Abstract:
The present invention relates to novel compounds that are CGRP receptor antagonists, processes for their preparation, to compositions containing them and to their use in the treatment of migraine, headache, and cluster headache.
The present invention relates to novel compounds, and to the use thereof in treating diseases and conditions mediated by Calcitonin-Gene-Related Peptide (CGRP). In addition, the invention relates to compositions containing compounds of the invention and processes for their preparation.

Calcitonin Gene Related Peptide, CGRP, is a 37 amino acid neurotransmitter, which is widely distributed throughout the central and peripheral nervous system. It is a potent dilator of arteries and veins, particularly in the cerebral vasculature and is released into the venous circulation in migraineurs. These actions together with its localisation in the trigeminovascular system, suggests a role for CGRP in the pathogenesis of migraine. This includes a vasodilator role as well as a possible involvement in the central sensitisation of nociceptive pathways, which are also thought to be a component of migraine. The actions of CGRP in the cerebral vasculature are mediated by CGRP1 receptors, which have a molecular correlate in the calcitonin receptor like receptor (CL) and the accessory protein, RAMP1, the association between which is essential for function.

CGRP receptor antagonists would therefore be expected to be effective in the treatment of migraine and other headache syndromes. The novel non-peptide CGRP receptor antagonist, BIBN 4096 antagonised the vasodilator effects of CGRP on human cerebral vessels and, when given intravenously, was effective in treating headache in migraineurs, thereby providing proof of concept for the use of CGRP receptor antagonists to treat migraine. It would therefore be desirable to identify a CGRP receptor antagonist that is selective for the human CGRP receptor and which could be given by a convenient route of administration, e.g. orally from a convenient pharmaceutical dosage form.

US Patent No 6,344,449 describes the compound N-[(1 R)-2-[[((1 S)-5-amino-1-[(4-(4-pyridinyl)-1-piperazinyl]carbonyl]penty]l]amino]-1-[(3,5-dibromo-4-hydroxyphenyl)methyl]-2-oxoethyl]-4-(1,4-dihydro-2-oxo-3(2H)-quinazolinyl)-1-piperidinecarboxamide (olcegepant; BIBN 4096) as an antagonist of CGRP for the treatment of migraine:
In trials, the compound was administered by intravenous infusion.

The pharmacological profile of MK-0974 (Merck & Co.), an oral calcitonin gene-related peptide (CGRP) receptor antagonist, was described at a recent meeting of the American Headache Society:

MK-0974 is described and claimed in WO04/092168.

WO04/092166, WO06/044504, and WO06/099268 inter alia describe as CGRP antagonists for the treatment of headache, migraine, and cluster headache certain compounds of formula

wherein $R'$ is a carbon-linked nitrogen-containing cyclic group, $n$ is 0, 1 or 2, and $R''$ and $R'''$ together form a fused six-membered aromatic ring which is optionally substituted and contains 0, 1 or 2 nitrogen atoms.
The object of the present invention is to identify a CGRP antagonist which is selective for the hCGRP receptor and, preferably, readily bioavailable from a convenient pharmaceutical dosage form.

According to a first aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:

\[
\text{(I)}
\]

wherein:
- \(R_1\) is selected from the group consisting of hydrogen, aryl, heterocyclyl, alkyl, alkoxy, alkylamino, dialkylamino, and arylamino;
- \(R_2\) is an aryl group;
- \(n\) is 0, 1 or 2; and
- \(R_3\) and \(R_4\) together form a fused six-membered aromatic ring which is optionally substituted and contains 0, 1 or 2 nitrogen atoms.

According to a second aspect, the invention provides a compound of formula (IA) or a pharmaceutically acceptable salt thereof:

\[
\text{(IA)}
\]

wherein \(R_1\) and \(R_2\) have the values set out hereinabove.

According to a third aspect, the invention provides a compound of formula (I) or (IA) as defined hereinabove or a pharmaceutically acceptable salt thereof, wherein \(R_1\) is instead selected from the group consisting of acetyl, amino, cyano, ethoxycarbonyl, and acetamido.
As used herein aryl includes optionally substituted phenyl. A phenyl group can be substituted by up to three substituents independently selected from the group consisting of halogen, trifluoromethyl, methyl and methoxy.

In a further aspect aryl includes phenyl, naphthyl, benzodioxolyl, benzofuranyl, and benzothienyl, any of which can be substituted by up to three substituents independently selected from the group consisting of halogen, trifluoromethyl, methyl, hydroxy, cyano, isopropyl, and methoxy.

As used herein halogen means fluorine, chlorine, bromine or iodine.

As used herein heterocyclyl means a saturated, partially saturated or unsaturated four to seven membered ring, containing one or two heteroatoms selected from nitrogen, oxygen and sulphur, and optionally substituted by up to three substituents independently selected from the group consisting of heterocyclyl, halogen, alkyl, and alkyloxycarbonyl. Heterocyclyl groups include 1-piperazinyl, 1-azetidinyl, 1-piperidinyl, 4-morpholinyl, 3-pyridinyl, and 1-pyrrolidinyl.

In a further aspect a heterocyclyl group can be substituted by up to three substituents independently selected from the group consisting of heterocyclyl, halogen, alkyl, alkylamino, dialkylamino, hydroxy, methoxy, cyano, and alkyloxycarbonyl.

The term 'alkyl' as used herein refers to a linear or branched saturated hydrocarbon group typically containing up to six, for example one, two or three, carbon atoms. Examples of alkyl groups include n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert butyl, n-pentyl, isopentyl (3-methylbutyl), neopentyl (2,2-dimethylpropyl), hexyl, 4-methylpentyl, 3,3-dimethylbutyl or heptyl and the like.

Any alkyl group referred to herein is optionally further substituted by a group selected from the group consisting of alkyloxy, alkylamino, dialkylamino, and heterocyclyl.

In a further aspect an alkyl group can be substituted by up to three substituents independently selected from the group consisting of alkyloxy, alkylamino, dialkylamino, hydroxy, halogen, and heterocyclyl.

In particular aspects of the invention:
R1 is selected from the group consisting of hydrogen; optionally substituted 1-piperazinyl, 1-azetidinyl, 1-piperidinyl, 4-morpholinyl, 3-pyridinyl, or 1-pyrrolidinyl; optionally substituted phenyl; optionally substituted phenylamino; methyl; ethyl; methoxy; methylamino; dimethylamino; dimethylaminoethyloxy; 2-(1-pyrrolidinyl)ethyloxy; and methyloxyethylamino;

and/or

R2 is phenyl optionally substituted by up to three substituents independently selected from the group consisting of chloro, fluoro and methyl;

and/or

n is 0 and R3 and R4 together form a fused pyridyl, or n is 1 or 2 and R3 and R4 together form a fused phenyl; or

R3 and R4 together with the ring to which they are attached form a group selected from Table 1:

Table I

Compounds of the invention include those listed below, and pharmaceutically acceptable salts thereof:

List 1

1-(1-{[5-(2-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

3-(1-{[5-(2-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one
1-(1-[[5-(2-chlorophenyl)-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

3-(1-[[5-(2-chlorophenyl)-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

1-(1-[[5-(2-chlorophenyl)-4-phenyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

3-(1-[[5-(2-chlorophenyl)-4-phenyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

1,1-dimethylethyl 4-(5-(2-chlorophenyl)-7-[2-oxo-2-[4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)-1-piperidinyl]ethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1-piperazinecarboxylate

1,1-dimethylethyl 4-(5-(2-chlorophenyl)-7-[2-oxo-2-[4-(2-oxo-1,2A 5-tetrahydroO-SH-1,3-benzodiazepin-3-yl)-1-piperidinyl]ethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1-piperazinecarboxylate

1-(1-[[5-(2-chlorophenyl)-4-(1-piperazinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

3-(1-[[5-(2-chlorophenyl)-4-(1-piperazinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

3-(1-[[5-(2-chlorophenyl)-4-(phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

3-(1-[[5-(2,3-difluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

1-(1-[[3-(2,3-difluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]acetyl]-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

3-(1-[[5-(2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

1-(1-[[3-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]acetyl]-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

3-(1-[[5-(2-chlorophenyl)-4-(dimethylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

1-(1-[[5-(2-chlorophenyl)-4-(1-piperidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one
piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

3-[(5-(2-chlorophenyl)-4-(1-piperidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

1-[(5-(2-chlorophenyl)-4-(1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

3-(1-[(5-(2-chlorophenyl)-4-(1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-6,7-dimethyl-1,3,4,5-tetrahydro-2H-1,3-diazepin-2-one

1-[(5-(2-chlorophenyl)-4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

3-(1-[(5-(2-chlorophenyl)-4-(4-morpholinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

1-[(5-(2-chlorophenyl)-4-(dimethylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3-diimidazo[4,5-b]pyridin-2-one

3-(1-[(5-(2-chlorophenyl)-4-(3,3-difluoro-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one

1-(1-[(5-(2-chlorophenyl)-4-(3,3-difluoro-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one
yl]acetyl}-4-piperidinyl)-1 ',3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

3-(1-[(5-(2-chlorophenyl)-4-(3,3-difluoro-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-1 ,3,4,5-tetrahydro-2H-1 ',3-benzodiazepin-2-one

1-(1-[(5-(2-chlorophenyl)-4-(4-methyl-1-piperazinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-1 ,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

3-(1-[(5-(2-chlorophenyl)-4-(4-methyl-1-piperazinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-1 ,3,4,5-tetrahydro-2H-1 ',3-benzodiazepin-2-one

1-(1-[(5-(2-chlorophenyl)-4-(3-pyridinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-1 ,3,4,5-tetrahydro-2H-1 ',3-benzodiazepin-2-one

3-(1-[(5-(2-chlorophenyl)-4-(3-pyridinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-3,4-dihydro-2(1 H)-quinazolinone

3-(1-[(5-(2-chlorophenyl)-4-(3-pyridinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-1 ,3,4,5-tetrahydro-2H-1 ',3-benzodiazepin-2-one

1-(1-[(5-(2-chlorophenyl)-4-(3-pyridinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-1 ,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

1-(1-[(5-(2,3-difluorophenyl)-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-1 ,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

3-(1-[(5-(2,3-difluorophenyl)-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-1 ,3,4,5-tetrahydro-2H-1 ',3-benzodiazepin-2-one

1-(1-[(5-(2-methylphenyl)-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-1 ,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

3-(1-[(5-(2-methylphenyl)-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-1 ,3,4,5-tetrahydro-2H-1 ',3-benzodiazepin-2-one

1-(1-[(5-(2-chlorophenyl)-4-[(2-(dimethylamino)ethyl]oxy]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-1 ,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

3-(1-[(5-(2-chlorophenyl)-4-[(2-(dimethylamino)ethyl]oxy]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-1 ,3,4,5-tetrahydro-2H-1 ',3-benzodiazepin-2-one

1-(1-[(5-(2-chlorophenyl)-4-[(2-(methyloxy)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-1 ,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

1-(1-[(5-(2-chlorophenyl)-4-[(2-(1-pyrrolidinyl)ethyl]oxy]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-1 ,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

1-(1-[(5-(2-chlorophenyl)-4-[(2-(1-pyrrolidinyl)ethyl]oxy]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-1 ,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one
Compounds of the invention further include those listed below by Example number and pharmaceutically acceptable salts thereof:

