H, m), 2.23-2.42 (1H, m), 3.06-3.17 (2H, m), 3.31-3.41 (1H, m), 3.72 (1H, t), 4.13 (2H, q), 7.03-7.07 (1H, m), 7.12-7.22 (4H, m); m/z (ES) $(M-H)^-$ = 293.

Method VII

Ethyl 2-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-3-cyclobutyl-3-oxo-propanoate

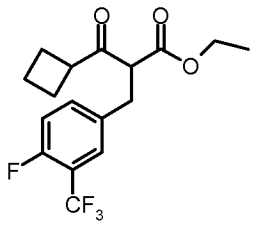


Lithium chloride (0.155 g, 3.66 mmol) was added to 4-(bromomethyl)-1-chloro-2-(trifluoromethyl)benzene (1g, 3.66 mmol), ethyl 3-cyclobutyl-3-oxopropanoate (0.623 g, 3.66 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (1.274 mL, 7.31 mmol) in THF (12 mL) at 20 °C under air. The resulting mixture was stirred at 80 °C for 18 hours. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with water (20 mL) and saturated brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (1.000 g, 75 %) as a yellow oil.

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.10-1.16 (3H, m), 1.68-1.79 (1H, m), 1.81-1.85 (2H, m), 1.87-1.94 (2H, m), 2.19-2.24 (1H, m), 3.03-3.15 (2H, m), 3.32 (1H, t), 3.64 (1H, t), 4.06 (2H, q), 7.19-7.24 (1H, m), 7.33 (1H, d), 7.42 (1H, d); m/z (ES) $(M-H)^-$ = 361.

Method VIII

Ethyl 3-cyclobutyl-2-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-3-oxo-propanoate

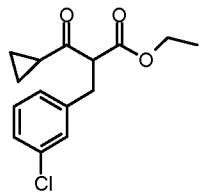


Lithium chloride (0.165 g, 3.89 mmol) was added to 4-(bromomethyl)-1-fluoro-2-(trifluoromethyl)benzene (1g, 3.89 mmol), ethyl 3-cyclobutyl-3-oxopropanoate (0.662 g, 3.89 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (1.355 mL, 7.78 mmol) in THF (12 mL) at 20 °C under air. The resulting mixture was stirred at 80 °C for 18 hours. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with water(20 mL) andsaturated brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the crude product which was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (1.040 g, 77 %) as a colourless oil.

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.15-1.23 (3H, m), 1.76-1.85 (1H, m), 1.88-1.99 (2H, m), 2.02-2.11 (2H, m), 2.23-2.30 (1H, m), 3.10-3.16 (2H, m), 3.38-3.42 (1H, m), 3.70 (1H, t), 4.10-4.20 (2H, m), 7.11 (1H, d), 7.34-7.41 (2H, m); m/z (ES) $(M–H)^-$ = 345.

Method IX

Ethyl 2-[(3-chlorophenyl)methyl]-3-cyclopropyl-3-oxo-propanoate



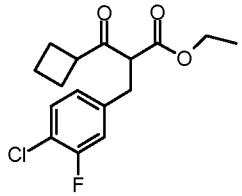
3-Chlorobenzyl bromide (0.354 mL, 2.70 mmol) was added to ethyl 3-cyclopropyl-3-oxopropanoate (505 mg, 3.24 mmol) in dry THF (3.2 mL) followed by *N,N*-diisopropylethylamine (0.939 mL, 5.39 mmol) and lithium chloride (114 mg, 2.70 mmol) and the reaction was heated under reflux for 16 hours. The solvent was evaporated and taken up in EtOAc (40 mL) and washed with 5% w/v citric acid (15 mL, aqueous) and sat. $NaHCO_3$ (15 mL, saturated. aqueous) and the organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution

gradient 5 to 15% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (593 mg, 78 %) as a colourless oil.

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.83-0.99 (2H, m), 1.01-1.16 (2H, m), 1.22 (3H, t), 2.02-2.08 (1H, m), 3.12-3.19 (2H, m), 3.89 (1H, t), 4.12-4.23 (2H, m), 7.07-7.09 (1H, m), 7.14-7.23 (3H, m).

Method X

Ethyl 2-[(4-chloro-3-fluoro-phenyl)methyl]-3-cyclobutyl-3-oxo-propanoate

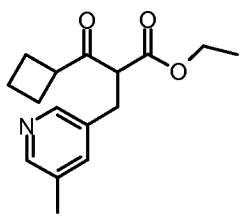


N-Ethyl-*N*-isopropylpropan-2-amine (2.047 mL, 11.75 mmol) was added to lithium chloride (0.249 g, 5.88 mmol), ethyl 3-cyclobutyl-3-oxopropanoate (1g, 5.88 mmol) and 4-(bromomethyl)-1-chloro-2-fluorobenzene (1.313 g, 5.88 mmol) in THF (12 mL) at 20 °C under air. The resulting mixture was stirred at 80 °C for 18 hours. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with water (20 mL) andsaturated brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (1.450 g, 79 %) as a colourless oil.

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.15-1.25 (3H, m), 1.73-1.78 (1H, m), 1.92-2.00 (2H, m), 2.02-2.10 (2H, m), 2.23-2.33 (1H, m), 3.05-3.17 (2H, m), 3.37-3.41 (1H, m), 3.69 (1H, t), 4.06-4.16 (2H, m), 6.89-6.91 (1H, m), 6.96-6.99 (1H, m), 7.29 (1H, d); m/z (ES) $(M-H)^-$ = 311.

Method XI

Ethyl 3-cyclobutyl-2-((5-methylpyridin-3-yl)methyl)-3-oxopropanoate



Ethyl 3-cyclobutyl-3-oxopropanoate (650 mg, 3.82 mmol) was added in one portion to 3-(chloromethyl)-5-methylpyridine hydrochloride (680mg, 3.82 mmol) in THF (4.83 mL) followed by lithium chloride (162 mg, 3.82 mmol) and *N*-ethyl-*N*-diisopropylamine (1.996 mL, 11.46 mmol) at 20 °C over a period of 3 minutes under argon. The resulting mixture was stirred at 70 °C for 16 hours. The reaction mixture was evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (144 mg, 13.7 %) as a tan liquid.

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.21 (3H, t), 1.72-1.81 (1H, m), 1.87-1.99 (1H, m), 2.01-2.14 (2H, m), 2.23-2.33 (2H, m), 2.30 (3H, s), 3.06-3.16 (2H, m), 3.34-3.40 (1H, m), 3.72 (1H, t), 4.13 (2H, q), 7.32 (1H, s), 8.25 (1H, s), 8.29 (1H, s); m/z (ES) $(M-H)^-$ = 274.

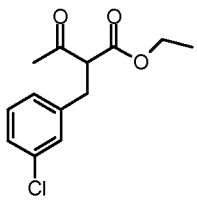
The 3-(chloromethyl)-5-methylpyridine hydrochloride used as starting material was prepared as follows:

Thionyl chloride (5.18 mL, 71.05 mmol) was added portion-wise to (5-methylpyridin-3-yl)methanol (0.5 g, 4.06 mmol), under argon in DCM (22 mL). The resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was evaporated to give 3-(chloromethyl)-5-methylpyridine hydrochloride (0.680 g, 94 %).

^{1}H NMR (400.13 MHz, MeOH-d4) δ 4.79 - 4.82 (4H, m), 8.50 (1H, d), 8.63 (1H, s), 8.73 (1H, d); m/z (ES) $(M+H)^+$ = 141.

Method XII

Ethyl 2-[(3-chlorophenyl)methyl]-3-oxo-butanoate



Ethyl 2-(3-chlorobenzylidene)-3-oxobutanoate (8.20g, 32.45 mmol), and platinum (10% on carbon) (420mg, 2.15 mmol) in EtOAc (200 mL) were hydrogenated in a Parr apparatus at 50 °C and 40 bar until uptake of hydrogen ceased. The catalyst was filtered and washed with EtOAc and the combined filtrates evaporated to give the crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in

isohexane. Pure fractions were evaporated to dryness to afford the title compound (7.34 g, 89 %) as a colourless oil.

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.22 (3H, t), 2.22 (3H, s), 3.11-3.14 (2H, m), 3.75 (1H, t), 4.16 (2H, q), 7.03-7.08 (1H, m), 7.14-7.23 (3H, m).

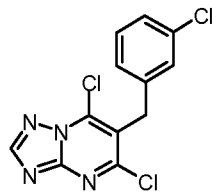
The ethyl 2-(3-chlorobenzylidene)-3-oxobutanoate used as starting material was prepared as follows:

Acetic acid (0.365 mL, 6.38 mmol) and piperidine (0.158 mL, 1.59 mmol) were added dropwise to a solution of ethyl 3-oxobutanoate (4.11 mL, 31.89 mmol) and 3-chlorobenzaldehyde (3.61 mL, 31.89 mmol) in toluene (20 mL), at room temperature. After stirring for 10 minutes the mixture was heated to 120 °C overnight. After cooling the mixture was partitioned between DCM (100 mL) and water (100 mL) and the organics separated, washed (water), dried ($MgSO_4$) and evaporated to give ethyl 2-(3-chlorobenzylidene)-3-oxobutanoate (8.23 g, 100 %) as a yellow oil.