<table>
<thead>
<tr>
<th>List 2</th>
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<tbody>
<tr>
<td>49</td>
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<td>61</td>
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<tr>
<td>62</td>
</tr>
</tbody>
</table>
| 63     | 1-{1-[[5-(2-fluorophenyl)]-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl]-1,3-
<table>
<thead>
<tr>
<th>Number</th>
<th>Chemical Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>64</td>
<td>3-{1-[[5-(2-chlorophenyl)-4-fluorophenyl]yl]amino}-7H-pyrrolo[2,3-d]pyrimidin-7-yl[1,3,4,5-tetrahydro-2H,1,3-benzodiazepin-2-yl]acetyl-4-piperidinyl]-1,3,4,5-tetrahydro-2H,1,3-benzodiazepin-2-one</td>
</tr>
<tr>
<td>65</td>
<td>3-{1-[[5-(2-chloro-4-fluorophenyl)-4-(1-pyrimidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl-4-piperidinyl]-1,3,4,5-tetrahydro-2H,1,3-benzodiazepin-2-one</td>
</tr>
<tr>
<td>66</td>
<td>1-{1-[[5-(2-chloro-4-fluorophenyl)-4-(1-pyrimidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>67</td>
<td>1-{1-[[5-(2-chlorophenyl)-4-(1-pyrimidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>68</td>
<td>1-{1-[[5-(2-chlorophenyl)-4-(1-methylthyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
</tr>
<tr>
<td>69</td>
<td>1-{1-[[5-(2-chlorophenyl)-4-[[1-methylthyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3,4,5-tetrahydro-2H,1,3-benzodiazepin-2-one</td>
</tr>
<tr>
<td>70</td>
<td>3-{1-[[5-(2-chlorophenyl)-4-(1,2,3,6-tetrahydro-4-pyridinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3,4,5-tetrahydro-2H,1,3-benzodiazepin-2-one</td>
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<td>71</td>
<td>1-{1-[[5-(2-chlorophenyl)-4-(1,2,3,6-tetrahydro-4-pyridinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<tr>
<td>72</td>
<td>1-{1-[[5-(2-chlorophenyl)-4-(3-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
</tr>
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<td>73</td>
<td>1-{1-[[5-(2,3-dichlorophenyl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3,4,5-tetrahydro-2H,1,3-benzodiazepin-2-one</td>
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<td>74</td>
<td>1-{1-[[5-(2-chlorophenyl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>3-{1-[[5-(2-chlorophenyl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3,4,5-tetrahydro-2H,1,3-benzodiazepin-2-one</td>
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<td>76</td>
<td>3-{1-[[5-(2-chlorophenyl)-4-(3-ethyl-3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3,4,5-tetrahydro-2H,1,3-benzodiazepin-2-one</td>
</tr>
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<td>3-{1-[[5-(2-chlorophenyl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3,4,5-tetrahydro-2H,1,3-benzodiazepin-2-one</td>
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<td>78</td>
<td>1-{1-[[5-(2-chlorophenyl)-4-(3-ethyl-3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>79</td>
<td>1-{1-[[5-(4-chlorophenyl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>80</td>
<td>3-{1-[[5-(2-chlorophenyl)-4-(4-hydroxy-1-piperidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3,4,5-tetrahydro-2H,1,3-benzodiazepin-2-one</td>
</tr>
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<td>81</td>
<td>3-{1-[[5-(2-chlorophenyl)-4-(2-hydroxyethyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
</tr>
<tr>
<td>82</td>
<td>3-(1-[5-(2,3-dichlorophenyl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-4-piperidinyl)</td>
</tr>
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<td>83</td>
<td>3-(1-[4-(1,4'-bipiperidin-1'-yl)-5-(2-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-4-piperidinyl)</td>
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<td>84</td>
<td>1-[1-[[5-(2-chlorophenyl)-4-(3-hydroxy-1-pyridinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<tr>
<td>85</td>
<td>3-(1-[5-(2-chlorophenyl)-4-(4-hydroxy-1-piperidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-4-piperidinyl)</td>
</tr>
<tr>
<td>86</td>
<td>1-[1-[[5-(2-chlorophenyl)-4-[3-dimethylamino]-1-propyn-1-yl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>87</td>
<td>1-[1-[[4-acetyl]-5-(2-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<tr>
<td>88</td>
<td>3-(1-[4-(3-hydroxy-1-azetidinyl)-5-(2-naphthalenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one</td>
</tr>
<tr>
<td>89</td>
<td>1-[1-[[5-(2-chlorophenyl)-4-(4-hydroxy-1-piperidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
</tr>
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<td>90</td>
<td>1-[1-[[5-(2-chlorophenyl)-4-[2-hydroxyethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
</tr>
<tr>
<td>91</td>
<td>1-[1-[[5-(2-chlorophenyl)-4-(1-hydroxyethyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
</tr>
<tr>
<td>92</td>
<td>1-[1-[[5-(2-chlorophenyl)-4-(3-hydroxy-3-methyl-1-butyn-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
</tr>
<tr>
<td>93</td>
<td>1-[1-[[4-(3-hydroxy-1-azetidinyl)-5-(2-naphthalenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
</tr>
<tr>
<td>94</td>
<td>1,1-dimethylethyl</td>
</tr>
<tr>
<td>95</td>
<td>1,1-dimethylethyl</td>
</tr>
<tr>
<td>96</td>
<td>1-[1-[[5-(2-chlorophenyl)-4-[2-(1-pyridinyl)ethylamino]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>97</td>
<td>3-[1-[[5-(2-chlorophenyl)-4-[1,1-dimethylethylamino]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one</td>
</tr>
<tr>
<td>98</td>
<td>3-[1-[[5-(2-4-methyl-1-piperazinyloxy)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one</td>
</tr>
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<td>99</td>
<td>1-(1-(5-(2-chlorophenyl))-4-[2-hydroxyethyl]oxy)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
</tr>
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<td>100</td>
<td>1-(1-(5-(2,3-dimethylphenyl))-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
</tr>
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<td>101</td>
<td>1-(1-(5-(2,3-dimethylphenyl))-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-spiro[piperidine-4,4-pyrrol[2,3-d][1,3]oxazine]-2(1H)-one</td>
</tr>
<tr>
<td>102</td>
<td>1-(1-(5-(2,3-dichlorophenyl))-4-[3-(methylxy)-1-azetidinyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>103</td>
<td>3-(1-(5-(2-chlorophenyl))-4-[3-(methylxy)-1-azetidinyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one</td>
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<td>104</td>
<td>1-(1-(5-(2-chlorophenyl))-4-[3-(methylxy)-1-azetidinyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>105</td>
<td>3-[4-(3-hydroxy-1-azetidinyl)-7-[2-oxo-2-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl]benzonitrile</td>
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<td>106</td>
<td>1-(1-(5-(2-chlorophenyl))-4-[3-(2,2-difluoromethyl)amino]-1-azetidinyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>107</td>
<td>1-(1-(5-(2,3-bis(methoxyl)phenyl))-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>108</td>
<td>1-(1-(4-(3-hydroxy-1-azetidinyl))-5-[2-(1-methylethyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<tr>
<td>109</td>
<td>1-(1-(4-(3-hydroxy-1-azetidinyl))-5-[3-(trifluoromethyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
</tr>
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<td>110</td>
<td>1-(1-(4-(3-hydroxy-1-azetidinyl))-5-[3-(1-methylthyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>111</td>
<td>1-(1-(5-(2-chlorophenyl))-4-[1,1-dimethylthyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>112</td>
<td>1-(1-(5-(2-chlorophenyl))-4-(3-hydroxy-3-methyl-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>113</td>
<td>1-(1-(5-(2-chlorophenyl))-4-(3-hydroxy-3-methyl-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-spiro[piperidine-4,4-pyrrol[2,3-d][1,3]oxazine]-2(1H)-one</td>
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<td>114</td>
<td>1-(1-(5-(2,3-dichlorophenyl))-4-(3-hydroxy-3-methyl-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>115</td>
<td>1-(1-(5-(2-chloro-2-fluorophenyl))-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-spiro[piperidine-4,4-pyrrol[2,3-d][1,3]oxazine]-2(1H)-one</td>
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<td>1-(1-(5-(3-chloro-2-fluorophenyl))-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>117</td>
<td>1-(1-(5-(3-chloro-2-methylphenyl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>118</td>
<td>1-(1-(5-(3-chloro-2-methylphenyl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl)spiro[piperidine-4,4'-pyridol[2,3-d][1,3]oxazin]-2(1H)-one</td>
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<td>119</td>
<td>1-(1-(5-(2,3-dichlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>1-(1-(5-(2,3-dichlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl)spiro[piperidine-4,4'-pyridol[2,3-d][1,3]oxazin]-2(1H)-one</td>
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<td>121</td>
<td>1-(1-(5-(2-chloro-3-(trifluoromethyl)phenyl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>1-(1-(5-(2-chloro-3-(trifluoromethyl)phenyl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl)spiro[piperidine-4,4'-pyridol[2,3-d][1,3]oxazin]-2(1H)-one</td>
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<td>123</td>
<td>1-(1-(4-acetyl-5-(2,3-dichlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>124</td>
<td>1-(1-(4-acetyl-5-(2,3-dichlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl)spiro[piperidine-4,4'-pyridol[2,3-d][1,3]oxazin]-2(1H)-one</td>
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<td>125</td>
<td>1-(1-(5-(2,4-dichlorophenyl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>126</td>
<td>1-(1-(5-(2,4-dichlorophenyl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl)spiro[piperidine-4,4'-pyridol[2,3-d][1,3]oxazin]-2(1H)-one</td>
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<td>127</td>
<td>1-(1-(5-(2,2-difluoro-1,3-benzodioxol-4-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>128</td>
<td>1-(1-(5-(2,2-difluoro-1,3-benzodioxol-4-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl)spiro[piperidine-4,4'-pyridol[2,3-d][1,3]oxazin]-2(1H)-one</td>
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<td>129</td>
<td>1-(1-(5-(2,4-difluorophenyl)-4-(1-hydroxyethyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl)spiro[piperidine-4,4'-pyridol[2,3-d][1,3]oxazin]-2(1H)-one</td>
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<td>130</td>
<td>1-(1-(5-(2,4-difluorophenyl)-4-(1-hydroxyethyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl)spiro[piperidine-4,4'-pyridol[2,3-d][1,3]oxazin]-2(1H)-one</td>
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<td>1-(1-(5-(2,4-difluorophenyl)-4-(1-hydroxyethyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>1-(1-(5-(2,2-difluoro-1,3-benzodioxol-4-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl)spiro[piperidine-4,4'-pyridol[2,3-d][1,3]oxazin]-2(1H)-one</td>
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<td>1-(1-(5-(2,2-difluoro-1,3-benzodioxol-4-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl)spiro[piperidine-4,4'-pyridol[2,3-d][1,3]oxazin]-2(1H)-one</td>
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<td>1-(1-(5-(2,2-difluoro-1,3-benzodioxol-4-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<tr>
<td>No.</td>
<td>Molecular Structure</td>
</tr>
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<td>-----</td>
<td>-----------------------------------------------------------------------------------</td>
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<tr>
<td>135</td>
<td>1-(1H-[1,2,3]triazolo[4,5-c]pyridin-7-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrolol[2,3-d][pyrimidin-7-y]acetyl-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>1-(1H-[1,2,3]triazolo[4,5-c]pyridin-7-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrolol[2,3-d][pyrimidin-7-y]acetyl-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>137</td>
<td>1-(1H-[1,2,3]triazolo[4,5-c]pyridin-7-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrolol[2,3-d][pyrimidin-7-y]acetyl-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>138</td>
<td>1-(1H-[1,2,3]triazolo[4,5-c]pyridin-7-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrolol[2,3-d][pyrimidin-7-y]acetyl-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>1-(1H-[1,2,3]triazolo[4,5-c]pyridin-7-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrolol[2,3-d][pyrimidin-7-y]acetyl-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>140</td>
<td>1-(1H-[1,2,3]triazolo[4,5-c]pyridin-7-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrolol[2,3-d][pyrimidin-7-y]acetyl-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>1-(1H-[1,2,3]triazolo[4,5-c]pyridin-7-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrolol[2,3-d][pyrimidin-7-y]acetyl-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>142</td>
<td>1-(1H-[1,2,3]triazolo[4,5-c]pyridin-7-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrolol[2,3-d][pyrimidin-7-y]acetyl-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>143</td>
<td>1-(1H-[1,2,3]triazolo[4,5-c]pyridin-7-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrolol[2,3-d][pyrimidin-7-y]acetyl-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>1-(1H-[1,2,3]triazolo[4,5-c]pyridin-7-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrolol[2,3-d][pyrimidin-7-y]acetyl-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>1-(1H-[1,2,3]triazolo[4,5-c]pyridin-7-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrolol[2,3-d][pyrimidin-7-y]acetyl-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>1-(1H-[1,2,3]triazolo[4,5-c]pyridin-7-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrolol[2,3-d][pyrimidin-7-y]acetyl-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>1-(1H-[1,2,3]triazolo[4,5-c]pyridin-7-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrolol[2,3-d][pyrimidin-7-y]acetyl-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
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<td>1-(1H-[1,2,3]triazolo[4,5-c]pyridin-7-yl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrolol[2,3-d][pyrimidin-7-y]acetyl-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one</td>
</tr>
</tbody>
</table>
Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. The term “pharmaceutically acceptable salts” refers to salts prepared from pharmaceutically acceptable acids including inorganic and organic acids. Such acids include acetic, L-ascorbic acid (vitamin C), L-aspartic acid, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanedisulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, malonic, mandelic, methanesulfonic, mucic, nicotinic, phosphoric, succinic, sulphuric, tartaric, p-toluene sulfonic, perchloric, fluoboric, and the like.

It will be appreciated by the person skilled in the art that the compound of formula (I) may exist in stereoisomeric forms (e.g. diastereoisomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates.
The different stereoisomeric forms of the compound of formula (I) may be obtained according to methods well known in the literature, for example by separation one from the other by the usual methods such as preparative HPLC or by chromatographic purifications. A racemic mixture may either be separated using preparative HPLC and a column with a chiral stationary phase or resolved to yield individual enantiomers utilising methods known to those skilled in the art. Any given isomer may also be obtained by stereospecific or asymmetric synthesis. In addition, racemic intermediate compounds may be resolved and used to prepare individual stereoisomeric forms of chiral compounds of the invention.

The invention also extends to any tautomeric forms and mixtures thereof.

Hereinafter, the compounds of formula (I) and their pharmaceutically acceptable salts are referred to as "the compounds of the invention".

The compounds of the invention may exist as pharmaceutically acceptable solvates such as hydrates and may form polymorphs and pseudopolymorphs.

The invention also includes all suitable isotopic variations of a compound of the invention. An isotopic variation of a compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine and chlorine such as $^2$H, $^3$H, $^{13}$C, $^{14}$C, $^{15}$N, $^{17}$O, $^{18}$O, $^{31}$P, $^{32}$P, $^{35}$S, $^{18}$F and $^{36}$Cl, respectively. Certain isotopic variations of the invention, for example, those in which a radioactive isotope such as $^3$H or $^{14}$C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e., $^3$H, and carbon-14, i.e., $^{14}$C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e., $^2$H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the compounds of the invention can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the Examples and Descriptions hereafter using appropriate isotopic variations of suitable reagents.
The compounds of the present invention have potential utility in treating, preventing, ameliorating, controlling or reducing the risk of one or more of the following conditions or diseases: headache; migraine; cluster headache; chronic tension type headache; pain; chronic pain; neurogenic inflammation and inflammatory pain; neuropathic pain; visceral pain; eye pain; tooth pain; cancer pain; diabetes; non-insulin dependant diabetes mellitus; vascular disorders; inflammation; arthritis; bronchial hyperreactivity; asthma; shock; sepsis; opiate withdrawal syndrome; morphine tolerance; hot flashes in men and women; allergic dermatitis; encephalitis, brain trauma; epilepsy; neurodegenerative diseases; skin diseases; psoriasis; prevention of tumour growth; neurogenic cutaneous redness, skin rosaceousness and erythema; tinnitus; thermal injury; circulatory shock; Reynaud's syndrome; peripheral arterial insufficiency; subarachnoid/cranial haemorrhage; ischaemia; stroke; inflammatory bowel disease, irritable bowel syndrome, cystitis; and other conditions that may be treated or prevented by antagonism of CGRP receptors. Of particular importance is the acute or prophylactic treatment of headache, including migraine and cluster headache.

As discussed hereinabove, it is believed that compounds of the invention are particularly useful for the treatment of migraine, headache, and cluster headache.

Therefore, according to a further aspect, the invention provides compounds of the invention for use as a medicament, such as a human medicament.

The invention further provides a method of treating migraine, headache, or cluster headache, which method comprises administering to a patient in need thereof an effective amount of a compound of the invention.

According to a further aspect the invention provides the use of compounds of the invention in the manufacture of a medicament for treating or preventing migraine, headache or cluster headache.

It will be appreciated that references herein to "treatment" extend to prophylaxis, prevention of recurrence and suppression or amelioration of symptoms (whether mild, moderate or severe) as well as the treatment of established conditions. The compound of the invention may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

According to a further aspect, the invention provides a pharmaceutical composition comprising a compound of the invention, in association with one or more
pharmaceutically acceptable carrier(s), diluents(s) and/or excipient(s). The carrier, diluent and/or excipient must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

The compounds of the invention may be administered in conventional dosage forms prepared by combining a compound of the invention with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical compositions of the invention may be formulated for administration by any route, and include those in a form adapted for oral, topical or parenteral administration to mammals including humans.

The compositions may be formulated for administration by any route. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatine, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulfate. The tablets may be coated according to methods well known
in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatine, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilising the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter-sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilised powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will
preferably range from 10 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 0.1 to 50 mg/kg per day.

It will be recognised by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of the invention will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of the invention given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The compounds of the present invention may be used in combination with one or more other drugs, which other drug(s) may be administered contemporaneously or sequentially with a compound of the invention. When the compounds are to be used contemporaneously, a pharmaceutical composition in unit dosage form containing the other drug(s) and the compound of the invention is preferred. However, the compound of the invention and one or more other drugs may alternatively be administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of the invention.

For example, the present compounds may be used in conjunction with an anti-inflammatory or analgesic agent or an anti-migraine agent, such as an ergotamine and dihydroergotamine, or other serotonin agonists (e.g. 5-HT₁ agonists), especially a 5-HT₁₈ agonist, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan, doniitriptan, and rizatriptan; a 5-HT₁D agonist such as PNU-142633 and a 5-HT₁F agonist such as LY334370; a cyclooxygenase inhibitor, such as a selective cyclooxygenase-2 inhibitor, for example rofecoxib, etoricoxib, celecoxib, valdecoxib or paracoxib; a non-steroidal anti-inflammatory agent or a cytokine-suppressing anti-inflammatory agent, for example with a compound such as, ibuprofen, ketoprofen, fenoprofen, flurbiprofen, naproxen, naproxen sodium, indomethacin, sulindac, meloxicam, piroxicam, tenoxicam, lornoxicam, ketorolac,
etodolac, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, diclofenac, oxaprozin, apazone, nimesulide, nabumetone, tenidap, etanercept, tolmetin, phenylbutazone, oxyphenylbutazone, diflunisal, salsalate, olsalazine or sulfasalazine and the like; or glucocorticoids; or a steroidal analgesic; or antidepressants such as amitriptyline or venlafaxine; or anticonvulsants such as gabapentin, pregabalin or memantine; or fatty acid derivative anticonvulsants such as divalproex; or carbonic anhydrase inhibitor anticonvulsants such as topiramate; or benzodiazepine anticonvulsants such as clonazepam; or N-type, P-type or Q-type calcium channel blocking anticonvulsants such as flunarizine, verapamil or cinnarizine; or sodium channel blocking anticonvulsants such as lamotrigine, lidocaine or zonisamide; or centrally acting antiadrenergic agents such as clonidine; or gamma amino butyric acid analogs such as pregabalin; or calcium channel blocking agents such as verapamil or nimodipine. Examples of anti-inflammatory agents which may be used in combinations of the invention include prostanoid receptor agonists or antagonists (e.g. EP1, EP2, EP3 or EP4) and VR1 receptor antagonists. Similarly, the compounds of the invention may be administered with an analgesic such as aspirin, choline magnesium trisalicylate, diflunisal, acetaminophen, phenacetin, fentanyl, sufentanil, methadone, acetyl methadol, buprenorphine, hydromorphone, levorphanol, meperidine, oxycodone, oxymorphone, propoxyphene, butorphanol, dezocine, nalbuphine, pentazocine or morphone. The compounds of the invention may also be used in combination with COX-2 inhibitors.

Additionally, the present compounds may be used in conjunction with an interleukin inhibitor, such as an interleukin-1 inhibitor; an NK-1 receptor antagonist, for example apreptant; an NMDA antagonist; an NR2B antagonist; a bradykinin-1 receptor antagonist; an adenosine A1 receptor agonist; an opiate agonist such as levomethadyl acetate or methadyl acetate; a lipoxygenase inhibitor, such as an inhibitor of 5-lipoxygenase; an alpha receptor antagonist, for example indoramin; an alpha receptor agonist; a vanilloid receptor antagonist; a renin inhibitor; a granzyme B inhibitor; a substance P antagonist; an endothelin antagonist; a norepinephrin precursor; anti-anxiety agents such as diazepam, alprazolam, clordiazepoxide and chlorazepate; serotonin 5-HT2 receptor antagonists; opioid agonists such as codeine, hydrocodone, tramadol, dextropropoxyphene and febtanyl; an mGluR5 agonist, antagonist or potentiator; a GABA A receptor modulator, for example acamprosate calcium; nicotinic antagonists or agonists including nicotine; muscarinic agonists or antagonists; a selective serotonin reuptake inhibitor, for example fluoxetine, paroxetine, sertraline, duloxetine, escitalopram, or citalopram; an antidepressant, for
example amitriptyline, nortriptyline, clomipramine, imipramine, venlafaxine, doxepin, protriptyline, desipramine, trimipramine, or imipramine; a leukotriene antagonist, for example montelukast or zafirlukast; an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide. The compounds of the invention may also be used in conjunction with gap junction inhibitors; neuronal calcium channel blockers such as civamide; AMPA/KA antagonists such as LY293558; sigma receptor agonists; and vitamin B2.

The compounds of the invention may also be used in conjunction with ergot alkaloids other than ergotamine and dihydroergotamine, for example ergonovine, ergonovine, methylergonovine, metergoline, ergoloid mesylates, dihydroergocornine dihydroergocristine, dihydroergocryptine, dihydro-α-ergocryptine, dihydro-β-ergocryptine, ergotoxine, ergocornine, ergocristine, ergocryptine, α-ergocryptine, β-ergocryptine, ergosine, ergostane, bromocriptine, or methysergide.

The compounds of the present invention may be used in conjunction with a beta-adrenergic antagonist such as timolol, propanolol, atenolol, metoprolol or nadolol, and the like; a MAO inhibitor, for example phenelzine; a calcium channel blocker, for example, diltiazem, amlodipine, felodipine, nisoldipine, isradipine, nimodipine, lomerizine, nifedipine, or prochlorperazine; neuroleptics such as olanzapine, droperidol, prochlorperazine, chlorpromazine and quetiapine; an anticonvulsant such as topiramate, tonabersat, carabersat, levetiracetam, or tiagabine; an anti-hypertensive such as an angiotensin II antagonist, for example losartan, irbesartan, valsartan, eprosartan, telmisartan, ondesartan, medoxomil, candesartan and candesartan cilexetil, an angiotensin I antagonist, an angiotensin converting enzyme inhibitor such as lisinopril, enalapril, captopril, benazepril, quinapril, perindopril, ramipril and trandolapril; or botulinum toxin type A or B.

The compounds of the present invention may be used in conjunction with a potentliator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as oxymetazoline, epinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxy-ephedrine; an antitussive such as caramiphen, carbetapentane, or dextromethorphan; a diuretic; a prokinetic agent such as metoclopramide or domperidone; a sedating or non-sedating antihistamine such as acrivastine, azatadine, bromodiphenhydramine, brompheniramine, caramiphen, chlorpheniramine, clemastine, dextromethorphan, dexamethasone, diphenhydramine, doxylamine,
loratadine, phenindamine, pheniramine, phenyltoloxamine, promethazine, pyrilamine, terfenadine, triprolidine, phenylephrine, phenylpropanolamine, or pseudoephedrine. The compounds of the present invention may also be used in conjunction with anti-emetics.

Additionally, nondrug analgesic approaches may be utilized in conjunction with administration of one or more compounds of the invention. For example, anesthesiology (intraspinal infusion, neural blockade), neurosurgical (neurolysis of CNS pathways), neurostimulatory (transcutaneous electrical nerve stimulation, dorsal column stimulation), physiatric (physical therapy, orthotic devices, diathermy), or psychologic (cognitive methods-hypnosis, biofeedback, or behavioral methods) approaches may also be utilized.

The present invention also provides a process for the preparation of a compound of formula (I) or (IA), which process comprises:

(a) reacting a compound of formula (II) or a salt or protected derivative thereof:

\[
\text{(H)}
\]

with a compound of formula (III) or (NIA):

\[
\text{(III)}
\]

\[
\text{(III A)}
\]

and/or
(b) converting a compound of formula (I) or (IA) to a different compound of formula
(I) or (IA); and/or

(c) removing any protecting group; and/or

(d) as appropriate, separating diastereomeric or enantiomeric mixtures of
compounds of formula (I) or (IA).

Compounds of formula (II) wherein R1 is hydrogen or alkyl can be prepared as
shown in Scheme 1:

Scheme 1.

(The starting material for Scheme 1 wherein R1 is alkyl can be prepared by treating a
corresponding chloro-compound with a Grignard reagent of formula R1MgX wherein
X is a halide, in dry THF in the presence of ferric acetylacetonate.)

Compounds of formula (II) wherein R1 is a nitrogen-linked group can be prepared as
shown in Scheme 2:
Compounds of formula (II) wherein R₁ is a non-nitrogen-linked heterocyclic group or an aryl group can be prepared as shown in Scheme 3:
Compounds of formula (II) wherein R₁ is an oxygen-linked group can be prepared as shown in Scheme 4:

Scheme 4.

Generally the sodium alkoxide is preformed from the parent alcohol using sodium hydride. The displacement reaction is performed at elevated temperature, e.g. in a microwave at 100°C. In the case of R₁=OMe commercially available 25% sodium methoxide in methanol is used directly.

In the Schemes, PG=protecting group such as lower alkyl; the compound of formula (II) can be isolated as the free acid (as shown) or, where a protecting group is removed by base hydrolysis, as the salt of the base used.

Compounds of formula (III) and (NIA) can be prepared as described in *inter alia* WO06/044504

The invention is illustrated by the Examples described below.

In the procedures that follow, after each starting material, reference to a description is typically provided. This is provided merely for assistance to the skilled chemist. The starting material may not necessarily have been prepared from the batch referred to.
Compounds of the invention are named using ACD/Name PRO 6.02 chemical naming software (Advanced Chemistry Development Inc., Toronto, Ontario, M5H2L3, Canada).

LC/Mass spectra were obtained using an Agilent 1100 series HPLC system coupled with a Waters ZQ Mass Spectrometer. LC analysis was performed on a Waters Atlantis column (50 x 4.6 mm, 3μm) (mobile phase: 97% [water +0.05% HCO₂H]/ 3% [CH₃CN +0.05% HCO₂H] for 0.1 min, then a gradient to 3% [water +0.05% HCO₂H]/97% [CH₃CN +0.05% HCO₂H] over 3.9 min, and then held under these conditions for 0.8 min); temperature = 30 °C; flow rate = 3 mL/min; Mass spectra were collected using electrospray and/or APCI. The UV detection range is from 220 to 330nm.

Alternatively a 2 minute generic LC/MS method may be employed using a Waters Acquity system coupled with a Waters ZQ Mass Spectrometer. LC analysis was performed on a Waters Acquity BEH UPLC C18 (50 x 2.1 mm, 1.7μm) (mobile phase: 97% [water +0.05% HCO₂H]/ 3% [CH₃CN +0.05% HCO₂H] for 0.1 min, then a gradient to 3% [water +0.05% HCO₂H]/97% [CH₃CN +0.05% HCO₂H] over 1.4 min, and then held under these conditions for 0.4 min); temperature = 40 °C; flow rate = 1 mL/min.

Proton Magnetic Resonance (NMR) spectra were recorded on a Bruker instrument at 250 or 400 MHz. Chemical shifts are reported in ppm (δ) using tetramethylsilane as internal standard. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The NMR spectra were recorded at a temperature ranging from 25 to 90°C. When more than one conformer was detected the chemical shifts for the most abundant one are reported.

Chromatography was carried out on silica gel cartridges either on a Flashmaster II (Argonaut), Biotage Horizon or a Biotage SP4 automated chromatography system and an appropriate elution solvent system. Where indicated a free base was isolated from a salt using a Varian SCX cartridge.

Atlantis, dimensions are 19mm x 100mm (<100mg scale) and 30mm x 100mm
(>100mg scale), particle size is 5µm. Solvents, A : Aqueous solvent = Water + 0.1%
Formic Acid B : Organic solvent = Acetonitrile + 0.1% Formic Acid. Gradients range
from 5-30%B in A to 80-99%B in A, depending on HPLC retention time, run time =
13.5 minutes. Flow rate = 20ml/min (<100mg scale), 40ml/min (>100mg scale)

Description 1
5-Bromo-7H-pyrrolo[2,3-d]pyrimidine (D1)

7H-Pyrrolo[2,3-d]pyrimidine (100 mg, 0.839 mmol) was dissolved in N,N-
dimethylformamide (3.5 ml), cooled in an ice bath and treated with N-
bromosuccinimide (149 mg, 0.839 mmol) portionwise under argon. The resulting
mixture was stirred for 20 minutes, allowed to warm to room temperature and stirred
for 10 minutes. The reaction was quenched by addition of methanol (5 ml.) and the
solvent removed under reduced pressure. The residue was purified by column
chromatography eluting with 1:1 ethyl acetate/iso-hexane. Product containing
fractions were combined and evaporated under reduced pressure. The residue was
dissolved in methanol and passed down an SCX column (10 g) eluting with methanol
followed by 2M ammonia/methanol. Basic fractions were combined and evaporated
under reduced pressure to give the title compound as a white solid.
LC/MS (ES+ve): [M+H]+ at m/z 198, 200 (C6H4BrN3 requires [M+H]+ at m/z 198, 200).

Description 2
Ethyl (5-bromo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (D2)

5-Bromo-7H-pyrrolo[2,3-d]pyrimidine (D1, 123 mg, 0.621 mmol) was dissolved in
tetrahydrofuran (3 ml), cooled in an ice bath and treated with sodium hydride (60%
by weight, 27.3 mg, 0.683 mmol) portionwise under argon. The resulting mixture was
stirred for 15 minutes, allowed to warm to room temperature and stirred for 45
minutes. Ethyl bromoacetate (0.069 ml, 0.621 mmol) was added and the resulting
mixture was stirred for 30 minutes. The solvent was removed under reduced
pressure. The residue taken up in water, neutralised using saturated ammonium
chloride and extracted with ethyl acetate (x 3). The ethyl acetate layers were
combined, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 1:1 ethyl acetate/iso-hexane. Product containing fractions were combined and evaporated under reduced pressure to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]+ at m/z 284, 286 (C10H10BrN3O2 requires [M+H]+ at m/z 284, 286).

Description 3

Ethyl [5-(2-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D3)

Ethyl (5-bromo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (D2, 109 mg, 0.384 mmol) (2-chlorophenyl)boronic acid (120 mg, 0.767 mmol), bis(triphenylphosphine)palladium(II) chloride (13.46 mg, 0.019 mmol) and sodium carbonate (81 mg, 0.767 mmol) were added together in 1,2-dimethoxyethane (1.6 mL) and water (0.4 mL) and the resulting mixture was heated at 100°C in the microwave for 20 minutes at normal absorption. The reaction mixture was diluted with water and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 1:1 ethyl acetate/iso-hexane. Product containing fractions were combined and evaporated under reduced pressure to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]+ at m/z 316, 318 (C6H14ClN3O2 requires [M+H]+ at m/z 316, 318).

Description 4

[5-(2-Chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetic acid (D4)
mmol) was dissolved in 1,4-dioxane (2 ml_), treated with 0.5 M aqueous lithium hydride solution (0.931 ml_, 0.466 mmol) and stirred at room temperature for 30 minutes. The reaction mixture was diluted with methanol and passed down a PE-AX cartridge (10 g) eluting with methanol, followed by 10 % acetic acid/methanol. The product containing fractions were combined and evaporated under reduced pressure to give the desired title compound as a white solid.

LC/MS (ES+ve): [M+H] + at m/z 288, 290 (C4₅H₁₀ClN₃O₂ requires [M+H] + at m/z 288, 290).

**Description 5**

5-Bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (D5)

4-Chloro-7H-pyrrolo[2,3-d]pyrimidine (0.5 g, 3.26 mmol) was dissolved in N,N-dimethylformamide (11 ml_), cooled in an ice bath and treated with N-bromosuccinimide (0.579 g, 3.26 mmol) portionwise under argon. The resulting mixture was stirred for 20 minutes, allowed to warm to room temperature and stirred for 10 minutes. The solvent was removed under reduced pressure. The residue was triturated with water and the solid collected by filtration, washed with water and dried at 50°C under high vacuum overnight to give the title compound as a solid.

LC/MS (ES+ve): [M+H] + at m/z 232, 234, 236 (C₆H₃BrN₄ requires [M+H] + at m/z 232, 234, 236).

**Description 6**

5-Bromo-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidine (D6)

5-Bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (D5, 560 mg, 2.409 mmol) was suspended in 1,4-dioxane (11 ml_), treated with pyrrolidine (0.199 ml_, 2.409 mmol) and the resulting mixture stirred at room temperature under argon for 3 hours. The solvent was removed under reduced pressure. The residue was purified by column chromatography eluting with ethyl acetate/iso-hexane (4:1). Product containing fractions were combined and evaporated under reduced pressure to give the title compound as a white solid.

LC/MS (ES+ve): [M+H] + at m/z 267, 269 (C₆H₁₁BrN₄ requires [M+H] + at m/z 267,
5-Bromo-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidine (D6) may also be prepared by heating 5-bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (D5) and pyrrolidine in dioxane at 90 °C for 4.5 hours, from 5-bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (D5) and pyrrolidine in iso-propylalcohol at reflux for 20 minutes and from 5-bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (D5), pyrrolidine and N,N'-diisopropylethylamine in iso-propylalcohol at reflux for 1 hour. The experimental procedure described in Description 6 is the highest yielding for the desired product, 5-bromo-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidine (D6), and minimises the yield of the undesired side product, 4,5-di-1-pyrrolidinyl-7H-pyrrolo[2,3-c]pyrimidine.

The displacement reaction is analogous to a literature method: see Tetrahedron Lett, 2006, 47(25), 4149-4151 for the displacement of 4-Cl from 5-bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (D5) with a nitrogen nucleophile.

**Description 7**

**Ethyl [5-bromo-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D7)**

![Chemical Structure](image)

5-Bromo-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidine (D6, 332 mg, 1.243 mmol) was dissolved in tetrahydrofuran (8 mL), cooled in an ice bath and treated with sodium hydride (60% by weight, 59.7 mg, 1.491 mmol) portionwise under argon. The resulting mixture was stirred for 15 minutes, allowed to warm to room temperature and stirred for 45 minutes. Ethyl bromoacetate (0.138 mL, 1.243 mmol) was added and the resulting mixture was stirred for 30 minutes. The solvent was removed under reduced pressure. The residue taken up in water, neutralised using saturated ammonium chloride and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 1:1 ethyl acetate/isoo-hexane. Product containing fractions were combined and evaporated under reduced pressure to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]$^+$ at m/z 353, 355 (Cl$_4$H$_7$BrN$_4$O$_2$ requires [M+H]$^+$ at m/z 353, 355).
Description 8
Ethyl [5-(2-chlorophenyl)-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D8)

5 Ethyl [5-bromo-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D7, 344 mg, 0.974 mmol), (2-chlorophenyl)boronic acid (305 mg, 1.948 mmol), bis(triphenylphosphine)palladium(II) chloride (34.2 mg, 0.049 mmol) and sodium carbonate (206 mg, 1.948 mmol) were added together in 1,2-dimethoxyethane (4 ml.) and water (1 ml.) and the resulting mixture was heated at 100°C in the microwave for 20 minutes at normal absorption. The reaction mixture was diluted with water and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 1:1 ethyl acetate/iso-hexane. Product containing fractions were combined and evaporated under reduced pressure to give the title compound as a solid.