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.25-1.36 (3H, m), 2.28-2.43 (3H, m), 4.28-4.37 (2H, m), 7.28-7.87 (5H, m); m/z (ES) $(M+H)^+$ = 253.

Method XIII

5,7-Dichloro-6-[(3-chlorophenyl)methyl]-[1,2,4]triazolo[1,5-a]pyrimidine



Phosphorus oxychloride (16.89 mL, 181.2 mmol) was added to 6-[(3-chlorophenyl)methyl]-4H-[1,2,4]triazolo[1,5-a]pyrimidine-5,7-dione tri-n-butylamine salt (5.775 g, 12.50 mmol). The resulting suspension was stirred at 120 °C under argon for 2 hours. It was cooled to room temperature and phosphorus oxychloride removed in vacuo. The residue was partitioned between brine (100 mL) and ethyl acetate (2 x 200 mL). The combined organics were dried (sodium sulphate), concentrated in vacuo and adsorbed onto silica. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (2.50 g, 63.8 %) as a white solid.

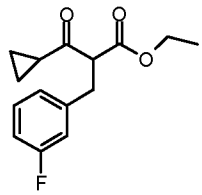
^{1}H NMR (400.13 MHz, DMSO-d6) δ 4.35 (2H, s), 7.25-7.41 (4H, m), 8.8 (1H, s).

The 6-[(3-chlorophenyl)methyl]-4H-[1,2,4]triazolo[1,5-a]pyrimidine-5,7-dione tri-n-butylamine salt used as starting material was prepared as follows:
Tri-n-butylamine (8.37 mL, 35.12 mmol) was added to diethyl 2-[(3-chlorophenyl)methyl]propanedioate (5.0 g, 17.56 mmol) and 1H-1,2,4-triazol-5-amine (1.476 g, 17.56 mmol). The resulting suspension was stirred at 180 °C for 6 hours. It was cooled to room temperature and excess tri-n-butylamine decanted away from the solid product. The latter was triturated overnight with isohexane, filtered and dried under vacuum to give 6-[(3-chlorophenyl)methyl]-4H-[1,2,4]triazolo[1,5-a]pyrimidine-5,7-dione tri-n-butylamine salt (6.75 g, 83%) as a white solid.
^{1}H NMR (400.13 MHz, DMSO-d6) δ 0.85 (9H, t), 1.20-1.35 (6H, m), 1.50-1.61 (6H, m), 2.97-3.07 (6H, m), 3.6 (2H, s), 7.10-7.12 (1H, m), 7.18-7.27 (2H, m), 7.25 (1H, s), 7.75 (1H, s), 11.2 (1H, s); m/z (ES) $(M+H)^+$ = 277.

The diethyl 2-[(3-chlorophenyl)methyl]propanedioate used as starting material was prepared as follows:
Sodium hydride, 60% dispersion (2.497 g, 62.43 mmol) was added to diethyl malonate (9.48 mL, 62.43 mmol) in THF (85 mL) at 20 °C over a period of 10 minutes under argon. The resulting solution was stirred at 20 °C for 10 minutes. 1-(bromomethyl)-3-chloro-benzene (8.19 mL, 62.43 mmol) was added and the resulting solution stirred at 20 °C for 18 hours. The solvent was removed in vacuo and the residue partitioned between 50% brine (200mL) and ethyl acetate (2 x 400mL). Combined organics were dried (sodium sulphate) and concentrated in vacuo. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% DCM in isohexane. Pure fractions were evaporated to dryness to afford diethyl 2-[(3-chlorophenyl)methyl]propanedioate (7.94 g, 44.7 %) as a colourless oil.
^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.1 (6H, t), 3.1 (2H, d), 3.9 (1H, t), 4.02-4.15 (4H, m), 7.2 (1H, d), 7.25-7.36 (3H, m); m/z (ES) $(M+H)^+$ = 285.

Method XIV

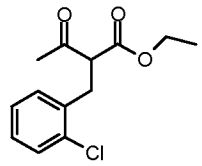
Ethyl 3-cyclopropyl-2-[(3-fluorophenyl)methyl]-3-oxo-propanoate



1-(Bromomethyl)-3-fluorobenzene (1.571 mL, 12.81 mmol) was added to ethyl 3-cyclopropyl-3-oxopropanoate (2 g, 12.81 mmol), tBuOH (0.122 mL, 1.28 mmol) and potassium 2-methylpropan-2-olate (1.437 g, 12.81 mmol) in THF (20 mL) at 0 °C under argon. The resulting mixture was stirred at 80 °C for 16 hours. The reaction mixture was diluted with EtOAc (20 mL), and washed sequentially with water (10 mL), saturated brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (1.830 g, 54.1 %) as a colourless oil. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.84-0.92 (1H, m), 0.93-0.97 (1H, m), 1.05-1.09 (2H, m), 1.22 (3H, t), 2.02-2.08 (1H, m), 3.17-3.20 (2H, m), 3.90 (1H, t), 4.15-4.20 (2H, m), 6.86-6.94 (2H, m), 6.97 (1H, d), 7.21-7.25 (1H, m); m/z (ES) $(M+H)^+$ = 265.

Method XV

Ethyl 2-[(2-chlorophenyl)methyl]-3-oxo-butanoate



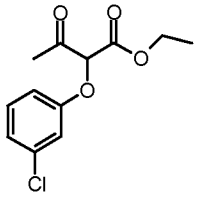
Ethyl acetoacetate (0.292 mL, 2.3 mmol) in THF (0.5 mL) was added dropwise to a stirred slurry of sodium hydride (60% dispersion in mineral oil) (0.092 g, 2.30 mmol) in THF (4 mL) at 0°C, over a period of 2 minutes under nitrogen. The resulting colourless solution was stirred at room temperature for 30 minutes. A solution of [1-(bromomethyl)-2-chlorobenzene (0.473 g, 2.30 mmol) in THF (0.5 mL) was then added dropwise to the stirred solution at 10°C, over a period of 2 minutes under nitrogen. The resulting solution was stirred at 75 °C for 16 hours. The reaction mixture was diluted with DCM (15 mL) and washed with water. The organic layer was evaporated to afford crude product which was

purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound (0.385 g, 65.7 %) as a colourless liquid.

^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.10 (3H, t), 2.22 (3H, s), 3.15-3.25 (2H, m), 4.01-4.12 (3H, m), 7.22-7.30 (3H, m), 7.40-7.47 (1H, m); m/z (ES) $(M-H)^-$ = 253.

Method XVI

ethyl 2-(3-chlorophenoxy)-3-oxobutanoate

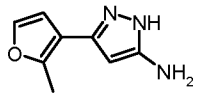


To a solution of fresh sodium hydride (0.339 g, 7.78 mmol) in dimethyl formamide (20 ml) was added 3-chlorophenol (0.826 ml, 7.78 mmol). The mixture was stirred for 30 min at room temperature. ethyl 2-chloro-3-oxobutanoate (1.664 g, 10.11 mmol) was added and the mixture was stirred at 80 °C over night. The mixure was diluted with ethyl acetate and washed with 0.5 M citric acid, sat sodium hydrogencarbonate (aq) and sat sodium chloride (aq). Dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash silica chromatograpy heptan/ethyl acetate 95/5 => 80/20 to give ethyl 2-(3-chlorophenoxy)-3-oxobutanoate (1.300 g, 64 %) as an oil.
Keto form/enol form 50/50

^{1}H NMR (399.988 MHz, $CDCl_3$) δ 11.36 (1H, s, enol), 7.25 - 7.17 (1H, m, keto and enol), 7.06 - 6.97 (1H, m, keto and enol), 6.98 - 6.90 (1H, m, keto and enol), 6.84 - 6.77 (1H, m, keto and enol), 5.06 (1H, s, keto), 4.31 (2H, q, keto), 4.22 (2H, q, enol), 2.38 (3H, s, keto), 1.99 (3H, s, enol), 1.30 (3H, t, keto), 1.19 (3H, t, enol).

Method XVII

3-(2-methylfuran-3-yl)-1H-pyrazol-5-amine



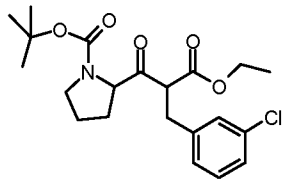
Hydrazine hydrate (0.244 mL, 5.03 mmol) was added to a solution of 3-(2-methylfuran-3-yl)-3-oxopropanenitrile (0.75 g, 5.03 mmol) and methanesulfonic acid (0.033 mL, 0.50

mmol) in ethanol (25 mL). The reaction mixture obtained was stirred at reflux over night and solvent was evaporated. The crude product was purified by flash silica chromatoghrapy hepatan/ethylacetate to give 3-(2-methylfuran-3-yl)-1H-pyrazol-5-amine (0.380 g, 46.3 %).

^{1}H NMR (399.988 MHz, $CDCl_3$) δ 7.31 (1H, d), 6.55 (1H, d), 5.69 (1H, s), 2.45 (3H, s)

Method XVIII

(2S)-tert-butyl 2-(2-(3-chlorobenzyl)-3-ethoxy-3-oxopropanoyl)pyrrolidine-1-carboxylate



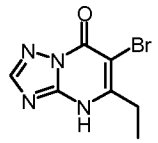
N,N'-methanediylidenedicyclohexanamine (0.773 mL, 4.65 mmol) was added in portions to a solution of (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (1 g, 4.65 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (0.670 g, 4.65 mmol) and N,N-dimethylpyridin-4-amine (1.135 g, 9.29 mmol) in dichloromethane (20 mL). After stirring at room temperature over night the reaction mixture was filtered. The filtrate was washed with 0.5 M citric acid, sat sodium hydrogencarbonate (aq), and sat sodium chloride. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure to give a solid (1.6 g)

The crude (S)-tert-butyl 2-(2,2-dimethyl-4,6-dioxo-1,3-dioxane-5-carbonyl)pyrrolidine-1-carboxylate (1.6 g, 4.69 mmol) was dissolved in ethanol (25 mL). The reaction was heated to reflux for 3 hrs. The solution was concentrated under reduced pressure to give crude (S)-tert-butyl 2-(3-ethoxy-3-oxopropanoyl)pyrrolidine-1-carboxylate (1.200 g, 90 %) as an oil.

^{1}H NMR (399.988 MHz, $CDCl_3$) δ 4.44 - 4.15 (3H, m), 3.64 - 3.39 (4H, m), 2.30 - 1.77 (4H, m), 1.53 - 1.37 (9H, m), 1.29 (3H, t).

Method XIX

6-bromo-5-ethyl-[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one

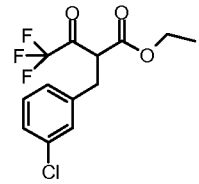


To a solution of ethyl 3-oxopentanoate (6.93 mL, 48.55 mmol) in acetic acid (80 mL) was added 1H-1,2,4-triazol-3-amine (4.08 g, 48.55 mmol). The mixture was heated at 120 °C for 4 hrs. To the reaction was added dibromine (2.495 mL, 48.55 mmol) over a period of 20 minutes. The mixture was stirred at room temperature for 2 h. diethyl ether 100 ml was added. The solid was filtered and washed several times with diethyl ether, dried to give 6-bromo-5-ethyl-[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one (9.75 g, 83 %) as a solid.

^{1}H NMR (399.99 MHz, DMSO-d6) δ 8.35 (1H, s), 2.80 (2H, q), 1.22 (3H, t); m/z (APCI) $(M+H)^+$ 243,245

Method XX

ethyl 2-(3-chlorobenzyl)-4,4,4-trifluoro-3-oxobutanoate

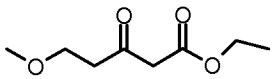


To a suspension of sodium hydride (0.195 g, 4.87 mmol) in dimethoxy ethanol (2 mL) was dropwise added ethyl 4,4,4-trifluoro-3-oxobutanoate (0.717 mL, 4.87 mmol) in dimethoxy ethanol (3 mL). The solution was stirred for 0.5 hr at RT, a solution of 1-(bromomethyl)-3-chlorobenzene (0.637 mL, 4.87 mmol) in dimethoxy ethanol (2 mL) was added. The reaction mixture was stirred at reflux over night. The reaction was diluted with ethyl acetate and citric acid 0.25M. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure to give ethyl 2-(3-chlorobenzyl)-4,4,4-trifluoro-3-oxobutanoate (0.750 g, 49.9 %) as a liquid.

^{1}H NMR (399.988 MHz, $CDCl_3$) δ 7.34 - 7.17 (3H, m), 7.16 - 7.05 (1H, m), 4.24 (2H, q), 4.03 (1H, q), 3.35 - 3.20 (2H, m), 1.27 (3H, t).

Method XXI

Ethyl 5-methoxy-3-oxopentanoate

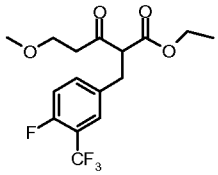


To a suspension of potassium 3-ethoxy-3-oxopropanoate (5.35 g, 31.42 mmol) in acetonitrile (80ml) was addded magnesium chloride hydrate (4.23 g, 37.40 mmol) and triethylamine (6.64 mL, 47.87 mmol) at roomtemperature. The thick warm suspension was stirred for 1 hr under Argon. A suspension of di (1H-imidazol-1-yl)methanone (2.91 g, 17.95 mmol) in acetonitrile (15ml) was prepared and 3-methoxypropanoic acid (1.403 mL, 14.96 mmol) was added slowly at roomtemperature and the reaction was stirred for 15 min. The solution was added to the original suspension and the reaction was stirred for 16 hr. The reaction was diluted with 1M hydrochloric acid (65 ml) until the suspension was separated in two layers and the salt was totally dissolved. The acetonitrile layer was separated and evaporated. The aqueous layer was then re-extracted with ethylacetate. All organics were combined and washed with sodiumhydrogencarbonate (aq) and the combined organic layers dried (magnesiumsulphate), filtered and evaporated to afford the title compound (1.89 g, 73%).

^{1}H NMR (399.99MHz,DMSO-d6) δ 4.14 (2H, q), 3.61 (2H, t), 3.54 (2H, s), 3.26 (3H, s), 2.79 (2H, t), 0.95 (3H, t).

Method XXII

Ethyl 2-[4-fluoro-3-(trifluoromethyl)benzyl]-5-methoxy-3-oxopentanoate

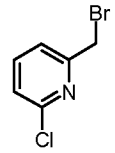


Sodium hydride (0.661 g, 16.53 mmol) was added to ethyl 5-methoxy-3-oxopentanoate (2.4 g, 13.78 mmol) in tetrahydrofurane (8ml) at 0 °C under an inert atmosphere (Argon). The resulting solution was stirred at 20 °C for 10 min. 4-(bromomethyl)-1-fluoro-2-(trifluoromethyl)benzene (3.54 g, 13.78 mmol) dissolved in dichloromethane (8 ml) was added and the resulting solution stirred at 50 °C for 23 hr. The reaction mixture was neutralized with diluted hydrochloric acid, solvent removed in vacuum and the residue partitioned between water and dichloromethane. The combined organics were dried

(magnesiumsulphate) and concentrated in vacuum. The crude product was purified by flash silica chromatography, elution gradient ethylacetate in petroleumeter 10 to 30%. Fractions containing product was evaporated to give the title compound (3.6 g, 75%).
^{1}H NMR (399.99MHz, acetone-d6) δ 7.64-7.49 (2H), 7.31(1H, m), 4.12 (2H, m), 3.56 (2H, m), 3.32-3.14 (6H), 2.80 (2H, m), 1.13 (3H, t). m/z (APCI) $(M+H)^+$ 351.

Method XXIII

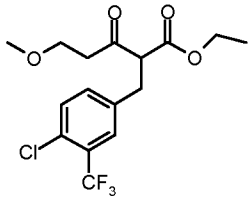
2-(bromomethyl)-6-chloropyridine



A solution of 2-chloro-6-methylpyridine (2 g, 15.68 mmol), N-bromosuccinimide (1.462 mL, 17.25 mmol) and benzoyl peroxide (0.380 g, 1.57 mmol) in carbontetrachloride (35ml) was refluxed for 16 hr. The succinimide was removed by filtration and the solution washed with water, dried (magnesiumsulphate), filtered and evaporated to give the title compound (1.44g, 45%). m/z (APCI) $(M+H)^+$ 207.