LC/MS (ES+ve): [M+H]$^+$ at m/z 385, 387 ($C_{20}H_{21}ClN_4O_2$ requires [M+H]$^+$ at m/z 385, 387).

Description 9
[S^-Chlorophenyl]-[i-pyrrolidinyl]^-H-pyrrolo^-S-dlpyrimidin^-ylacetic acid (D9)

20 Ethyl [5-(2-chlorophenyl)-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D8, 173 mg, 0.450 mmol) was dissolved in 1,4-dioxane (3 ml.), treated with 0.5 M aqueous lithium hydroxide solution (1.349 ml, 0.674 mmol) and stirred at room temperature for 30 minutes. The reaction mixture was diluted with methanol and passed down a PE-AX cartridge (10 g) eluting with methanol, followed by 10% acetic acid/methanol. The product containing fractions were combined and evaporated under reduced pressure to give the title compound as a white solid.
LC/MS (ES+ve): \([M+H]^+\) at m/z 357, 359 (C\(_{8}\)H\(_{17}\)ClN\(_{4}\)O\(_{2}\) requires \([M+H]^+\) at m/z 357, 359).

**Description 10**

4-Phenyl-7H-pyrrolo[2,3-cf]pyrimidine (D10)

4-Chloro-7H-pyrrolo[2,3-d]pyrimidine (500 mg, 3.26 mmol), phenylboronic acid (794 mg, 6.51 mmol), 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium (II) complex with dichloromethane (1:1) (133 mg, 0.163 mmol) and sodium carbonate (690 mg, 6.51 mmol) were added together in 1,4-dioxane (16 ml.) and water (4 ml.). The resulting mixture was heated at 150\(^\circ\)C in the microwave for 30 minutes at normal absorption. The reaction mixture was diluted with 1:1 brine / water and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (Biotage SP4, eluting with a gradient of 0 - 50 % ethyl acetate / isohexane). The fractions containing the product were combined, evaporated under reduced pressure and dried overnight under high vacuum at 50\(^\circ\)C to give the title compound as a solid.

LC/MS (ES+ve): \([M+H]^+\) at m/z 196 (C\(_{12}\)H\(_{9}\)N\(_{3}\) requires \([M+H]^+\) at m/z 196).

**Description 11**

5-Bromo-4-phenyl-7H-pyrrolo[2,3-cf]pyrimidine (D1 1)

4-Phenyl-7H-pyrrolo[2,3-d]pyrimidine (D10, 290 mg, 1.486 mmol) was dissolved in N,N-dimethylformamide (5 ml.), cooled in an ice bath and treated with N-bromosuccinimide (264 mg, 1.486 mmol) portionwise under argon. The resulting mixture was stirred for 20 minutes, allowed to warm to room temperature and stirred for 10 minutes. The solvent was removed under reduced pressure. The residue was triturated with water and the solid was collected by filtration, washed with water and dried at 50\(^\circ\)C under high vacuum overnight to give the title compound as a solid.

LC/MS (ES+ve): \([M+H]^+\) at m/z 274, 276 (C\(_{12}\)H\(_{9}\)BrN\(_{3}\) requires \([M+H]^+\) at m/z 274, 276).
Description 12
Ethyl (5-bromo-4-phenyl-7H-pyrrolo[2,3-c]pyrimidin-7-yl)acetate (D12)

5-Bromo-4-phenyl-7H-pyrrolo[2,3-d]pyrimidine (D11, 430 mg, 1.569 mmol) was dissolved in tetrahydrofuran (7.5 ml), cooled in an ice bath and treated with sodium hydride (60 % by weight, 69.0 mg, 1.726 mmol) portionwise under an atmosphere of argon. The resulting mixture was stirred for 15 minutes, allowed to warm to room temperature and stirred for 45 minutes. Ethyl bromoacetate (0.175 ml, 1.569 mmol) was added and the resulting mixture was stirred for 60 minutes. The solvent was removed under reduced pressure. The residue was taken up in water, neutralised using saturated ammonium chloride and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (Biotage SP4, eluting with 0 - 30 % ethyl acetate/ iso-hexane). The product containing fractions were combined and evaporated under reduced pressure to give the title compound as a yellow solid.

LC/MS (ES+ve): [M+H]+ at m/z 360, 362 (C6H14BrN3O2 requires [M+H]+ at m/z 360, 362).

Description 13
Ethyl (5-(2-chlorophenyl)-4-phenyl-7H-pyrrolo[2,3-c]pyrimidin-7-yl)acetate (D13)

Ethyl (5-bromo-4-phenyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (D12, 365 mg, 1.013 mmol), (2-chlorophenyl)boronic acid (317 mg, 2.027 mmol), bis(triphenylphosphene)palladium(II) chloride (35.6 mg, 0.051 mmol) and sodium carbonate (215 mg, 2.027 mmol) were added together in 1,2-dimethoxycethane (4 ml) and water (1 ml). The resulting mixture was heated at 100°C in the microwave for 20 minutes at normal absorption. The reaction mixture was diluted with water (25 ml) and extracted with ethyl acetate (3 x 25 ml). The ethyl acetate layers were combined, dried under magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (Biotage SP4, eluting with a gradient of 0 - 40% ethyl acetate/ iso-hexane). The fractions containing the
product were combined and evaporated under reduced pressure. It was then dried overnight under vacuum to yield the title compound as a powder.

LC/MS (ES+ve): [M+H]+ at m/z 392, 394 (C_{22}H_{18}ClN_{3}O_{2} requires [M+H]+ at m/z 392, 394).

Description 14

[5-(2-Chlorophenyl)-4-phenyl-7H-pyrrolo[2,3-cf]pyrimidin-7-yl]acetic acid (D14)

Ethyl [5-(2-chlorophenyl)-4-phenyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D13, 271 mg, 0.692 mmol) was suspended in ethanol (3.5 ml), treated with 2M sodium hydroxide (0.692 ml, 1.383 mmol) and the resulting mixture stirred at room temperature overnight. The reaction mixture was diluted with methanol (40 ml) to aid solubility and was then applied to a 20 g PE-AX cartridge (prewetted with methanol). The cartridge was washed with methanol (50 ml) and the acid product was eluted with 10% acetic acid in methanol (200 ml). The fractions containing the acid product were combined, concentrated under reduced pressure and then azeotroped with toluene and methanol to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]+ at m/z 364, 366 (C_{20}H_{14}ClN_{3}O_{2} requires [M+H]+ at m/z 364, 366).

Description 15

1,1-Dimethylethyl 4-(5-bromo-7H-pyrrolo[2,3-cf]pyrimidin-4-yl)-1-piperazinecarboxylate (D15)

5-Bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (D5, 625 mg, 2.69 mmol) was suspended in 1,4-dioxane (13 ml), treated with N-Boc-piperazine (501 mg, 2.69 mmol) and N,N-diisopropylethylamine (0.470 ml, 2.69 mmol) and the resulting mixture heated at 80°C under argon for 3 hours. The reaction was allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was purified by column chromatography eluting with a gradient of 0-70 % ethyl acetate/iso-hexane. Product containing fractions were combined and evaporated under reduced pressure to give the title compound as a white solid.
LC/MS (ES+ve): [M+H]^+ at m/z 382, 384 (C_{15}H_{20}BrN_{5}O_{2} requires [M+H]^+ at m/z 382, 384).

**Description 16**

5 1,1-Dimethylethyl 4-{5-bromo-7-[2-(ethyloxy)-2-oxoethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}-1-piperazinecarboxylate (D16)

1,1-Dimethylethyl 4-(5-bromo-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1-piperazinecarboxylate (D15, 552 mg, 1.444 mmol) was dissolved in N,N-dimethylformamide (14 mL), cooled in an ice bath and treated with sodium hydride (60% by weight, 69.3 mg, 1.733 mmol) portionwise and stirred under argon for 15 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. Ethyl bromoacetate (0.160 mL, 1.444 mmol) was added and the resulting mixture stirred for 1 hour. The solvent was removed under reduced pressure. The residue taken up in water, neutralised using saturated ammonium chloride and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography eluting with a gradient of 0-50 % ethyl acetate/iso-hexane. Product containing fractions were combined and evaporated under reduced pressure to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]^+ at m/z 468, 470 (C_{19}H_{26}BrN_{5}O_{4} requires [M+H]^+ at m/z 468, 470).

**Description 17**

25 1,1-Dimethylethyl 4-{5-(2-chlorophenyl)-7-[2-(ethyloxy)-2-oxoethyl]-7H-pyrrolo[2,3-cf]pyrimidin-4-yl}-1-piperazinecarboxylate (D17)

1,1-Dimethylethyl 4-(5-bromo-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1-piperazinecarboxylate (D16, 487 mg, 1.040 mmol), (2-chlorophenyl)boronic
acid (325 mg, 2.080 mmol), bis(triphenylphosphine)palladium(II) chloride (36.5 mg, 0.052 mmol) and sodium carbonate (220 mg, 2.080 mmol) were added together in 1,2-dimethoxyethane (4 ml.) and water (1 ml.) and the resulting mixture was heated at 100°C in the microwave for 20 minutes at normal absorption. The reaction mixture was diluted with water and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography eluting with a gradient of 0-50% ethyl acetate/iso-hexane. Product containing fractions were combined and evaporated under reduced pressure to give the title compound as a white solid.

**LC/MS (ES+ve):** [M+H]^+ at m/z 500, 502 (C_{25}H_{30}ClN_{5}O_{4} requires [M+H]^+ at m/z 500, 502).

**Description 18**

1,1-Dimethylethyl 4-{5-(2-chlorophenyl)-7-[2-(ethyloxy)-2-oxoethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}-1-piperazinecarboxylate (D17, 324 mg, 0.648 mmol) was dissolved in ethanol (5 ml.), treated with aqueous 2M sodium hydroxide solution (0.324 ml., 0.648 mmol) and stirred at room temperature for 30 minutes. The solvent was removed under reduced pressure to give the title compound as a white solid.

**LC/MS (ES+ve):** [M+H]^+ at m/z 472, 474 (C_{23}H_{26}ClN_{5}O_{4} requires [M+H]^+ at m/z 472, 474).

**Description 19**

5-Bromo-\(N\)-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (D19)

5-Bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (D5, 604 mg, 2.60 mmol) was suspended in 1,4-dioxane (12 ml.), treated with aniline (0.237 ml, 2.60 mmol) and the resulting mixture heated at 90°C under argon for 4 hours. The reaction was allowed to cool to room temperature, diluted with diethyl ether and the resulting solid
collected by filtration, washed with diethyl ether and dried at 50°C under high vacuum overnight. The resulting solid was purified by column chromatography eluting with a gradient of 0-50% ethyl acetate/iso-hexane. Fractions containing the product were combined and evaporated under reduced pressure to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]+ at m/z 289, 291 (\(\text{C}_{24}\text{H}_{15}\text{BrN}_{4}\) requires [M+H]+ at m/z 289, 291).

**Description 20**

**Ethyl [5-bromo-4-(phenylamino)-7H-pyrrolo[2,3-c]pyrimidin-7-yl]acetate (D20)**

5-Bromo-N-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (D19, 300 mg, 1.038 mmol) was dissolved in N,N-dimethylformamide (7.5 ml), cooled in an ice bath and treated with sodium hydride (60% by weight, 83 mg, 2.075 mmol) portionwise and stirred under argon for 15 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. Ethyl bromoacetate (0.115 ml, 1.038 mmol) was added and the resulting mixture stirred for 1 hour. The solvent was removed under reduced pressure. The residue taken up in water, neutralised using saturated ammonium chloride and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography eluting with a gradient of 0-50 % ethyl acetate/iso-hexane. Product containing fractions were combined and evaporated under reduced pressure to give the title compound as a yellow oil.

LC/MS (ES+ve): [M+H]+ at m/z 375, 377 (\(\text{C}_{36}\text{H}_{15}\text{BrN}_{4}\text{O}_{2}\) requires [M+H]+ at m/z 375, 377).

**Description 21**

**Ethyl [5-(2-chlorophenyl)-4-(phenylamino)-7H-pyrrolo[2,3-c]pyrimidin-7-yl]acetate (D21)**

**Ethyl [5-bromo-4-(phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D20, 276**
mg, 0.736 mmol), (2-chlorophenyl)boronic acid (230 mg, 1.471 mmol), 
bis(triphenylphosphine)palladium(II) chloride (25.8 mg, 0.037 mmol) and sodium 
carbonate (156 mg, 1.471 mmol) were added together in 1,2-dimethoxyethane (4 
ml.) and water (1 ml.) and the resulting mixture was heated at 100°C in the 
microwave for 20 minutes at normal absorption. The reaction mixture was diluted 
with water and extracted with ethyl acetate (x 3). The ethyl acetate layers were 
combined, dried under magnesium sulfate and evaporated under reduced pressure. 
The residue was purified by column chromatography eluting with a gradient of 0-40 
% ethyl acetate/iso-hexane. Product containing fractions were combined and 
evaporated under reduced pressure to give the title compound as a yellow oil.

LC/MS (ES+ve): [M+H]^+ at m/z 407, 409 (C_{22}H_{19}ClN_{4}O_{2} requires [M+H]^+ at m/z 407, 
409).

Description 22

5-[(2-Chlorophenyl)-4-(phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetic acid 
(D22)

Ethyl [5-(2-chlorophenyl)-4-(phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate 
(D21, 215 mg, 0.528 mmol) was dissolved in 1,4-dioxane (4 ml.), treated with 
aqueous lithium hydroxide solution (1.585 ml, 0.793 mmol) and stirred at room 
temperature for 30 minutes. The reaction mixture was diluted with methanol and 
passed down a PE-AX cartridge (10 g) eluting with methanol, followed by 10 % 
acetic acid/methanol. The product containing fractions were combined and 
evaporated under reduced pressure to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]^+ at m/z 379, 381 (C_{22}H_{15}ClN_{4}O_{2} requires [M+H]^+ at m/z 379, 
381).

Description 23

4-Ethyl-7H-pyrrolo[2,3-d]pyrimidine (D23)

4-Chloro-7H-pyrrolo[2,3-d]pyrimidine (154 mg, 1 mmol) was dissolved in 
tetrahydrofuran (2 ml.) and N-methyl-2-pyrrolidone (0.3 ml.) under argon and iron (III)
acetylacetonate (35.3 mg, 0.1 mmol) was added. The mixture was stirred at room temperature while 2M ethylmagnesium chloride in tetrahydrofuran (1.0 ml, 2.0 mmol) was added dropwise and the reaction stirred for 17 hours. Ice-cold saturated ammonium chloride was added and the mixture extracted with ethyl acetate (x2). The combined organics were washed with brine, dried under magnesium sulfate and concentrated under reduced pressure. The product was purified by column chromatography, eluting with 0-100% ethyl acetate/iso-hexane to give the title compound as a waxy solid.

**LC/MS (ES+ve):** [M+H]+ at m/z 148 (C₈H₉N₃ requires [M+H]+ at m/z 148).

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**Description 24**

5-Bromo-4-ethyl-7H-pyrrolo[2,3-d]pyrimidine (D24)

![5-Bromo-4-ethyl-7H-pyrrolo[2,3-d]pyrimidine](image)

4-Ethyl-7H-pyrrolo[2,3-d]pyrimidine (D23, 100 mg, 0.679 mmol) was dissolved in N,N-dimethylformamide (2 ml) under argon, cooled in an ice bath and N-bromosuccinimide (121 mg, 0.679 mmol) was added portionwise. The mixture was stirred for 30 minutes, then allowed to warm to room temperature. After stirring for 30 minutes, the solvent was concentrated under reduced pressure and water (10 ml) added. The solid was filtered, washed with water and dried at 50°C under high vacuum to give the title compound as a buff solid.