Method XXIV

Ethyl 2-[4-chloro-3-(trifluoromethyl)benzyl)-5-methoxy-3-oxopentanoate



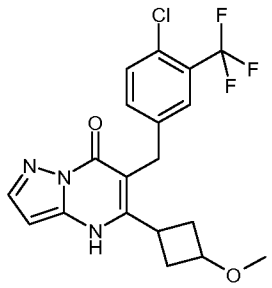
Ethyl 2-(4-chloro-3-(trifluoromethyl)benzyl)-5-methoxy-3-oxopentanoate (0.528 g, 1.44 mmol) was dissolved in dichloromethane (3ml) and cooled to – 40 °C with stirring under an inert atmosphere (Argon). A saturated solution of potassium iodide (0.344 ml, 6.48 mmol) and 1,4,7,10,13,16-hexaoxacyclooctadecane (1.571 ml, 6.48 mmol) in dichloromethane (12ml) was added slowly. After 10 min tribromoborane (4.32 ml, 4.32 mmol) was added and the reactionmixture stirred at – 40 °C for 3 hr. The reaction was allowed to reach 0 °C and then quenched by the addition of saturated sodiumhydrogencarbonate (4 ml). The organic phase was separated, the water phase extracted with dichloromethane and the combined organic phases dried

(magnesiumsulphate), filtered and evaporated. Purification by flash silica chromatography with elution gradient ethylacetate in petroleumeter 0 to 10%. Fractions containing product was evaporated to give the title compound (0.170 g, 34%).

^{1}H NMR (399.99MHz, acetone-d6) δ 7.73 (1H, bs), 7.57 (2H, m), 4.10 (2H, m), 3.77 (2H, m), 3.62 (1H, t), 3.21 (2H, m), 2.79 (2H, m), 1.16 (3H, m).

Method XXV

6-[4-chloro-3-(trifluoromethyl)benzyl]-5-(3-methoxycyclobutyl)pyrazolo[1,5-a]pyrimidin-7(4H)-one



Ethyl 3-(3-methoxycyclobutyl)-3-oxopropanoate was prepared as follows:

To a suspension of potassium 3-ethoxy-3-oxopropanoate (8.24 g, 48.41 mmol) in acetonitrile (120ml) was addded magnesium chloride hydrate (6.53 g, 57.63 mmol) and triethylamine (10.23 mL, 73.77 mmol) at room temperature. The thick warm suspension was stirred for 1 hr under an inert atmosphere (Argon). A suspension of di(1H-imidazol-1-yl)methanone (4.49 g, 27.66 mmol) in acetonitrile (25ml) was prepared and 3-methoxycyclobutanecarboxylic acid (3 g, 23.05 mmol) was added slowly at 20 °C and the reaction was stirred for 15 min. The solution was then added to the origanal suspension and the reaction was stirred for 16 hr. The reaction was diluted with 1M hydrochloric acid (65 ml) until the suspension separated in two phases and the salt was totally dissolved. The acetonitrile layer was separated and evaporated. The aqueous layer was re-extracted with ethylacetate. The combined organics were washed with sodiumhydrogencarbonate twice and the combined organic layers dried (magnesiumsulphate), filtered and evaporated to afford the intermediate (3.55g, 77%).

Ethyl 2-(4-chloro-3-(trifluoromethyl)benzyl)-3-(3-methoxycyclobutyl)-3-oxopropanoate was prepared as follows:

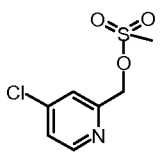
Sodium hydride (0.399 g, 9.99 mmol) was added to ethyl 3-(3-methoxycyclobutyl)-3-oxopropanoate (2 g, 9.99 mmol) in tetrahydrofurane (8ml) at 0 °C under an inert atmosphere (Argon). The resulting solution was stirred at 20 °C for 10 min. 4-(bromomethyl)-1-chloro-2-(trifluoromethyl)benzene (2.73 g, 9.99 mmol) in dichloromethane (8ml) was added and the resulting solution stirred at 50 °C for 23 hr. The reaction mixture was neutralized with diluted hydrochloric acid, solvent removed in vacuum and the residue partitioned between water and ethylacetate. The separated organic phase was dried (magnesiumsulphate), filtered and concentrated in vacuum. The crude product was purified by flash silica chromatography with elution gradient ethylacetate in petroleumeter 0 to 40%. Fractions containing product was evaporated to give the intermediate (2.34 g, 60%).

Ethyl 2-(4-chloro-3-(trifluoromethyl)benzyl)-3-(3-methoxycyclobutyl)-3-oxopropanoate (1 g, 2.55 mmol), 4-methylbenzenesulfonic acid hydrate (0.474 g, 2.49 mmol) and 1H-pyrazol-3-amine (0.74 g, 8.91 mmol) was stirred in n-butanol at 150 °C for 45 min in an open vial. The reactionmixture was dissolved in dichloromethane, the organic phase washed with water, dried (magnesiumsulphate), filtered and evaporated. The product was stirred in a 10% methanolic ethylacetate mixture. The mixture was cooled to 4 °C for 4 hr and the solid filtered off to give the title compound (0.280 g, 27%).

^{1}H NMR (399.99MHz, DMSO-d6) δ 11.84 (1H, bs), 7.83 (1H, d), 7.71 (1H, m), 7.58 (1H, m), 7.47 (1H, m) 6.15 (1H, d), 3.95 (2H, s), 3.80 (1H, m), 3.32 (2H, m), 3.16 (3H, s), 2.43 (1H, m), 2.14 (2H, m). m/z (APCI) $(M+H)^+$ 412.

Method XXVI

(4-chloropyridin-2-yl)methyl methanesulfonate



To a solution of (4-chloropyridin-2-yl)methanol (3 g, 20.90 mmol) in dichloromethane (60 ml) was added triethylamine (2.90 mL, 20.90 mmol) and methanesulfonyl chloride (1.617 mL, 20.90 mmol) at 0 °C. The reactionmixture was stirred at 20 °C for 30 min. The reaction was quenched with addition of water. The reaction mixture was extracted with

dichloromethane and the organic layer dried (magnesiumsulphate) and evaporated. Purification with flash silica chromatography with elution gradient ethylacetate in petroleumeter 20 to 40%. Fractions containing product was evaporated to give the title compound (4.13 g, 89%). m/z (APCI) $(M+H)^+$ 222.

ethyl 2-[(5-tert-butyl-1,2,4-oxadiazol-3-yl)methyl]-3-oxo-butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 269

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.25 (3H, t), 1.44 (9H, s), 2.37 (3H, s), 3.25 (1H, dd), 3.35 (1H, dd), 4.10 (1H, t), 4.23 (2H, q).

ethyl 2-[(5-methyl-1,2-oxazol-3-yl)methyl]-3-oxo-butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 226

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.27 (3H, t), 2.27 (3H, s), 2.37 (3H, s), 3.13 (1H, dd), 3.27 (1H, dd), 4.05 (1H, t), 4.24 (2H, q), 5.83 (1H, s).

ethyl 2-(m-tolylmethyl)-3-oxo-butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 235

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.21 (3H, t), 2.18 (3H, s), 2.31 (3H, s), 3.12 (2H, d), 3.76 (1H, t), 4.18 (2H, q), 6.99 (3H, m), 7.17 (1H, m).

ethyl 3-oxo-2-[[5-(trifluoromethyl)furan-2-yl]methyl]butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 279

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.27 (3H, t), 2.27 (3H, s), 3.23 (2H, m), 3.90 (1H, t), 4.21 (2H, q), 6.14 (1H, d), 6.67 (1H, d).

ethyl 2-[(5-chloro-2-thienyl)methyl]-3-oxo-butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 259 $(M-H)^-$

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.26 (3H, t), 2.25 (3H, s), 3.28 (2H, t), 3.72 (1H, t), 4.22 (2H, q), 6.58 (1H, d), 6.72 (1H, d).

ethyl 2-[(5-tert-butyl-1,2,4-oxadiazol-3-yl)methyl]-3-cyclopropyl-3-oxo-propanoate

The title compound was prepared according to the procedure described in method II.

m/z: 295

^{1}H NMR (399.99 MHz, $CDCl_3$) 0.98 (2H, m), 1.22 (2H, m), 1.3 (3H, m), 1.45 (9H, s), 2.2 (1H, m), 3.4 (2H, m), 4.3 (3H, m).

ethyl 2-[(3-chlorophenyl)methyl]-4-methyl-3-oxo-pentanoate

The title compound was prepared according to the procedure described in method II.

m/z: 283

^{1}H NMR (399.99 MHz, $CDCl_3$) 0.96 (3H, d), 1.07 (3H, d), 1.21 (3H, t), 2.64 (1H, m), 3.17 (2H, m), 3.90 (1H, t), 4.17 (2H, m), 7.06 (1H, m), 7.20 (3H, m).

ethyl 2-[(3-chlorophenyl)methyl]-3-oxo-hexanoate

The title compound was prepared according to the procedure described in method II.

m/z: 283

^{1}H NMR (399.99 MHz, $CDCl_3$) 0.85 (3H, m), 1.20 (3H, m), 1.53 (2H, m), 2.34 (1H, m), 2,52 (1H, m), 3.13 (2H, m), 3.72 (1H, m), 4.18 (2H, m), 7.06 (1H, m), 7.18 (3H, m).

methyl 2-[(3-chlorophenyl)methyl]-3-oxo-pentanoate

The title compound was prepared according to the procedure described in method II.

m/z: 255

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.02 (3H, t), 2.34-2.55 (2H, m), 3.13 (2H, dd), 3.64 (3H, s), 3.78 (1H, dd), 7.01-7.03 (1H, m), 7.15-7.22 (3H, m).

ethyl 2-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]-3-oxo-butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 307

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.23 (3H, t), 2.24 (3H, t), 3.20 (2H, m), 3.73 (1H, t), 4.18 (2H, q), 7.10 (1H, m), 7.16 (1H, m), 7.24 (1H, m).

ethyl 2-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-3-oxo-butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 323

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.20 (3H, t), 2.23 (3H, s), 3.15 (2H, d), 3.71 (1H, t), 4.12 (2H, q), 7.31 (1H, d), 7.39 (1H, d), 7.51 (1H, s).

ethyl 2-[[4-methoxy-3-(trifluoromethyl)phenyl]methyl]-3-oxo-butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 317

ethyl 2-[[4-methyl-3-(trifluoromethyl)phenyl]methyl]-3-oxo-butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 303

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.20 (3H, t), 2.22 (3H, s), 2.43 (3H, s), 3.17 (2H, m), 3.77 (1H, t), 4.18 (2H, q), 7.16 (1H, m), 7.23 (1H, m), 7.41 (1H, s).

ethyl 2-[(4-methoxyphenyl)methyl]-3-oxo-butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 251

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.19 (3H, t), 2.18 (3H, s), 3.11 (2H, d), 3.72 (1H, t), 3.80 (3H, s), 4.14 (2H, m), 6.79 (2H, m), 7.30 (2H, m).

ethyl 2-[(3-methoxyphenyl)methyl]-3-oxo-butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 251

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.22 (3H, t), 2.19 (3H, s), 3.11 (2H, d), 3.78 (4H, m), 4.12 (2H, m), 6.97 (3H, m), 7.20 (1H, m).

methyl 2-[(3-chlorophenyl)methyl]-4-methoxy-3-oxo-butanoate

The title compound was prepared according to the procedure described in method II.

m/z: 269 $[M-H]^-$

^{1}H NMR (399.99 MHz, $CDCl_3$) 3.14 (2H, m), 3.34 (3H, s), 3.51 (3H, s), 4.00 (3H, m), 7.06 (1H, m), 7.20 (3H, m).

ethyl 2-[(3-bromophenyl)methyl]-3-oxo-butanoate

The title compound was prepared according to the procedure described in method XIV.

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.22 (3H, t), 2.22 (3H, s), 3.10-3.18 (2H, m), 3.72 (1H, t), 1.12 (2H, q), 7.02-7.17 (2H, m), 7.30-7.38 (2H, m).

ethyl 2-[[3,5-bis(trifluoromethyl)phenyl]methyl]-3-oxo-butanoate

The title compound was prepared according to the procedure described in method XIV.

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.22 (3H, t), 2.25 (3H, s), 3.22-3.29 (2H, m), 3.78 (1H, t), 4.18 (2H, q), 7.55 (1H, s), 7.65 (1H, s), 7.75 (1H, s).

ethyl 2-[(4-bromophenyl)methyl]-3-oxo-butanoate

The title compound was prepared according to the procedure described in method XIV.

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.22 (3H, t), 2.20 (3H, s), 3.09-3.12 (2H, m), 3.72 (1H, t), 4.14 (2H, q), 7.03 (2H, d), 7.37 (2H, d).

ethyl 3-oxo-2-[[3-(trifluoromethyl)phenyl]methyl]butanoate

The title compound was prepared according to the procedure described in method XIV.

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.22 (3H, t), 2.23 (3H, s), 3.16-3.25 (2H, m), 3.77 (1H, t), 4.14 (2H, q), 7.34-7.49 (4H, m).

ethyl 3-oxo-2-phenethyl-butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 235

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.32 (3H, t), 2.14-2.18 (2H, m), 2.19 (3H, s), 2.58-2.65 (2H, m), 3.42 (1H, t), 4.28 (2H, q), 7.16-7.34 (5H, m).

ethyl 2-acetyl-5-phenylpentanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 249

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.28 (3H, t), 1.57-1.66 (2H, m), 1.85-1.89 (2H, m), 2.20 (3H, s), 2.64 (2H, t), 3.3 9 (1H, t), 2.10 (2H, q), 7.15-7.31 (5H, m).

ethyl 2-[(3,4-dichlorophenyl)methyl]-3-oxo-butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 290

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.21 (3H, t), 2.22 (3H, s), 3.09 (2H, m), 3.72 (1H, t), 4.16 (2H, q), 7.01 (1H, d), 7.28 (1H, d), 7.34 (1H, s).

ethyl 2-[(3-chloro-5-fluoro-phenyl)methyl]-3-oxo-butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 273

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.25 (3H, t), 2.23 (3H, s), 3.14 (2H, m), 3.72 (1H, t), 4.17 (2H, q), 6.78 (1H, d), 6.95 (1H, d), 6.99 (1H, s).

ethyl 3-oxo-2-(4-pyridylmethyl)butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 222

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.21 (3H, t), 2.24 (3H, s), 3.15 (1H, dd), 3.80 (1H, t), 4.16 (2H, q), 7.13 (2H, d), 8.50 (2H, d).

ethyl 3-oxo-2-(3-pyridylmethyl)butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 222

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.21 (3H, t), 2.23 (3H, s), 3.16 (2H, m), 3.76 (1H, t), 4.16 (2H, q), 7.21 (1H, dd), 7.52 (1H, d), 8.46-8.48 (2H, m).

ethyl 3-oxo-2-(2-pyridylmethyl)butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 290

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.22 (3H, t), 2.32 (3H, s), 3.35 (2H, m), 4.18 (2H, q), 4.30 (1H, t), 7.10 (1H, dd), 7.19 (1H, d), 7.57 (1H, t), 8.47 (1H, d).

ethyl 2-[(3-chlorophenyl)methyl]-3-oxo-3-phenylpropanoate

The title compound was prepared according to the procedure described in method II.

m/z: 317

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.12 (3H, t), 3.29 (2H, d), 4.13 (2H, q), 4.59 (1H, t), 7.10-7.28 (4H, m), 7.45 (2H, t), 7.56 (1H, t), 7.96 (2H, d).

methyl 2-[(3-chlorophenyl)methyl]-3-oxo-heptanoate

The title compound was prepared according to the procedure described in method II.

m/z: 283

^{1}H NMR (399.99 MHz, $CDCl_3$) 0.85 (3H, t), 1.22-1.28 (2H, m), 1.46-1.53 (2H, m), 2.31-2.39 (1H, m), 2.50-2.58 (1H, m), 3.13 (1H, dd), 3.13 (1H, dd), 3.71 (3H, s), 3.77 (1H, t), 7.04-7.06 (1H, m), 7.16-7.21 (3H, m).

ethyl 2-[(3-chlorophenyl)methyl]-6-methyl-3-oxo-heptanoate

The title compound was prepared according to the procedure described in method II.

m/z: 311

^{1}H NMR (399.99 MHz, $CDCl_3$) 0.85 (6H, d), 1.21 (3H, t), 1.38-1.48 (3H, m), 2.31-2.39 (1H, m), 2.51-2.59 (1H, m), 3.12 (1H, dd), 3.12 (1H, dd), 3.76 (1H, t), 4.15 (2H, q), 7.04-7.07 (1H, m), 7.17-7.20 (3H, m).

ethyl 2-[(3-chlorophenyl)methyl]-3-cyclopentyl-3-oxo-propanoate

The title compound was prepared according to the procedure described in method II.

m/z: 309

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.22 (3H, t), 1.46-1.83 (8H, m), 2.97 (1H, pent), 3.15 (1H, dd), 3.15 (1H, dd), 4.17 (2H, q), 7.07-7.09 (1H, m), 7.19-7.22 (3H, m).

ethyl 2-[(3-chlorophenyl)methyl]-3-oxo-3-tetrahydrofuran-2-yl-propanoate

The title compound was prepared according to the procedure described in method II.

m/z: 311

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.10-1.15 (3H, t), 1.51-12.10 (4H, m), 3.59-3.65 (1H, m), 2.94-3.15 (2H, m), 3.65-3.83 (1H, m), 3.98-4.12 (3H, m), 4.28 (1H, dt), 7.00-7.05 (1H, m), 7.10-7.17 (3H, m).

ethyl 2-[(3-chlorophenyl)methyl]-3-oxo-3-tetrahydropyran-4-yl-propanoate

The title compound was prepared according to the procedure described in method II.

m/z: 325

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.22-1.26 (3H, t), 1.41-1.54 (2H, m), 1.70-1.77 (2H, m), 2.60-2.62 (1H, m), 3.16 (2H, m), 3.32-3.42 (2H, m), 3.89-4.00 (3H, m), 4.18 (2H, q), 7.05-7.08 (1H, m), 7.18-7.22 (3H, m).

methyl 2-[(3-chlorophenyl)methyl]-5-methoxy-3-oxo-pentanoate

The title compound was prepared according to the procedure described in method II.