**LC/MS (ES+ve):** [M+H]+ at m/z 226, 228 (C₈H₈BrN₃ requires [M+H]+ at m/z 226, 228).

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**Description 25**

Ethyl (5-bromo-4-ethyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (D25)

![Ethyl (5-bromo-4-ethyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate](image)

5-Bromo-4-ethyl-7H-pyrrolo[2,3-d]pyrimidine (D24, 122 mg, 0.54 mmol) was dissolved in N,N-dimethylformamide (2 ml), cooled in an ice-bath under argon and sodium hydride (60% by weight, 21.58 mg, 0.54 mmol) was added portionwise. The bath was removed after 10 minutes and the mixture stirred at room temperature for 30 minutes. Ethyl bromoacetate (0.06 ml, 0.54 mmol) was added dropwise and the
reaction was stirred at room temperature for 4 hours. The solvent was evaporated under reduced pressure and the residue treated with saturated ammonium chloride and extracted with ethyl acetate (x2). The combined organics were washed with brine, dried under magnesium sulfate and concentrated under reduced pressure. The product was purified by column chromatography, eluting with 0-50% ethyl acetate/iso-hexane to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]+ at m/z 312, 314 (Cl₂H₁₄BrN₃O₂ requires [M+H]+ at m/z 312, 314).

**Description 26**  
**Ethyl [5-(2-chlorophenyl)-4-ethyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D26)**

![Image of compound](image)

**Ethyl (5-bromo-4-ethyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (D25, 122 mg, 0.391 mmol), (2-chlorophenyl)boronic acid (D25, 122 mg, 0.782 mmol), bis(triphenylphosphine)palladium(II) chloride (13.72 mg, 0.020 mmol) and sodium carbonate (83 mg, 0.782 mmol) were added together in 1,2-dimethoxyethane (2 ml.) and water (0.5 ml.) and the resulting mixture was heated at 100°C in the microwave for 20 minutes. The reaction mixture was diluted with water and extracted with ethyl acetate (x 2). The ethyl acetate layers were combined, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 0-50% ethyl acetate/iso-hexane to give the title compound as a yellow oil which crystallised.

**Description 27**  
**[S^-ChlorophenylJ^-ethyl^H-pyrrolo[2,3-d]pyrimidin^-yllacetic acid lithium salt (D27)**

![Image of compound](image)
Ethyl [5-(2-chlorophenyl)-4-ethyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D26, 111 mg, 0.323 mmol) was dissolved in tetrahydrofuran (2 ml.) and 0.5M lithium hydroxide (0.646 ml, 0.323 mmol) added. The mixture was stirred for 24 hours at room temperature then at 60°C for 2 hours. The solvent was concentrated under reduced pressure and the residue was azeotroped with toluene to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]+ at m/z 316, 318 (C_{6}H_{14}ClN_{3}O_{2} requires [M+H]+ at m/z 316, 318).

Description 28

4-(3-Pyridinyl)-7H-pyrrolo[2,3-d]pyrimidine (D28)

\[
\text{\includegraphics[width=0.2\textwidth]{pyrrole.png}}
\]

4-Chloro-7H-pyrrolo[2,3-d]pyrimidine (1.02 g, 6.64 mmol), 3-pyridinylboronic acid (1.633 g, 13.28 mmol), sodium carbonate (1.408 g, 13.28 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.233 g, 0.332 mmol) were heated in the microwave in 1,2-dimethoxyethane (12.45 ml) and water (4.15 ml) at 100°C, normal absorption, for 30 minutes. LCMS showed both starting materials remaining, so was heated for a further 6 hours at 100°C. Ethyl acetate and water were added, and then passed down a hydromatrix cartridge, washed well with ethyl acetate, concentrated in vacuo and azeotroped with toluene. Purification by chromatography (Biotage SP4, 50 g snap, 0-12% 2M ammonia in methanol/dichloromethane) over 10 column volumes). Relevant fractions were combined and concentrated in vacuo to give the title compound.

LC/MS (ES+ve): [M+H]+ at m/z 197 (C_{n}H_{8}N_{4} requires [M+H]+ at m/z197)

Description 29

{2-[[5-Bromo-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]ethyl}dimethylamine (D29)

\[
\text{\includegraphics[width=0.2\textwidth]{dimethylamine.png}}
\]
2-(Dimethylamino)ethanol (0.216 ml, 2.151 mmol) was dissolved in tetrahydrofuran (4 ml), cooled in an ice bath, treated with sodium hydride (60% by wt, 86 mg, 2.151 mmol) and stirred for 15 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 30 minutes. 5-Bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (D5, 100 mg, 0.430 mmol) was added and the resulting mixture stirred at room temperature for 30 minutes. The mixture was heated in the microwave at 100°C for 60 minutes at normal absorption. The solvent was removed under reduced pressure and the residue was diluted with water and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography eluting with a gradient of 0-10 % 2M ammonia/methanol and dichloromethane. Product containing fractions were combined and evaporated under reduced pressure to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]^+ at m/z 285, 287 (Cl_3H_{13}BrN_4O requires [M+H]^+ at m/z 285, 287).

Description 30
Ethyl (545romo-4-chloro-7H-yrrrolo[2,3-c^pyrimidin-7-yl)acetate (D30)

5-Bromo-4-chloro-7H-pyrrolo[2,3-c/]pyrimidine (D5, 3 g, 12.91 mmol) was dissolved in \&\&.N-dimethylformamide (30 ml), cooled in an ice bath and treated with 60% sodium hydride in mineral oil (0.568 g, 14.20 mmol) portionwise and stirred under argon for 15 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 45 minutes. Ethyl bromoacetate (1.580 ml, 14.20 mmol) was added and the resulting mixture stirred for 1 hour. The solvent was removed under reduced pressure. The residue was taken up in water, neutralised using saturated ammonium chloride and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography eluting with a gradient of 0-35 % ethyl acetate / iso-hexane. Product containing fractions were combined and evaporated under reduced pressure to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]^+ at m/z 318, 320, 322 (Cl_3H_5BrCIN_5O_2 requires [M+H]^+ at m/z 318, 320, 322).
Description 31

Ethyl {5-bromo-4-[3-(dimethylamino)-1-azetidinyl]-7H-pyrrolo[2,3-c/lpyrimidin-7-yl]acetate (D31)

Ethyl (5-bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (D30, 400 mg, 1.256 mmol) was dissolved in 1,4-dioxane (10 mL) and treated with N,N-dimethyl-3-azetidinamine (172 mg, 1.256 mmol) and N,N-diisopropylethylamine (0.439 mL, 2.51 mmol). The resulting mixture was stirred at room temperature for 20 hours. A further 0.5 equivalents of N,N-dimethyl-3-azetidinamine (86 mg, 628 µmol) and 1 equivalent of N,N-diisopropylethylamine (0.2 mL, 1.26 mmol) were added and the reaction mixture was stirred at room temperature for a further 24 hours. The solvent was removed under reduced pressure. The residue was purified by column chromatography (SP4, eluting with a gradient of 0 - 5% 2M ammonia in methanol / dichloromethane). The product containing fractions were collected under reduced pressure and dried under vacuum overnight to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]^+ at m/z 382, 384 (C_{16}H_{20}BrN_{5}O_{2} requires [M+H]^+ at m/z 382, 384).

Description 32

Ethyl {5-bromo-4-[(1-methylethyl)amino]-7H-pyrrolo[2,3-c/lpyrimidin-7-yl]acetate (D32)
Ethyl (5-bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (D30, 500 mg, 1.570 mmol) was dissolved in 1,4-dioxane (15 ml), treated with isopropylamine (0.134 ml, 1.570 mmol) and N,N-diisopropylethylamine (0.548 ml, 3.14 mmol) and the resulting mixture was stirred at room temperature under argon for 18 hours. The reaction mixture was then heated under reflux for 5 hours. A further quantity of isopropylamine (0.067 ml, 0.785 mmol) was added and the mixture was heated under reflux for 8 hours. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was purified by column chromatography eluting with a gradient of 0-50 % ethyl acetate in iso-hexane. Product containing fractions were combined and evaporated under reduced pressure to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]+ at m/z 341, 343 (Cl$_3$H$_7$BrN$_4$O$_2$ requires [M+H]+ at m/z 341, 343).

Description 33

5-Bromo-4-(methyloxy)-7H-pyrrolo[2,3-d]pyrimidine (D33)

The reaction was performed in two portions, splitting the quantities. For the total reaction, 5-bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (D5, 5 g, 21.51 mmol) was suspended in tetrahydrofuran (40 ml), treated with 25% sodium methoxide in methanol (30 ml, 131 mmol) and heated at 100°C in the microwave for 30 minutes at normal absorption. The reaction vials were combined. The solvent was removed under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried over magnesium sulfate and evaporated under reduced pressure to give the title compound as a cream solid.

LC/MS (ES+ve): [M+H]+ at m/z 228, 230 (C$_7$H$_6$BrN$_3$O requires [M+H]+ at m/z 228, 230).
**Description 34**

**Ethyl [5-bromo-4-(methyloxy)-7H-pyrrolo[2,3-c]pyrimidin-7-yl]acetate (D34)**

5-Bromo-4-(methyloxy)-7H-pyrrolo[2,3-d]pyrimidine (D33, 4.1 g, 17.98 mmol) was dissolved in N,N-dimethylformamide (100 ml), cooled in an ice bath and 60% sodium hydride in mineral oil (0.863 g, 21.57 mmol) added portionwise. The mixture was stirred under argon for 10 minutes, warmed to room temperature and stirred for 30 minutes. Ethyl bromoacetate (2.402 ml, 21.57 mmol) was added dropwise and the reaction stirred at room temperature for 16 hours. The solvent was evaporated and the residue treated with saturated ammonium chloride solution. The mixture was extracted with ethyl acetate (x2) and the combined organics washed with brine, dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography, eluting with 0-50% ethyl acetate/isohexane to give the title compound.

**LC/MS (ES+ve): [M+H]^+ at m/z 314, 316 (C_{n2}H_{12}BrN_{3}O_{3} requires [M+H]^+ at m/z 314, 316).**

**Description 35**


Ethyl [5-bromo-4-(methyloxy)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D34, 4.47 g, 14.23 mmol), (2-chlorophenyl)boronic acid (4.45 g, 28.5 mmol), bis(triphenylphosphine)palladium(II) chloride (0.499 g, 0.711 mmol) and sodium
carbonate (3.02 g, 28.5 mmol) were mixed together in 1,2-dimethoxyethane (30 ml.) and water (7.5 mL) and the resulting mixture was heated at 100°C in the microwave for 20 minutes. The reaction mixture was diluted with water and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography eluting with a gradient of 0-50% ethyl acetate/isoheaxane to give a yellow oil. The product was dissolved in 1,2-dimethoxyethane (30 mL) and (2-chlorophenyl)boronic acid (2.225 g, 14.23 mmol), bis(triphenylphosphine)palladium(II) chloride (0.25 g, 0.356 mmol), sodium carbonate (1.508 g, 14.23 mmol) and water (7.50 mL) added. The mixture was heated at 100°C in the microwave for 30 minutes. The reaction mixture was diluted with water and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography, eluting with a gradient of 0-50% ethyl acetate/isoheaxane to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]^+ at m/z 346, 348 (C_{17}H_{16}ClN_{3}O_{3} requires [M+H]^+ at m/z 346, 348).

Description 36

Ethyl [5-(2-chlorophenyl)-4-oxo-1,4-dihydro-7H-pyrrolo[2,3-c]pyrimidin-7-yl]acetate (D36)

![Chemical Structure](image)

Ethyl [5-(2-chlorophenyl)-4-(methyloxy)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D35, 3.7 g, 10.70 mmol) was stirred in ethanol (20 mL) and 1M hydrogen chloride in diethyl ether (64.2 mL, 64.2 mmol) added. The solution was then heated to reflux for 16 hours. The solvent was evaporated and the residue re-evaporated from toluene to leave the title compound as a cream solid.

LC/MS (ES+ve): [M+H]^+ at m/z 332, 334 (C_{16}H_{14}ClN_{3}O_{3} requires [M+H]^+ at m/z 332, 334).
Description 37
Ethyl [4-chloro-5-(2-chlorophenyl)-7H-pyrrolo[2,3-c]pyrimidin-7-yl]acetate (D37)

![Chemical Structure]

5 Ethyl [5-(2-chlorophenyl)-4-oxo-1,4-dihydro-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D36, 3.55 g, 10.70 mmol) was dissolved in phosphorus oxychloride (5.98 ml, 64.2 mmol) and heated to reflux for 2 hours. The mixture was poured into ice-cold 20% sodium acetate solution with stirring and extracted with ethyl acetate (x2). The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated to give the title compound as a cream solid.

LC/MS (ES+ve): [M+H]^+ at m/z 350, 352, 354 (C_{16}H_{13}Cl_2N_3O_2 requires [M+H]^+ at m/z 350, 352, 354).

Description 38
15 Ethyl [5-(2-chlorophenyl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-c]pyrimidin-7-yl]acetate (D38)

![Chemical Structure]

20 Ethyl [4-chloro-5-(2-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D37, 2.86 g, 8.17 mmol) was dissolved in acetonitrile (50 ml.) and 3-azetidinol hydrochloride (1.074 g, 9.80 mmol) and N,N-diisopropylethylamine (3.42 ml, 19.60 mmol) added. The mixture was stirred at 50°C for 8 hours. 3-Azetidinol hydrochloride (0.358 g, 3.27 mmol) and N,N-diisopropylethylamine (0.713 ml, 4.08 mmol) were added and stirring continued at 50°C for a further 14 hours. The solvent was evaporated and the
residue partitioned between ethyl acetate and 0.5M hydrochloric acid. The organic phase was washed with water and brine, dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography, eluting with 0-5% methanol/ethyl acetate to give the title compound. A further quantity of product was obtained from the aqueous layer above, which was extracted with dichloromethane (x2), dried over magnesium sulphate and evaporated to a white foam.

LC/MS (ES+ve): [M+H]+ at m/z 387, 389 (C_{19}H_{19}ClN_{4}O_{3} requires [M+H]+ at m/z 387, 389).
bis(triphenylphosphine)palladium(II) chloride (35.1 mg, 0.050 mmol) were dissolved in N,N-dimethylformamide (5 mL) under argon and the mixture heated at 100 °C in the microwave for 30 minutes, then at 120 °C for a further 60 minutes. The reaction was diluted with diethyl ether and washed with water (x3), dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography, eluting with 0-50% ethyl acetate/iso-hexane to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]+ at m/z 386, 388 (C_{29}H_{20}ClN_{3}O_{3} requires [M+H]+ at m/z 386, 388).

Description 41

Ethyl [4-acetyl-5-(2-chlorophenyl)-7H-pyrrolo[2,3-c]pyrimidin-7-yl]acetate (D41)

Ethyl [5-(2-chlorophenyl)-4-[1-(ethyloxy)ethenyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D40, 271 mg, 0.702 mmol) was stirred in a mixture of acetone (2 mL) and 1M hydrochloric acid (4.214 mL, 4.21 mmol) at room temperature for 18 hours. Water was added and the mixture extracted with ethyl acetate (x2), which was washed with brine, dried (magnesium sulfate) and evaporated to give the title compound.

LC/MS (ES+ve): [M+H]+ at m/z 358, 360 (C_{18}H_{16}ClN_{3}O_{3} requires [M+H]+ at m/z 358, 360).