^{1}H NMR (399.99 MHz, $CDCl_3$) 2.58-2.74 (2H, m), 3.01-3.13 (2H, m), 3.22 (3H, s), 3.49-3.54 (2H, m), 3.63 (3H, s), 3.77 (1H, t), 6.97-7.00 (1H, m), 7.10-7.15 (3H, m).

ethyl 3-cyclobutyl-2-[(3-fluorophenyl)methyl]-3-oxo-propanoate

The title compound was prepared according to the procedure described in method I.

m/z: 277 $[M-H]^-$

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.12-1.14 (2H, m), 1.15 (1H, s), 1.65-1.74 (1H, m), 1.79-1.88 (1H, m), 1.86-1.91 (1H, m), 1.94-2.01 (1H, m), 1.96-2.03 (1H, m), 2.18-2.25 (1H, m), 3.01-3.12 (2H, m), 3.24-3.34 (1H, m), 3.65 (1H, t), 4.03-4.09 (2H, m), 6.79 (1H, t), 6.83 (1H, d), 6.87 (1H, d), 7.15 (1H, d) .

ethyl 2-[(2-methoxyphenyl)methyl]-3-oxo-butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 273 (M+H +Na)

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.10 (3H, t), 2.16 (3H, s), 2.94 (1H, m), 3.05 (1H, m), 3.79 (3H, s), 3.90 (1H, m), 4.05 (2H, m), 6.84 (1H, t), 6.96 (1H, d), 7.08 (1H, d), 7.21 (1H, t)

ethyl 2-[(3-chloro-2-fluoro-phenyl)methyl]-3-oxo-butanoate

The title compound was prepared according to the procedure described in method XV.

m/z: 273

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.14 (3H, t), 2.20 (3H, s), 3.00-3.23 (2H, m), 3.71-3.82 (1H, m), 4.00-4.15 (2H, m), 6.87-6.95 (1H, m), 7.00-7.07 (1H, m), 7.15-7.24 (1H, m).

ethyl 3-cyclobutyl-2-((5,6-dichloropyridin-3-yl)methyl)-3-oxo-propanoate

The title compound was prepared according to the procedure described in method I.

m/z: 330

^{1}H NMR (399.99 MHz, $CDCl_3$) 0.86-0.95 (1H, m), 1.20-1.23 (1H, m), 1.23 (3H, t), 1.92-2.01 (2H, m), 2.04-2.13 (2H, m), 2.23-2.34 (1H, m), 3.09-3.17 (1H, m), 3.38-3.44 (1H, m), 3.68 (1H, t), 4.20 (2H, q), 7.63 (1H, s), 8.13 (1H, s).

methyl 2-[(3-chlorophenyl)methyl]-4,4-dimethyl-3-oxo-pentanoate

The title compound was prepared according to the procedure described in method I.

m/z: 281 $(M–H)^-$

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.02 (9H, s), 3.06-3.20 (2H, m), 3.67 (3H, s), 4.14-4.18 (1H, m), 7.04-7.07 (1H, m), 7.17-7.18 (2H, m), 7.26 (1H, s).

ethyl 3-cyclobutyl-2-[(3,5-difluorophenyl)methyl]-3-oxo-propanoate

The title compound was prepared according to the procedure described in method I.

m/z 295 $(M–H)^-$

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.16-1.24 (3H, m), 1.76-1.85 (1H, m), 1.94-2.01 (1H, m), 2.04-2.10 (2H, m), 2.03-2.12 (1H, m), 2.24-2.33 (1H, m), 3.06-3.18 (2H, m), 3.33-3.42 (1H, m), 3.70 (1H, t), 4.08-4.17 (2H, m), 6.58-6.65 (1H, m), 6.67-6.70 (2H, m).

ethyl 3-cyclobutyl-2-[[3-fluoro-4-(trifluoromethyl)phenyl]methyl]-3-oxo-propanoate

The title compound was prepared according to the procedure described in method I.

m/z: 345 $(M–H)^-$

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.19 (3H, q), 1.73-1.80 (1H, m), 1.76-1.85 (1H, m), 1.89-1.95 (1H, m), 1.99 (1H, d), 2.05 (1H, d), 2.23-2.31 (1H, m), 3.14-3.20 (1H, m), 3.13-3.24 (1H, m), 3.37-3.43 (1H, m), 3.72 (1H, t), 4.12-4.22 (2H, m), 7.04-7.06 (2H, m), 7.50 (1H, t).

ethyl 3-cyclobutyl-2-[[4-methyl-3-(trifluoromethyl)phenyl]methyl]-3-oxo-propanoate

The title compound was prepared according to the procedure described in method I.

m/z: 341 $(M–H)^-$

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.14-1.25 (3H, m), 1.72-1.81 (1H, m), 1.83-1.99 (1H, m), 1.86-1.97 (1H, m), 2.00-2.07 (2H, m), 2.23-2.32 (1H, m), 2.43-2.43 (3H, m), 3.09-3.20 (2H, m), 3.32-3.41 (1H, m), 3.72 (1H, t), 4.07-4.18 (2H, m), 7.17 (1H, d), 7.22 (1H, s), 7.39 (1H, s).

ethyl 3-cyclobutyl-2-[(3-isopropylphenyl)methyl]-3-oxo-propanoate

The title compound was prepared according to the procedure described in method I.

m/z: 301 $(M–H)^-$

^{1}H NMR (399.99 MHz, $CDCl_3$) 1.18-1.26 (9H, m), 1.71-1.76 (1H, m), 1.85-1.94 (2H, m), 1.95-2.07 (1H, m), 1.98-2.05 (1H, m), 2.20-2.30 (1H, m), 2.82-2.89 (1H, m), 3.08-3.18 (2H, m), 3.26-3.35 (1H, m), 3.74 (1H, t), 4.12 (2H, q), 6.98 (2H, t), 7.06 (1H, d), 7.18 (1H, t).

ethyl 2-(4-chloro-3-(trifluoromethyl)benzyl)-3-oxopentanoate

The title compound was prepared according to the procedure described in method IV.

^{1}H NMR (399.99 MHz, $CDCl_3$) 7.50 (1H, s), 7.41 (1H, d), 7.31 (1H, d), 4.16 (2H, q), 3.75 (1H, t), 3.25 - 3.12 (2H, m), 2.69 - 2.54 (1H, m), 2.47 - 2.33 (1H, m), 1.22 (3H, t), 1.04 (3H, t).

ethyl 2-(3-chlorobenzyl)-4-cyclopropyl-3-oxobutanoate

The title compound was prepared according to the procedure described in method IV.

^{1}H NMR (399.99 MHz, $CDCl_3$). 7.24 - 7.13 (3H, m), 7.10 - 7.03 (1H, m), 4.24 - 4.12 (2H, m), 3.84 (1H, t), 3.23 - 3.07 (2H, m), 2.46 - 2.31 (2H, m), 1.36 - 1.25 (0.5H, m), 1.22 (3H, t), 0.94 - 0.85 (0.5H, m), 0.63 - 0.46 (2H, m), 0.19 - 0.01 (2H, m).

Ethyl 2-[4-fluoro-3-(trifluoromethyl)benzyl)-5-methoxy-3-oxopentanoate

The title compound was prepared according to the procedure described in method XXIV.

^{1}H NMR (399.99 MHz, $CDCl_3$). 7.63 (2H, m), 7.31 (1H, m), 4.10 (2H, m), 3.78 (2H, m), 3.62 (1H, t), 3.21 (2H, m), 2.79 (2H, m), 1.16 (3H, m).

Ethyl 2-[4-chloro-3-(trifluoromethyl)benzyl]-5-methoxy-3-oxopentanoate

The title compound was prepared according to the procedure described in method XXII.

^{1}H NMR (399.99 MHz, $CDCl_3$) 7.81 (1H, bs), 7.65 (2H, m), 4.20 (2H, m), 3.65 (2H, m), 3.42-3.24 (3H), 3.29 (3H, s), 2.91 (2H, m), 1.26 (3H, t).

ethyl 2-[(6-chloropyridin-2-yl)methyl]-3-cyclobutyl-3-oxopropanoate

The title compound was prepared according to the procedure described in method XXII.
m/z: 296
^{1}H NMR (399.99 MHz, $CDCl_3$) 7.54 (1H, t), 7.14 (2H, m), 4.26 (1H, t), 4.15 (2H, q) 3.54 (1H, m), 3.32 (2H, m), 2.30 (1H, m), 2.19-2.06 (3H, m), 1.94 (1H, m), 1.77 (1H, m), 1.24 (3H, t).

ethyl 2-[(4-chloropyridin-2-yl)methyl]-3-cyclobutyl-3-oxopropanoate

The title compound was prepared according to the procedure described in method XXII.
m/z: 296
^{1}H NMR (399.99 MHz, $CDCl_3$) 8.39 (1H, d), 7.27 (1H, d), 7.17 (1H, dd), 4.29 (1H, t), 4.18 (2H, q) 3.56 (1H, m), 3.34 (2H, m), 2.33 (1H, m), 2.20-2.11 (3H, m), 1.98 (1H, m), 1.81 (1H, m), 1.26 (3H, t).

5-chloro-6-(3-chloro-4-fluorobenzyl)[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one

The title compound was prepared according to the procedure described in method XXII.
m/z: 314
^{1}H NMR (399.99 MHz, $CDCl_3$) 8.78 (1H, s), 7.43 (1H, m), 7.28 (2H, m), 3.91 (2H, s).

5,7-dichloro-6-(3-chloro-4-fluorobenzyl)-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine

The title compound was prepared according to the procedure described in method XIII.
m/z: 322
^{1}H NMR (399.99 MHz, $CDCl_3$) 8.50 (1H, s), 7.28 (1H, m), 7.11 (2H, m), 4.35 (2H, s).

ethyl 2-[(5-chloropyridin-3-yl)methyl]-3-cyclobutyl-3-oxopropanoate

The title compound was prepared according to the procedure described in method XXII.
m/z: 296
^{1}H NMR (399.99 MHz, $CDCl_3$) 8.41 (2H, m), 7.74 (1H, m), 4.10 (2H, q), 4.03 (1H, t), 3.54 (1H, m), 3.14 (2H, m), 2.2 (1H, m), 2.11-1.88 (4H), 1.72 (1H, m), 1.17 (3H, t).

2-(bromomethyl)-5-chloropyridine

The title compound was prepared according to the procedure described in method XXIII.
m/z: 207

The synthesis of 5-pyrrolidin-1-yl-2H-1,2,4-triazol-3-amine and 5-morpholino-2H-1,2,4-triazol-3-amine is described in Al-Khamees, Hamad A.; Al-Deeb, O.A.; Bayomi, Said M. Indian Journal of Heterocyclic Chemistry (1993), 2(4), 237-44.

Assays

Antagonism of CCR2b function was determined by inhibition of MCP-1 induced calcium flux in the human monocyte THP-1 cell line. Briefly, THP-1 cells were loaded with the calcium sensitive dye fluo-4 and seeded onto assay plates. Cell were then incubated with increasing concentrations of compound before exposure to hMCP-1. The intracellular Ca^{2+} concentrations were monitored using a fluorescence laser imaging plate reader equipped with an automated 384-well pipettor. Fluorescence versus time data was recorded and analyzed. The data obtained from each replicate experiment were analysed using the software ActivityBase, (ID Business Solutions Ltd). The molar concentration of test compound producing 50% inhibition (IC_{50}) of the MCP-1 effect was derived utilising the Excel-based program XLfit to fit data to a 4-parameter logistic function.

Example	CCR2b IC50 (μM)
1	0.016
2	0.025
3	<0.0051
4	<0.013
5	0.014
6	0.0088
7	0.11
8	<0.0046
9	0.0053

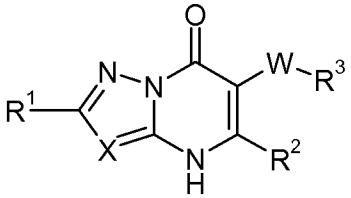
10	0.26
11	0.061
12	>0.49
13	0.54
14	0.0072
15	0.0037
16	>1
17	>1
18	0.16
19	0.38
20	0.021
21	0.38
22	>1
23	0.18
24	0.49
25	0.32
26	0.19
27	0.13
28	0.025
29	0.57
30	>30
31	2.7
32	0.16
33	5.4
34	5.3
35	2.9
36	>10
37	0.99
38	0.93
39	>10
40	0.041

41	0.13
42	0.39
43	0.34
44	0.18
45	>10
46	0.23
47	2.6
48	0.15
49	1.8
50	0.32
51	>9.9
52	>10
53	0.036
54	0.035
55	3
56	>10
57	>10
58	0.043
59	0.39
60	0.12
61	0.21
62	0.33
63	>1
64	>1
65	>1
66	0.059
67	>0.89
68	>1
69	0.068
70	0.1
71	0.02

72	>1
73	>1
74	6.7
75	6.1
76	>10
77	0.029
78	0.22
79	0.17
80	0.044
81	0.2
82	2.9
83	>10
84	>4.8
85	0.28
86	0.02
87	0.064
88	0.35
89	0.011
90	0.086
91	0.053
92	>0.62
93	0.36
94	0.043
95	0.031
96	0.0028
97	>0.81
98	>0.62

CLAIMS

1. A compound of formula (I)



wherein

X is NH;

W is-C_{1-4}alkyl-,-C_{1-4}alkyl-O-, -OC_{1-4}alkyl-, -O- or -S- or -S(O)-, wherein said -C_{1-4}alkyl- is optionally substituted with C_{1-2}alkyl or OH;

R^1 is selected from hydrogen, methyl or NH_2;

R^2 is selected from CF_3, halogen, NR^5R^6, SC_{1-6}alkyl, OC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkoxy, aryl, carbocyclyl, heterocyclyl, heteroaryl, C_{1-6}alkyl, carbocyclyl and C_{1-6}alkylheterocyclyl wherein said C_{1-6}alkyl, aryl, carbocyclyl, heterocyclyl or heteroaryl is optionally substituted with one or more groups selected from C_{1-4}alkoxy, C_{1-4}alkyl, OH, heterocyclyl and halogen;

R^3 is phenyl or heteroaryl, wherein said phenyl or heteroaryl is optionally substituted with one or more groups selected from halogen, CF_3, C_{1-4}alkyl, carbocyclyl and C_{1-4}alkoxy;

R^5 and R^6 are independently selected from hydrogen, C_{1-4}alkyl and carbocyclyl;
or R^5 and R^6 are joined together to form a heterocyclyl ring containing up to 7 ring atoms, wherein said ring optionally is containing up to 3 atoms selected from nitrogen, oxygen and sulphur, and wherein said heterocyclyl ring is optionally substituted with C_{1-2}alkyl or hydroxyl;

with the proviso that if R^3 is pyridyl then said pyridyl has at least one substituent;

as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

2. A compound according to claim 1, wherein W is -C_{1-4}alkyl-.

3. A compound according to claim 2, wherein W is -C_{1-2}alkyl-.

4. A compound according to claim 2, wherein W is -C_1-alkyl-.

5. A compound according to any one of claims 1 to 4, wherein R^2 is carbocyclyl, C_{1-6}alkyl or heterocyclyl, wherein said carbocyclyl, C_{1-6}alkyl or heterocyclyl is optionally substituted with one or more groups selected from C_{1-4}alkoxy, C_{1-4}alkyl, OH, heterocyclyl and halogen.

6. A compound according to any one of claims 1 to 5, wherein R^2 is carbocyclyl, optionally substituted with one or more groups selected from C_{1-4}alkoxy, C_{1-4}alkyl, OH and halogen.

7. A compound according to claim 6, wherein said carbocyclyl is not substitituted.

8. A compound according to claim 6, wherein said carbocyclyl is substituted with OH.

9. A compound according to any one of claims 6 to 8, wherein said carbocyclyl is selected from cyclopropyl, cyclobutyl and cyclopentyl.

10. A compound according to any one of claims 1 to 5, wherein R^2 is C_{1-6}alkyl optionally substituted with one or more groups selected from C_{1-4}alkoxy, C_{1-4}alkyl, heterocyclyl, OH and halogen.

11. A compound according to claim 10, wherein R^2 is not substituted.

12. A compound according to claim 10, wherein said C_{1-6}alkyl is substituted with heterocyclyl, C_{1-4}alkoxy, C_{1-4}alkyl or OH.

13. A compound according to any one of claims 10 to 12, wherein R^2 is C_5alkyl.

14. A compound according to any one of claims 10 to 12, wherein R^2 is C_4alkyl.

15. A compound according to any one of claims 10 to 12, wherein R^2 is C_3alkyl.

16. A compound according to any one of claims 10 to 12, wherein R^2 is C_2alkyl.

17. A compound accodinf to any one of claims 10 to 12, wherein R^2 is C_1alkyl.

18. A compound according to any one of claims 1 to 5, wherein said R^2 is heterocyclyl, optionally substituted with one or more groups selected from C_{1-4}alkoxy, C_{1-4}alkyl, OH and halogen.