Description 42

Ethyl [5-(2-chlorophenyl)-4-(1-hydroxyethyl)-7H-pyrrolo[2,3-r]pyrimidin-7-yl]acetate (D42)

Ethyl [4-acetyl-5-(2-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D41, 71.6 mg, 0.2 mmol) was dissolved in ethanol (2 mL) and stirred under argon in an ice-bath. Sodium borohydride (7.57 mg, 0.200 mmol) was added and the mixture stirred at 0°C for 2 hours. Saturated ammonium chloride solution was added and the product extracted with ethyl acetate (x2), which was washed with brine, dried (magnesium sulfate) and evaporated to leave the title compound as a cream solid.

LC/MS (ES+ve): [M+H]+ at m/z 360, 362 (C_{18}H_{16}ClN_{3}O_{3} requires [M+H]+ at m/z 360,
Description 43
Methyl (2-nitrophenyl)acetate (D43)

A suspension of 2-nitrophenyl acetic acid (50 g, 276.2 mmol) in methanol (500 ml) was cooled to 0°C, then thionyl chloride (98 ml, 828.6 mmol) was added dropwise over two hours. The resulting solution was stirred for 12 hours at room temperature. The solvent was then evaporated and the resulting residue was dissolved in ethyl acetate (150 ml) and then washed with water (100 ml) and aqueous sodium bicarbonate solution (150 ml). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (60-120 mesh silica gel) using 10% ethyl acetate / petroleum ether as eluent to afford the title compound.

LC/MS (ES+ve): [M+H]^+ at m/z 196 (C_9H_9NO_4 requires [M+H]^+ at m/z 196).

Description 44
Methyl 2-methyl-2-(2-nitrophenyl)propanoate (D44)

A solution of methyl (2-nitrophenyl)acetate (D43, 30 g, 153.84 mmol) and methyl iodide (48 g, 338.46 mmol) in tetrahydrofuran (390 ml) was cooled to -78 °C. Potassium tert-butoxide (37.9 g, 338.46 mmol) was added to above stirred solution over an hour and 18-crown ether-6 (0.5 g, 38.46 mmol) was added at -78 °C. The reaction was stirred for 2 hours at -78 °C, and then for 2 hours at room temperature. The reaction mixture was then recooled to -78 °C and quenched with saturated ammonium chloride solution. The reaction mixture was allowed to warm to room temperature and extracted with dichloromethane, the organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford the title compound which was used without further purification.
Description 45
2-Methyl-2-(2-nitrophenyl)propanoic acid (D45)

A suspension of methyl 2-methyl-2-(2-nitrophenyl)propanoate (D44, 30 g, 134.5 mmol) in methanol (300 ml) was cooled to 0 °C then aqueous sodium hydroxide solution (7.9 gm, 201.7 mmol in 30 ml water) was added. The resulting mixture was stirred for 72 hours at reflux temperature. The solvent was evaporated, and the resulting residue was acidified with 5N hydrochloric acid then extracted with ethyl acetate (150 mL). The organic layer was washed with brine (25 mL), dried over sodium sulfate, and concentrated. The crude residue was purified by column chromatography (60-120 mesh silica gel) using 50% ethyl acetate / petroleum ether to give the title compound.

Description 46
[1-Methyl-1-(2-nitrophenyl)ethyl]amine (D46)

To a solution of 2-methyl-2-(2-nitrophenyl)propanoic acid (D45, 10 g, 47.84 mmol) in toluene (100 ml) at 0 °C under nitrogen was added triethylamine (8 ml, 57.4 mmol) and stirred for 5 minutes, then diphenyl phosphoryl azide (12 ml, 52.6 mmol) was added slowly. The resulting solution was stirred for 2 hours the reaction mixture was concentrated under reduced pressure and then diluted with toluene (100 ml) and refluxed for 30 minutes at 90 °C. The reaction mixture was allowed to cool to room temperature and then further cooled to 0 °C and 6N hydrochloric acid (150 ml) added. The resulting solution was heated at reflux for 3 hours. The crude mixture was concentrated under reduced pressure, diluted with ice-cold water and basified with 5N sodium hydroxide solution, extracted with ethyl acetate (200 ml), washed with brine (50 ml) and dried over sodium sulphate, then concentrated under reduced pressure. Purification by column chromatography (60-120 mesh silica gel) using 70% ethyl acetate / petroleum ether as solvent afforded the title compound.

LC/MS (ES+ve): [M+H]^+ at m/z 181 (C_9H_{12}N_2O_2 requires [M+H]^+ at m/z 181).
**Description 47**

1,1-Dimethylethyl 4-[(1-methyl-1-(2-nitrophenyl)ethyl)amino]-1-piperidinecarboxylate (D47)

To a solution of 1-methyl-1-(2-nitrophenyl)ethyl)amine (D46, 3.24 g, 18.89 mmol) and t-f-butyl 4-oxo-1-piperidinecarboxylate (3.84 g, 18.89 mmol) in dry tetrahydrofuran (40 ml.) and acetic acid (1.0 ml.) under nitrogen at 0 °C was stirred for 20 minutes. To this solution sodium triacetoxyborohydride (8.37 g, 53.7 mmol) was added over 45 minutes. The resulting solution was stirred at 0 °C for 30 minutes and slowly brought to room temperature, and stirred for 2.5 hours under nitrogen. The crude mixture was diluted with ethyl acetate and water. The organic layer was washed with brine and dried over sodium sulfate, then concentrated under reduced pressure. The title compound was obtained after purification by column chromatography (60 -120 mesh silica gel), the product eluting in 20% ethyl acetate / petroleum ether.

LC/MS (ES+ve): [M+H]+ at m/z 364 (C_{19}H_{29}N_{3}O_{4} requires [M+H]+ at m/z 364).

**Description 48**

1,1-Dimethylethyl 4-[(1-(2-aminophenyl)-1-methylethyl)amino]-1-piperidinecarboxylate (D48)

To a solution of 1,1-dimethylethyl 4-[(1-methyl-1-(2-nitrophenyl)ethyl)amino]-1-piperidinecarboxylate (D47, 10 g, 27.54 mmol) in ethanol (100 ml.) was added 10% palladium on charcoal (1.0 g, 1.37 mmol) and the mixture was stirred under hydrogen at 20 psi for 4 hours at room temperature. The reaction mixture was filtered through
a bed of celite, washed with methanol (2 x 50 ml.) and the filtrate then concentrated under reduced pressure. The crude product was purified by column chromatography (60-120 mesh silica gel), the title compound eluting at 30% ethyl acetate / petroleum ether.

**LC/MS (ES+ve):** [M+H]+ at m/z 334 (C_{19}H_{31}N_3O_2 requires [M+H]+ at m/z 334).

### Description 49

**1,1-Dimethylethyl 4-(4,4-dimethyl-2-oxo-1,4-dihydro-3(2H)-quinazolinyl)-1-piperidinecarboxylate (D49)**

![Chemical Structure](image)

Triethylamine (7.8 ml, 56.15 mmol) was added to a solution of 1,1-dimethylethyl 4-\{[1-(2-aminophenyl)-1-methylethyl]amino\}-1-piperidinecarboxylate (D48, 8.5 g, 25.52 mmol) in acetonitrile (85 ml), followed by 1,1'-carbonyldiimidazole (12.4 g, 78.46 mmol) at room temperature under nitrogen and the mixture stirred for 2 hours. The resulting mixture was heated at reflux for 30 minutes. The reaction mixture was then concentrated under reduced pressure, and diluted with ethyl acetate and water. The organic layer was washed with brine, dried over sodium sulphate, and concentrated under reduced pressure. Purification by column chromatography (60-120 meshed silica gel) eluting with ethyl acetate / petrol ether gave the title compound as a white solid.

**LC/MS (ES+ve):** [M+H]+ at m/z 360 (C_{20}H_{29}N_3O_3 requires [M+H]+ at m/z 360).

### Description 50

**4,4-Dimethyl-3-(4-piperidinyl)-3,4-dihydro-2(1H)-quinazolinone hydrochloride salt (D50)**

![Chemical Structure](image)

To a solution of 1,1-dimethylethyl 4-(4,4-dimethyl-2-oxo-1,4-dihydro-3(2H)-quinazolinyl)-1-piperidinecarboxylate (D49, 8 g, 22.28 mmol) in diethyl ether (50 ml) was added ethereal hydrochloric acid (80 ml) and the mixture stirred under nitrogen at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The crude product was triturated with first diethyl ether, and then...
diethyl ether and n-pentane to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]^+ at m/z 260 (C_{5}H_{11}N_{3}O requires [M+H]^+ at m/z 260).

Description 51

1,1-Dimethylethyl 4-[[trifluoromethyl)sulfonyl]oxy]-3,6-dihydro-1(2H)-pyridinecarboxylate (D51)

To a solution of diisopropylamine (0.858 ml, 6.02 mmol) in tetrahydrofuran (20.99 ml) at -78°C was added n-butyl lithium (3.76 ml, 6.02 mmol). The reaction mixture was stirred for 5 minutes at -78°C. A solution of 1,1-dimethylethyl 4-oxo-1-piperidinecarboxylate (1 g, 5.02 mmol) in tetrahydrofuran (6.00 ml) was added, and the reaction mixture was stirred for 10 minutes. Then a solution of 1,1,1-trifluoro-N-phenyl-N-[(trifluoromethyl)sulfonyl]methanesulfonamide (1.972 g, 5.52 mmol) in tetrahydrofuran (2 ml) was added. The reaction mixture was stirred at -78 °C for 30 minutes and the cooling bath was removed to allow warming to room temperature for 1.5 hours, until no more starting material remained. The reaction was quenched with saturated sodium bicarbonate solution and left to stand overnight. The mixture was then extracted with diethyl ether and 5% citric acid and the organic layer washed with 1M sodium hydroxide solution, water and brine, then dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography (Biotage SP4, 25M, 0-20% ethyl acetate/hexane), and relevant fractions combined and concentrated in vacuo to give the title compound.

^1H NMR δ (DMSOd$_6$): 1.41 (9H, s), 2.41 (2H, m), 3.54 (2H, m), 3.98 (2H, m), 6.02 (1H, app s).
Description 52
1,1-Dimethylethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-1(2H)-pyridinecarboxylate (D52)

1,1-Dimethylethyl 4-{(trifluoromethyl)sulfonyl}oxy)-3,6-dihydro-1(2H)-pyridinecarboxylate (D51, 990 mg, 2.99 mmol), bis(pinacolato)diboron (835 mg, 3.29 mmol), potassium acetate (880 mg, 8.96 mmol), 1,1′-bis(diphenylphosphino)ferrocene (49.7 mg, 0.090 mmol) and 1,1′-bis(diphenylphosphino)ferrocenedichloropalladium(II) (73.2 mg, 0.090 mmol) were suspended in 1,4-dioxane (14.9 ml.) and stirred at 80°C for 18 hours. The mixture was cooled to room temperature and concentrated. Ethyl acetate was added, washed with water, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by chromatography (Biotage SP4, 25M, 0-10% ethyl acetate in hexane over 10 column volumes, collecting all fractions). Relevant fractions were combined and concentrated in vacuo to give the title compound.

1H NMR $\delta$ (CDCl$_3$): 1.26 (12H, m), 1.46 (9H, s), 2.22 (2H, app br s), 3.44 (2H, m), 3.95 (2H, m), 6.46 (1H, app br s).

Description 53
1,1-Dimethylethyl 4-(7H-pyrrolo[2,3-cf]pyrimidin-4-yl)-3,6-dihydro-1(2H)-pyridinecarboxylate (D53)

4-Chloro-7H-pyrrolo[2,3-d]pyrimidine (1.13 g, 7.36 mmol), 1,1-dimethylethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-1(2H)-pyridinecarboxylate (DS2, 2.5 g, 8.09 mmol), sodium carbonate (1.542 g, 14.55 mmol) and 1,1′-
bis(diphenylphosphino)ferrocenedichloropalladium(II) dichloromethane adduct (0.297 g, 0.364 mmol) were heated in the microwave in 1,4-dioxane (20 mL) and water (4 mL) at 100°C, normal absorption, for 20 minutes. The mixture was heated in the microwave for a further 6 hours at 100°C then passed down a hydromatrix cartridge, and washed well with ethyl acetate. The organic solution was concentrated in vacuo and then purified by column chromatography (Biotage SP4, 100 g snap cartridge, 50-100% ethyl acetate in hexane over 10 column volumes). Relevant fractions were combined and concentrated in vacuo to give the title compound.

LC/MS (ES-ve): [M-H]⁻ at m/z 299 (C₁₆H₂₀N₄O₂ requires [M-H]⁻ at m/z 299).

Description 54

1,1-Dimethylethyl 4-(5-bromo-7H-pyrrolo[2,3-fl]pyrimidin-4-yl)-3,6-dihydro-1(2H)-pyridinecarboxylate (D54)

To a stirring solution of 1,1-dimethylethyl 4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-3,6-dihydro-1(2H)-pyridinecarboxylate (D53, 1.43 g, 4.76 mmol) in N,N-dimethylformamide (23.81 mL) at 0°C was added N-bromosuccinimide (0.847 g, 4.76 mmol) portionwise. The reaction was stirred at 0°C for 20 minutes, before being warmed to room temperature for 10 minutes, concentrated in vacuo, and then azeotroped with toluene. The product was purified by column chromatography (Biotage SP4, 50 g snap cartridge, 0-10% ammonia in methanol / dichloromethane over 10 column volumes). Relevant fractions were combined, and concentrated in vacuo to afford the title compound which was used without further purification.

Description 55
1,1-Dimethylethyl 4-{5-bromo-7-[2-(ethyloxy)-2-oxoethyl]-7H-pyrrolo[2,3-c]pyrimidin-4-yl}-3,6-dihydro-1(2H)-pyridinecarboxylate (D55)

To a stirring suspension of 1,1-dimethylethyl 4-(5-bromo-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-3,6-dihydro-1(2H)-pyridinecarboxylate (D54, 1.81 g, 4.77 mmol) in dry tetrahydrofuran (23.86 ml) at 0°C under argon was added sodium hydride (60% dispersion, 0.210 g, 5.25 mmol). The mixture was stirred at 0°C for 15 minutes, warmed to room temperature and stirred for a further 15 minutes, before addition of ethyl bromoacetate (0.584 ml, 5.25 mmol). The reaction was stirred at room temperature under argon for 2 hours, then quenched with methanol and partitioned between ethyl acetate and water/brine. The aqueous layer was re-extracted with ethyl acetate and the organic layers combined, washed with water and brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography (Biotage SP4, 50 g snap cartridge, 30-70% ethyl acetate in hexane over 10 column volumes). Relevant fractions were combined and concentrated in vacuo to give the title compound.

LC/MS (ES-ve): [M+H]^+ at m/z 465, 467 \((\text{C}_{20}\text{H}_{26}\text{BrN}_4\text{O}_4\text{ requires [M+H]^+ at m/z 465, 467).}}\)
Description 56
1,1-Dimethylethyl 4-{5-(2-chlorophenyl)-7-[2-(ethyloxy)-2-oxoethyl]-7H-pyrrolo[2,3-cf]pyrimidin-4-yl}-3,6-dihydro-1(2H)-pyridinecarboxylate (D56)

The quantities quoted for this reaction were split between 2 reaction vessels. 1,1-Dimethylethyl 4-{5-bromo-7-[2-(ethyloxy)-2-oxoethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}-3,6-dihydro-1(2H)-pyridinecarboxylate (D55, 2.1 g, 4.51 mmol), sodium carbonate (0.957 g, 9.03 mmol), (2-chlorophenyl)boronic acid (1.411 g, 9.03 mmol), and bis(triphenylphosphine)palladium(II) chloride (0.317 g, 0.451 mmol) were added together in 1,2-dimethoxyethane (16.92 ml) and water (5.64 ml) and heated in the microwave at 100°C for 20 minutes at normal absorption. Ethyl acetate and water were added, the organics extracted x2, combined and washed with brine, then dried over magnesium sulfate and concentrated in vacuo. The crude material was purified by column chromatography (Biotage SP4, 50 g snap cartridge, 50-100% ethyl acetate/hexane over 10 column volumes. Relevant fractions were combined, and concentrated in vacuo. The residue was further purified by column chromatography (Biotage SP4, 10 g snap cartridge, 0-40% ethyl acetate/hexane over 10 column volumes). Relevant fractions were combined and concentrated in vacuo to give the title compound.

LC/MS (ES+ve): [M+H]+ at m/z 497, 499 (C_{26}H_{29}ClN_{4}O_{4} requires [M+H]+ at m/z 497, 499).
Description 57
1,1-Dimethylethyl 3-[(5-bromo-1H-pyrrolo[2,3-c]pyrimidin-4-yl)oxy]-1-pyrrolidinecarboxylate (D57)

1,1-Dimethylethyl 3-hydroxy-i-pyrrolidinecarboxylate (2.014 g, 10.75 mmol) was dissolved in tetrahydrofuran (20 ml), cooled in an ice bath, treated with 60 % sodium hydride in mineral oil (430 mg, 10.75 mmol) and stirred for 15 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 30 minutes. 5-Bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (D5, 500 mg, 2.151 mmol) was added and the resulting mixture stirred at room temperature for 30 minutes. The mixture was heated in the microwave at 100°C for 60 minutes at normal absorption. The solvent was removed under reduced pressure and the residue was diluted with water and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography eluting with a gradient of 0-70 % ethyl acetate in iso-hexane. Product containing fractions were combined and evaporated under reduced pressure to give the title compound as a colourless oil which was used without further purification.

LC/MS (ES+ve): [M+H]+ at m/z 383, 385 (C_{5}H_{19}BrN_{4}O_{3} requires [M+H]+ at m/z 383, 385).

Description 58
Ethyl {5-(2-chlorophenyl)-4-[3-(dimethylamino)-1-propyn-1-yl]-7H-pyrrolo[2,3-cf]pyrimidin-7-yl}acetate (D58)

Ethyl [4-chloro-5-(2-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D37, 178)
mg, 0.508 mmol), bis(triphenylphosphine)palladium(II) chloride (17.84 mg, 0.025 mmol), copper (I) iodide (9.68 mg, 0.051 mmol) and N,N-dimethylpropargylamine (0.109 ml, 1.017 mmol) were suspended in N,N-dimethylformamide (2 ml.) and triethylamine (1 ml.) and mixture heated at 120°C for 90 minutes. The mixture was partitioned between ethyl acetate and water and the organic layer washed with water (x2) and brine, dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography, eluting with 0-5% 2M ammonia in methanol / dichloromethane to provide the title compound.

LC/MS (ES+ve): [M+H]⁺ at m/z 397, 399 (C₂₀H₂₁ClIN₄O₂ requires [M+H]⁺ at m/z 397, 399).

**Description 59**

Methyl [5-(2-chlorophenyl)-4-(3-hydroxy-3-methyl-1-butyn-1-yl)-7H-pyrrolo[2,3-cf]pyrimidin-7-yl]acetate (D59)

![Chemical Structure](attachment:image.png)

Methyl [4-chloro-5-(2-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate [obtainable by a similar procedure to the corresponding ethyl ester D37] (101 mg, 0.300 mmol), bis(triphenylphosphine)palladium(II) chloride (21.09 mg, 0.030 mmol), triphenylphosphine (42.6 mg, 0.162 mmol) and triethylamine (0.084 ml, 0.601 mmol) were suspended in N,N-dimethylformamide (1 ml.) and argon bubbled through the mixture for 10 minutes. 2-Methyl-3-butyn-2-ol (0.029 ml, 0.300 mmol) and copper(I) iodide (1.144 mg, 0.060 mmol) were added and the mixture heated at 140°C in the microwave for 30 minutes. The mixture was diluted with ethyl acetate and washed with water (x2), dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography, eluting with 0-50% ethyl acetate/iso-hexane to give a yellow oil.

LC/MS (ES+ve): [M+H]⁺ at m/z 384, 386 (C₂₀H₁₈ClIN₃O₃ requires [M+H]⁺ at m/z 384, 386).
Description 60

Ethyl \(\{(5\text{-bromo-4-[(1,1\text{-dimethylethyl)amino]-7H-pyrrolo[2,3-c]pyrimidin-7-yl}})\}\text{acetate} \ (D60)

\[
\begin{align*}
\text{Br} & \quad \text{O} \\
\text{N} & \quad \text{N} & \quad \text{O}
\end{align*}
\]

Ethyl (5-bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate \ (D30), 1.593 g, 5 mmol) was stirred in acetonitrile (10 ml) under argon and N,N-diisopropylethylamine (1.921 ml, 11 mmol) added, followed by t-butylamine (0.525 ml, 5 mmol). The mixture was heated at 55°C for 18 hours. The solvent was evaporated and the residue redissolved in t-butylamine (5 ml, 47.6 mmol). The solution was heated at reflux for 76 hours. The solvent was evaporated and the residue dissolved in ethyl acetate and washed with water (x2), dried (magnesium sulfate) and evaporated. As starting material was still present by LCMS the residue was redissolved in t-butylamine (5 ml, 47.6 mmol) and heated to reflux for a further 20 hours. The solvent was evaporated and the residue dissolved in ethyl acetate and washed with water (x2), dried (magnesium sulfate) and evaporated and the residue purified by flash chromatography, eluting with 0-5% methanol/ethyl acetate to give the title compound as an oil still containing some starting material. This was carried forward without further purification.

LC/MS (ES+ve): [M+H]^+ at m/z 355, 357 \((C_{14}H_{19}BrN_4O_2\) requires [M+H]^+ at m/z 355, 357).

Description 61

5-iodo-7H-pyrrolo[2,3-c]pyrimidine \ (D61)

\[
\begin{align*}
\text{I} & \quad \text{N} & \quad \text{N} \\
\text{N} & \quad \text{H}
\end{align*}
\]

7H-Pyrrolo[2,3-d]pyrimidine \ (1 g, 8.39 mmol) was stirred in N,N-dimethylformamide (10 ml) containing potassium hydroxide (0.471 g, 8.39 mmol) and iodine (2.131 g, 8.39 mmol) was added portionwise under argon. The mixture was stirred at room temperature for 1 hour. 20% Sodium thiosulfate solution (50 ml) was added and the resulting cream solid filtered, washed well with water and dried at 60°C \textit{in vacuo} over potassium hydroxide to give the title compound.

LC/MS (ES+ve): [M+H]^+ at m/z 246 \((C_6H_4IN_3\) requires [M+H]^+ at m/z 246).
Description 62
Ethyl (5-iodo-7H-pyrrolo[2,3-cf]pyrimidin-7-yl)acetate (D62)

5-iodo-7H-pyrrolo[2,3-d]pyrimidine (D61, 490 mg, 2 mmol) was dissolved in N,N-dimethylformamide (5 ml), cooled to 0°C under argon and 60% sodium hydride in mineral oil (88 mg, 2.2 mmol) added portionwise. The mixture was stirred at 0°C for 10 minutes then allowed to warm to room temperature over 30 minutes. Ethyl bromoacetate (0.245 ml, 2.200 mmol) was added dropwise and the mixture stirred at room temperature for 17 hours. The solvent was evaporated and the residue dissolved in ethyl acetate, washed with saturated ammonium chloride solution and brine, dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography, eluting with 0-50% ethyl acetate/iso-hexane to give the title compound as a yellow oil.

LC/MS (ES+ve): [M+H]+ at m/z 332 (C10H10IN3O2 requires [M+H]+ at m/z 332).

Description 63
Ethyl (5-[2-(4-methyl-1-piperazinyl)phenyl]-7H-pyrrolo[2,3-cGpyrimidin-7-yl]acetate (D63)

Ethyl (5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (D62, 250 mg, 0.755 mmol) and [2-(4-methyl-1-piperazinyl)phenyl]boronic acid (175 mg, 0.795 mmol; prepared as described in EP 0957099A2) were dissolved in toluene (3 ml.) and ethanol (1.5 ml.) under argon. Tetrakis(triphenylphosphine)palladium(0) (18.38 mg, 0.016 mmol) and cesium carbonate (259 mg, 0.795 mmol) were added and the mixture heated at
100°C in the microwave for 90 minutes. Ethyl acetate and saturated ammonium chloride solution were added and the aqueous layer re-extracted with ethyl acetate. The combined organics were washed with water, dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography, eluting with 0-10% 2M ammonia in methanol/ dichloromethane to give the title compound as a pale yellow gum.

LC/MS (ES+ve): [M+H]⁺ at m/z 380 (C₂₁H₂₅N₅O₂ requires [M+H]⁺ at m/z 380).

Description 64

{5-[2-(4-Methyl-1-piperazinyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl}acetic acid lithium salt (D64)

15 Ethyl {5-[2-(4-methyl-1-piperazinyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl}acetate (D63, 191 mg, 0.503 mmol) was dissolved in tetrahydrofuran (2 ml.) and 0.5M lithium hydroxide solution (1.007 ml, 0.503 mmol) added. The mixture was stirred at room temperature for 2 hours. The solvent was evaporated and the residue re-evaporated from toluene to give the title compound.

LC/MS (ES+ve): [M+H]⁺ at m/z 352 (C₁₉H₂₁N₅O₂ requires [M+H]⁺ at m/z 352 for the free acid).
Description 65
Ethyl {5-bromo-4-[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-1-azetidinyl]-7 H-pyrrolo[2,3-d]pyrimidin-7-yl}acetate (D65)

Ethyl (5-bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (D30, 1.593 g, 5 mmol) was stirred in acetonitrile (10 mL) under argon and N,N-diisopropylethylamine (1.921 mL, 11 mmol) added, followed by 1,1-dimethylethyl 3-azetidinylcarbamate (0.861 g, 5 mmol). The mixture was stirred at room temperature for 22 hours. Ethyl acetate was added and the mixture washed with water (X2), dried (magnesium sulfate) and evaporated to a cream solid which was purified by flash chromatography, eluting with 30-100% ethyl acetate/isohexane to give the title compound.

LC/MS (ES+ve): [M+H]⁺ at m/z 398, 400 (C₁₈H₂₄BrN₅O₄ requires [M-Bu⁴⁺2H]⁺ at m/z 398, 400).

Description 66
Ethyl {5-(2-chlorophenyl)-4-[3-({[(1, 1- dimethylethyl)oxy]carbonyl} amino)-1-azetidinyl] H-pyrrolo[2,3-d]pyrimidin-7-yl}acetate (D66)

Ethyl (5-bromo-4-[3-({[(1 ,1-dimethylethyl)oxy]carbonyl}amino)-1-azetidinyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (D65, 454 mg, 0.999 mmol), (2-
chlorophenyl)boronic acid (313 mg, 1.999 mmol), bis(triphenylphosphine)palladium(II) chloride (35.1 mg, 0.050 mmol) and sodium carbonate (212 mg, 1.999 mmol) were added together in 1,2-dimethoxyethane (4 ml.) and water (1 ml.) and the resulting mixture was heated at 100°C in the microwave for 20 minutes. The reaction mixture was diluted with water and extracted with ethyl acetate (× 2). The ethyl acetate layers were combined, washed with brine, dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography eluting with 0-50% ethyl acetate/iso-hexane to give the title compound as a yellow oil.

LC/MS (ES+ve): [M+H]+ at m/z 486, 488 (C$_{24}$H$_{28}$ClN$_5$O$_4$ requires [M+H]$^+$ at m/z 486, 488).

Description 67


![Structural diagram](image)

Ethyl {5-(2-chlorophenyl)-4-[3-[[[1 ,1-dimethylethyl)oxy]carbonyl]amino]-1-azetidinyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl}acetate (D66, 411 mg, 0.846 mmol) was dissolved in 1,4-dioxan (1 ml.) and 4M hydrochloric acid in dioxan (2 ml., 8.00 mmol) added. The mixture was stirred at room temperature for 3 hours, during which a cream solid precipitated. The mixture was dissolved in methanol and passed through a 10 g SCX cartridge, eluting with methanol then 2M ammonia in methanol. The basic fractions were combined and evaporated to leave the title compound (containing a small amount of the corresponding methyl ester) as a clear gum.

LC/MS (ES+ve): [M+H]$^+$ at m/z 386, 388 (Cl$_9$H$_{20}$ClN$_5$O$_2$ requires [M+H]$^+$ at m/z 386, 388).
Description 68
Ethyl (5-(2-chlorophenyl)-4-{3-[(2,2-difluoroethyl)amino]-1-azetidinyl}-7H-pyrrolo[2,3-cf]pyrimidin-7-yl)acetate (D68)

![Chemical structure diagram]

Ethyl [4-(3-amino-1-azetidinyl)-5-(2-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D67, 149 mg, 0.386 mmol), 1,1-difluoro-2-iodoethane (148 mg, 0.772 mmol), and potassium carbonate (107 mg, 0.772 mmol) were heated in the microwave in acetonitrile (5 ml) at 120°C for 7 hours. The mixture was partitioned between ethyl acetate and water, the ethyl acetate washed with water and brine, dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography, eluting with 0-5% methanol/ethyl acetate to give the title compound as a yellow oil.

LC/MS (ES+ve): [M+H]⁺ at m/z 450, 452 (C₂₂H₂₂ClF₂N₅O₂ requires [M+H]⁺ at m/z 450, 452).

Description 69
Ethyl [5-(2,3-dichlorophenyl)-4-(1-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D69)

![Chemical structure diagram]

Ethyl [4-acetyl-5-(2,3-dichlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (prepared analogously to D41, 392 mg, 1 mmol) was dissolved in tetrahydrofuran (10 ml), cooled to 0°C under argon with stirring and 3M methylmagnesium bromide in diethyl ether (0.333 ml, 1 mmol) added dropwise. The mixture was stirred at 0°C for
2 hours. Saturated ammonium chloride was added and the mixture extracted with ethyl acetate (x2). The combined organics were washed with water, dried (magnesium sulfate) and evaporated. The residue was flash chromatographed, eluting with 0-100% ethyl acetate/iso-hexane to give the title compound as a clear oil.

LC/MS (ES+ve): [M+H]+ at m/z 408, 410, 412 (C_{9}H_{19}Cl_{2}N_{3}O_{3} requires [M+H]+ at m/z 408, 410, 412).

Description 70
1,1-Dimethylethyl 3-hydroxy-3-methyl-1-azetidinecarboxylate (D70)

A solution of 1,1-dimethylethyl 3-oxo-1-azetidinecarboxylate (3 g, 17.52 mmol) in anhydrous tetrahydrofuran (80 ml.) was cooled to 0°C under at atmosphere of argon. Methylmagnesium chloride (20.44 ml, 61.3 mmol) was added and the reaction mixture was allowed to warm to room temperature and was stirred for 6 hours. The reaction mixture was cooled to 0°C and saturated ammonium chloride solution (15 ml.) was added dropwise. Water (20 ml.) was then added and the reaction mixture was left stirring for 10 minutes at 0°C. Diethyl ether (100 ml.) was added and the layers were separated. The aqueous layer was washed with diethyl ether (2 x 100 ml.) and the combined organics were dried over magnesium sulfate, filtered and concentrated under reduced pressure to give a colourless oil which was purified using column chromatography, eluting with a gradient of 0 - 5% 2M ammonia in methanol / dichloromethane. The product containing fractions were collected and solvent evaporated to give the desired product as a white solid.

1H NMR δ (DMSO_d_6) 1.32 (3H, s), 1.37 (9H, s), 3.65 (4H, m), 5.56 (1H, s).

Description 71
3-Methyl-3-azetidinol (D71)

1,1-Dimethylethyl 3-hydroxy-3-methyl-1-azetidinecarboxylate (D70, 3.23 g, 17.25 mmol) was dissolved in dichloromethane (10 ml.), treated with trifluoroacetic acid (23.92 ml, 311 mmol) and stirred for 3 hours at room temperature. The solvent was removed under reduced pressure and the residue passed down an SCX column (2 x 20 g) eluting with methanol, followed by 2M ammonia in methanol. Basic fractions were combined and the solvent evaporated under reduced pressure to give the title
compound as an orange oil.