19. A compound according to claim 18, wherein said heterocyclyl is not substituted.

20. A compound according to claim 18, wherein said heterocyclyl is substituted with C_{1-4}alkyl or OH.

21. A compound according to any one of claims 1 to 20, wherein R^3 is phenyl substituted with one or more groups selected from halogen, CF_3, C_{1-4}alkyl and carbocyclyl

22. A compound according to claim 21, wherein said halogen is fluoro, bromo or chloro.

23. A compound according to claim 21, wherein said carbocyclyl is cyclopropyl.

24. A compound according to any one of claims 1 to 23, wherein R^3 is heteroaryl.

25. A compound according to claim 24, wherein said heteroaryl is selected from pyridyl or thiazolyl.

26. A compound acording to claim 25, wherein said heteroaryl is substituted with one or more groups selected from halogen, CF_3, C_{1-4}alkyl and C_{1-4}alkoxy.

27. A compound selected from

2-Amino-6-[(3-chlorophenyl)methyl]-5-cyclopropyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-Chlorophenyl)methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

5-Cyclobutyl-6-[(3,4-dichlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

5-Cyclobutyl-6-[(3,4-difluorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-Chloro-4-fluoro-phenyl)methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(4-Chloro-3-fluoro-phenyl)methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

5-Cyclobutyl-6-[(5-methyl-3-pyridyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[[4-Chloro-3-(trifluoromethyl)phenyl]methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

5-Cyclobutyl-6-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-Chlorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-Chlorophenyl)methyl]-5-pyrrolidin-1-yl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-Chlorophenyl)methyl]-5-methoxy-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

5-Chloro-6-[(3-chlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-Amino-5-cyclopropyl-6-[(3,4-dichlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-5-ethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-(3-chlorophenoxy)-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-chlorophenyl)methyl]-5-[(2S)-pyrrolidin-2-yl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-(3-chlorophenyl)sulfanyl-5-ethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-chlorophenyl)methyl]-5-(trifluoromethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-chlorophenyl)methyl]-5-methylsulfanyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

5-butoxy-6-[(3-chlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-(3-chlorophenyl)sulfinyl-5-ethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-5-(2-hydroxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-5-(2-hydroxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(6-chloro-2-pyridyl)methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-5-(2-hydroxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(5-chloro-3-pyridyl)methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-chloro-4-fluoro-phenyl)methyl]-5-pyrrolidin-1-yl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-benzyl-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(2,6-dichlorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(4-fluorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3-chlorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[[3,5-bis(trifluoromethyl)phenyl]methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-5-methyl-6-(3-phenylpropyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-benzyl-2,5-dimethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-5-methyl-6-phenethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-5-methyl-6-[[3-(trifluoromethyl)phenyl]methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(4-bromophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-5-methyl-6-[(5-methylisoxazol-3-yl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3,4-dichlorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3-chloro-5-fluoro-phenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(4-chlorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(5-tert-butyl-1,2,4-oxadiazol-3-yl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-5-methyl-6-(m-tolylmethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[[4-methoxy-3-(trifluoromethyl)phenyl]methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-5-methyl-6-[[4-methyl-3-(trifluoromethyl)phenyl]methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-5-methyl-6-[[5-(trifluoromethyl)-2-furyl]methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(5-chloro-2-thienyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(4-methoxyphenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-5-methyl-6-(2-pyridylmethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one ;

2-amino-6-[(3-chlorophenyl)methyl]-5-propyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3-chlorophenyl)methyl]-5-isopropyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3-methoxyphenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-5-methyl-6-(3-pyridylmethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-5-methyl-6-(4-pyridylmethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3-chlorophenyl)methyl]-5-ethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3-fluorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3-bromophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3-chlorophenyl)methyl]-5-isopentyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

2-amino-6-[(3-chlorophenyl)methyl]-5-(methoxymethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

6-[(3-chlorophenyl)methyl]-5-(methoxymethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one

2-amino-6-[(3-chlorophenyl)methyl]-5-(hydroxymethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chlorophenyl)methyl]-5-(hydroxymethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-5-butyl-6-[(3-chlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chlorophenyl)methyl]-5-tetrahydropyran-4-yl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chlorophenyl)methyl]-5-isopropyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chlorophenyl)methyl]-5-cyclopentyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chlorophenyl)methyl]-5-cyclopropyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chlorophenyl)methyl]-5-(2-methoxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-6-[(3-chloro-2-fluoro-phenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-6-[(2-fluorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-6-[(2-chlorophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-6-[(2-methoxyphenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
5-cyclobutyl-6-[(5,6-dichloro-3-pyridyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
5-cyclobutyl-6-[(3-fluorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
5-cyclobutyl-6-[(3,5-difluorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chlorophenyl)methyl]-5-cyclobutyl-2-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
5-tert-butyl-6-[(3-chlorophenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chlorophenyl)methyl]-5-morpholino-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chlorophenyl)methyl]-5-(4-methylpiperazin-1-yl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chlorophenyl)methyl]-5-(3-hydroxypyrrolidin-1-yl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chlorophenyl)methyl]-5-(1-piperidyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3,4-dichlorophenyl)methyl]-5-ethyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;

5-cyclobutyl-6-[[3-fluoro-4-(trifluoromethyl)phenyl]methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-bromophenyl)methyl]-5-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
5-cyclobutyl-6-[[4-methyl-3-(trifluoromethyl)phenyl]methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
5-cyclobutyl-6-[(3-isopropylphenyl)methyl]-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chlorophenyl)methyl]-5-(cyclopropylmethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
2-amino-6-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-5-(2-hydroxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-5-(2-methoxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one
6-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-5-(2-methoxyethyl)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-chloro-4-fluoro-phenyl)methyl]-5-(ethyl-methyl-amino)-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[(3-bromophenyl)methyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[2-(3-chlorophenyl)ethyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
6-[2-(4-chlorophenoxy)ethyl]-5-cyclobutyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one; and
5-cyclobutyl-6-[[4-fluoro-3-(trifluoromethyl)phenyl]methyl]-2-methyl-4H-[1,2,4]triazolo[5,1-b]pyrimidin-7-one;
and pharmaceutically acceptable salts thereof.

28. A pharmaceutical composition comprising a compound according to any one of claims 1 to 27 and a pharmaceutically acceptable adjuvant, diluent or carrier.

29. A compound according to any one of claims 1 to 27 for use in therapy.

30. The use of a compound according to any one of claims 1 to 27, in the manufacture of a medicament for use in the treatment of diseases in which the chemokine receptor belongs to the C-C receptor family.

31. The use of a compound according to any one of claims 1 to 27, in the manufacture of a medicament for use in the treatment of inflammatory disease.

32. The use of a compound according to any one of claims 1 to 27, in the manufacture of a medicament for use in the treatment of asthma.

33. The use of a compound according to any one of claims 1 to 27, in the manufacture of a medicament for use in the treatment of COPD.

34. The use of a compound according to any one of claims 1 to 27, atherosclerosis, diabetes, obesity , cancer, chronic obstructive rheumatoid arthritis and/or neuropathic pain.

35. A method of treating a disease in which the chemokine receptor belongs to the C-C receptor family, which comprises administering to a mammal in need of such treatment an effective amount of a compound according to any one of claims 1 to 27.

36. A method of treating a inflammatory disease, which comprises administering to a mammal in need of such treatment an effective amount of a compound according to any one of claims 1 to 27.

37. A method of treating a asthma, which comprises administering to a mammal in need of such treatment an effective amount of a compound according to any one of claims 1 to 27.

38. A method of treating COPD, which comprises administering to a mammal in need of such treatment an effective amount of a compound according to any one of claims 1 to 27.

39. A method of treating atherosclerosis, diabetes, obesity , cancer, chronic obstructive, rheumatoid arthritis and/or neuropathic pain, which comprises administering to a mammal in need of such treatment an effective amount of a compound according to any one of claims 1 to 27.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2011/050515

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519 A61P11/00 A61P9/10 A61P19/02
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/134449 A1 (WARATAH PHARMACEUTICALS INC [CA]; SLON-USAKIEWICZ JACEK [CA]) 29 November 2007 (2007-11-29) page 48, lines 9,16 page 143; compound 4 -----	1-39
X	KLEINPETER, E. ET AL: "13C and 15N NMR study of 1,2,4-triazolo[1,5-a]pyrimidines with one tautomerism-introducing substituent", JOURNAL OF MOLECULAR STRUCTURE , 355(3), 273-85 CODEN: JMOSB4; ISSN: 0022-2860, 1995, XP002637297, page 275; compounds 27,28 ----- -/--	1-27

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 June 2011	30/06/2011

Name and mailing address of the ISA/	Authorized officer
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2

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 2006/067401 A1 (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BOWER JUSTIN FAIRFIELD [) 29 June 2006 (2006-06-29) cited in the application pages 1,2,214 claim 13 -----	1-39

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2011/050515

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