$^1$H NMR $\delta$ (DMSOd$_6$) 1.32 (3H, s), 3.11 (2H, m, partially overlapped by water signal), 3.43 (2H, m, overlapped by water signal), 5.08 (1H, br s).

5 Description 72
1,1-Dimethylethyl (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (D72)

![Chemical Structure]

The 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (2.5 g, 16.28 mmol) was dissolved in dry N,N-dimethylformamide (50 ml.) and treated with sodium hydride (0.651 g, 16.28 mmol). After stirring at room temperature for 5 minutes, 1,1-dimethylethyl bromoacetate (2.404 ml, 16.28 mmol) was then added. The mixture was stirred at room temperature for 2 hours. Ethyl acetate was then added (200 ml.) and washed with water (2X200 ml.). Dried over magnesium sulfate and evaporated off the solvent. The residue after drying over magnesium sulfate and evaporation of solvent purified by column chromatography (Biotage, ethyl acetate/hexane 1:3) to obtain a the title compound as a white waxy solid.

LC/MS (ES+ve): [M+H]$^+$ at m/z 268, 270 ($C_{12}H_{14}ClIN_3O_2$ requires [M+H]$^+$ at m/z 268, 270).

Description 73
1,1-Dimethylethyl (4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (D73)

![Chemical Structure]

To a solution of 1,1-dimethylethyl (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (D72, 800 mg, 2.99 mmol) in dichloromethane (30 ml.) was added iodine
monochloride (0.165 ml, 3.29 mmol) and the solution stirred for 1 hour, then left standing overnight. Iodine monochloride (0.165 ml, 3.29 mmol) was then added and the mixture stirred for 5 hours. The solvent was evaporated and the residue reevaporated with toluene (20 ml). Dichloromethane (10 ml) was added followed by ether (20 ml). The title compound crystallised out of solution as a yellow solid which was filtered off and washed with ether.

LC/MS (ES+ve): [M+H]⁺ at m/z 394, 396 (Cl₂H₁₃ClIN₃O₂ requires [M+H]⁺ at m/z 394, 396).

Description 74
1,1-Dimethylethyl [4-chloro-5-(2,3-dichlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D74)

A mixture of 1,1-dimethylethyl (4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (D73, 1 g, 2.54 mmol), (2,3-dichlorophenyl)boronic acid (0.727 g, 3.81 mmol), tetrakis(triphenylphosphine)palladium(0) (0.147 g, 0.127 mmol) and cesium carbonate (1.656 g, 5.08 mmol) in a mixture of toluene (25 ml) and ethanol (12.5 ml) was refluxed for 2 hours. Inorganic material was filtered off and washed with ethyl acetate. The resultant solution was treated with ethyl acetate (100 ml) and washed with a mixture of water (100 ml) and brine (20 ml). After a final wash with brine (50 ml) the solution was dried over magnesium sulfate. Solvent was evaporated and the residue purified by column chromatography (Biotage, ethyl acetate/hexane 1:3) to obtain the title compound as a colourless oil.

LC/MS (ES+ve): [M+H]⁺ at m/z 412, 414, 416 (C₁₈H₁₆Cl₃N₃O₂ requires [M+H]⁺ at m/z 412, 414, 416, 418).
**Description 75**

[4-Chloro-5-(2,3-dichlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetic acid (D75)

1,1-Dimethylethyl [4-chloro-5-(2,3-dichlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D74, 400 mg, 0.969 mmol) was dissolved in hydrochloric acid (4M in dioxan) (2.423 ml, 9.69 mmol) and left standing for 4 hours to give one major product. The solvent was evaporated and the residue crystallised from ether/hexane to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]^+ at m/z 356, 358, 360 (C_{14}H_{8}Cl_{3}N_{3}O_{2} requires [M+H]^+ at m/z 356, 358, 360).

**Description 76**

1-(1-[^\^]-chloro-S\^S-dichlorophenyl\^H-pyrrolo\^S-dlpyrimidin\^yllacetyl\^-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (D76)

A mixture of [4-chloro-5-(2,3-dichlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetic acid (D75, 300 mg, 0.841 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (177 mg, 0.925 mmol) and 1-hydroxybenzotriazole (142 mg, 0.925...
mmol) in dry N,N-dimethylformamide (5 mL) was treated with N-methylmorpholine (0.462 ml, 4.21 mmol) and stirred for 5 minutes. 1-(4-Piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (269 mg, 0.925 mmol) was added and stirred for 4 hours to give one major product. Most of the N,N-dimethylformamide was evaporated, ethyl acetate (70 mL) added and washed with saturated sodium bicarbonate (50 mL) followed by water (50 mL). The solution was dried over magnesium sulfate and the solvent evaporated. The product was crystallised from ethyl acetate/ether to yield the title compound as a white solid.

LC/MS (ES+ve): [M+H]⁺ at m/z 556, 558, 560, 562 (C₂₅H₂₀C₃N₇O₂ requires [M+H]⁺ at m/z 556, 558, 560, 562).

**Description 77**

7-[(4-Methylphenyl)sulfonyl]-7H-pyrrolo[2,3-cf]pyrimidine-4-carbonitrile (D77)

4-Chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidine (1.0 g, 3.25 mmol), zinc (25.5 mg, 0.390 mmol), 1,1'-bis(diphenylphosphino)ferrocene (72.1 mg, 0.130 mmol), tris(dibenzylideneacetone)dipalladium(0) (59.5 mg, 0.065 mmol) and zinc cyanide (229 mg, 1.950 mmol) were added together in N,N-dimethylacetamide (6.5 mL) and the resulting mixture was heated at 120 °C under argon for 3 hours. The reaction mixture was allowed to cool to room temperature, diluted with water and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography eluting with a gradient of 0-40 % ethyl acetate and iso-hexane. Product containing fractions were combined and evaporated under reduced pressure to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]⁺ at m/z 299 (C₁₄H₁₀N₄O₂S requires [M+H]⁺ at m/z 299).

**Description 78**

7H-Pyrrolo[2,3-cf]pyrimidine-4-carbonitrile (D78)

7-[(4-Methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidine-4-carbonitrile (D77, 396 mg,
1.327 mmol) was dissolved in tetrahydrofuran (5 ml), treated with 1M tetrabutylammonium fluoride in tetrahydrofuran (5.31 ml, 5.31 mmol) and the resulting mixture was stirred at room temperature under argon for 1 hour. The solvent was removed under reduced pressure, the residue was diluted with water and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography eluting with a gradient of 0-50 % ethyl acetate and iso-hexane. Fractions containing the product were combined and evaporated under reduced pressure to give the title compound as a yellow solid.

**LC/MS (ES+ve):** [M+H]+ at m/z 145 (C₇H₄N₄ requires [M+H]+ at m/z 145).

**Description 79**

5-Bromo-7H-pyrrolo[2,3-cf]pyrimidine-4-carbonitrile (D79)

![Image of the compound](image_url)

7H-Pyrrolo[2,3-d]pyrimidine-4-carbonitrile (D78, 153 mg, 1.062 mmol) was dissolved in N,N-dimethylformamide (5 ml), cooled in an ice bath and treated with N-bromosuccinimide (189 mg, 1.062 mmol) portionwise. The resulting mixture was stirred under argon for 20 minutes, allowed to warm to room temperature and stirred for 2 hours. The solvent was removed under reduced pressure and the residue triturated with water. The resulting solid was collected by filtration and dried under high vacuum at 50 °C for 18 hours to give the title product as a yellow solid.

**LC/MS (ES+ve):** [M+H]+ at m/z 223, 225 (C₇H₃BrN₄ requires [M+H]+ at m/z 223, 225).

**Description 80**

1,1-Dimethylethyl (5-bromo-4-cyano-7H-pyrrolo[2,3-cf]pyrimidin-7-yl)acetate (D80)

![Image of the compound](image_url)

5-Bromo-7H-pyrrolo[2,3-d]pyrimidine-4-carbonitrile (D79, 224 mg, 1.004 mmol) was dissolved in N,N-dimethylformamide (6 ml), cooled in an ice bath and treated with 60% sodium hydride in mineral oil (48.2 mg, 1.205 mmol) portionwise and stirred under argon for 15 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 45 minutes. 1,1-Dimethylethyl bromoacetate (196 mg, 1.004 mmol) was added and the resulting mixture stirred for 1 hour. The solvent was
removed under reduced pressure. The residue taken up in water, neutralised using saturated ammonium chloride and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography eluting with a gradient of 0-50 % ethyl acetate and iso-hexane. Product containing fractions were combined and evaporated under reduced pressure to give the title compound as a yellow solid.

LC/MS (ES+ve): [M+H]⁺ at m/z 337, 339 (Cl₃H₁₃BrN₄O₂ requires [M+H]⁺ at m/z 337, 339).

Description 81
1,1-Dimethylethyl [5-(2-chlorophenyl)-4-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D81)

[Chemical Structure Image]

1,1-Dimethylethyl (5-bromo-4-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (D80, 234 mg, 0.694 mmol), (2-chlorophenyl)boronic acid (217 mg, 1.388 mmol), bis(triphenylphosphine)palladium(II) chloride (24.36 mg, 0.035 mmol) and sodium carbonate (147 mg, 1.388 mmol) were added together in 1,2-dimethoxyethane (4 ml) and water (1 ml) and the resulting mixture was heated at 100 °C in the microwave for 20 minutes at normal absorption. The reaction mixture was diluted with water and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography eluting with a gradient of 0-50 % ethyl acetate and iso-hexane. Product containing fractions were combined and evaporated under reduced pressure to give the title compound as a yellow solid.

LC/MS (ES+ve): [M+H]⁺ at m/z 369, 371 (Cl₉H₁₇ClIN₄O₂ requires [M+H]⁺ at m/z 369, 371).
Description 82

[5-(2-Chlorophenyl)-4-cyano-7H-pyrrolo[2,3-cf]pyrimidin-7-yl]acetic acid (D82)

\[
\begin{array}{c}
\text{CN} \\
\text{Cl} \\
\text{N} \\
\text{O} \\
\text{H}
\end{array}
\]

1,1-Dimethylethyl [5-(2-chlorophenyl)-4-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D81, 226 mg, 0.613 mmol) was dissolved in dichloromethane (2 ml), treated with trifluoroacetic acid (1 ml, 12.98 mmol) and the resulting mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and the residue was azeotroped with toluene to give the title compound as a yellow solid. LC/MS (ES+ve): [M+H]^+ at m/z 313, 315 (Cl_2H_9CIN_4O_2 requires [M+H]^+ at m/z 313, 315).

Description 83

Ethyl 7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-c]pyrimidine-4-carboxylate (E83)

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{N} \\
\text{S} \\
\text{O}
\end{array}
\]

4-Chloro-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidine (2 g, 6.50 mmol), 1,1'-bis(diphenylphosphino)ferrocene (0.36 g, 0.649 mmol), palladium(II) acetate (0.146 g, 0.650 mmol) and sodium acetate (1.066 g, 13.00 mmol) were stirred in ethanol (40 ml) in a 100 ml Parr apparatus. The vessel was pressurised to 20 bar with carbon monoxide then heated at 100 °C for 22 hours. After cooling and release of carbon monoxide, the solvent was evaporated and the residue purified by flash
chromatography (0-50% ethyl acetate/isohexane) to give the title compound. LC/MS (ES+ve): [M+H]^+ at m/z 346 (C_{6}H_{15}N_{3}O_{4}S requires [M+H]^+ at m/z 346).

**Description 84**

1,1-Dimethylethyl (4-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (D84)

![Chemical Structure](image)

To a solution of 4-iodo-7H-pyrrolo[2,3-d]pyrimidine (3 g, 8.07 mmol) in dry N,N-dimethylformamide (50 ml.) was added sodium hydride (0.71 g, 17.75 mmol) portionwise and the mixture stirred for 10 minutes to give a clear solution. tert-Butyl bromoacetate (2.62 ml., 17.75 mmol) was added and the mixture stirred for 1 hour. Ethyl acetate (250 ml.) was added and washed with water (2x200 ml.). Dried over magnesium sulfate and solvent evaporated to give a yellow oil. A small amount of solid started to form. Ether (10 ml.) was added followed by hexane (40 ml.) and a white solid slowly precipitated. After collection and washing with hexane the title compound was obtained as a white solid.

LC/MS (ES+ve): [M+H]^+ at m/z 360 (C_{6}H_{14}I_{1}N_{3}O_{2} requires [M+H]^+ at m/z 360).

**Description 85**

1,1-Dimethylethyl [4-(trifluoromethyl)-7H-pyrrolo[2,3-fl]pyrimidin-7-yl]acetate (D85)

![Chemical Structure](image)

A mixture of 1,1-dimethylethyl (4-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (D84, 1.6g, 4.45 mmol) and copper(I) iodide (2.121 g, 11.14 mmol) stirring in N-methyl-2-pyrroldione (3 ml.) and N,N-dimethylformamide (3 ml.) was treated with trimethyl(trifluoromethyl)silane (1.58 ml., 10.69 mmol). The mixture was stirred at room temperature for 5 minutes then at 60 °C for 15 minutes. Potassium fluoride (0.362 g, 6.24 mmol) was added and stirring continued at 60 °C for 30 minutes. Ether (100 ml.) was added and the mixture washed with water (100 ml.). On standing ether
separated from the inorganic precipitate. The ether layer was dried over magnesium sulfate and then the solvent evaporated. The resulting oil was purified by chromatography (Biotage, ethyl acetate/hexane 1:3) to give the title compound as a pale yellow oil.

LC/MS (ES+ve): [M+H]^+ at m/z 302 (C_{13}H_{14}F_{3}N_{3}O_{2} requires [M+H]^+ at m/z 302).

Description 86
1,1-Dimethylethyl [5-iodo-4-(trifluoromethyl)-7H-pyrrolo[2,3-r]pyrimidin-7-yl]acetate (D86)

1,1-Dimethylethyl [4-(trifluoromethyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (D85, 500 mg, 1.660 mmol) dissolved in N,N-dimethylformamide (10 ml) was treated with N-iodosuccinimide (1.12 g, 4.98 mmol) and heated at 60 °C for 5 hours to give a single product. Ethyl acetate (100 ml) was added and washed with water (2X100 ml). After drying over magnesium sulphate the solvent was evaporated, reevaporating with toluene (2X10 ml). The residue was purified by chromatography (Biotage, ethyl acetate/hexane 1:3) to the title compound as a colourless oil which slowly solidified to a pale pink waxy solid.

LC/MS (ES+ve): [M+H]^+ at m/z 428 (C_{13}H_{13}F_{3}I_{1}N_{3}O_{2} requires [M+H]^+ at m/z 428).

Example 1
1-(1-[[5-(2-Chlorophenyl)-7H-pyrrolo[2,3-c]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-fe]pyridin-2-one (E1)

5-(2-Chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetic acid, (D4, 72 mg, 0.250 mmol), 1-(4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (60.1 mg, 0.275 mmol), (2-(7-aza-1 H-benzotriazole-1-yl)-1,3,3-tetramethyluronium hexafluorophosphate) (105 mg, 0.275 mmol) and N,N'-disopropylethylamine (0.048 ml, 0.275 mmol) were added together in N,N-dimethylformamide (2 ml) at room
temperature under argon and the resulting mixture was stirred for 2 hours. The solvent was removed under reduced pressure and the residue was purified by MDAP. Product containing fractions were combined and evaporated under reduced pressure. The residue was purified by column chromatography eluting with a mixture of 2M ammonia/methanol and dichloromethane (5:95). Product containing fractions were combined and evaporated under reduced pressure. The resulting solid was dried under high vacuum at 50°C for 5 hours to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]⁺ at m/z 488, 490 (C₂₅H₂₂ClN₇O₂ requires [M+H]⁺ at m/z 488, 490).

¹H NMR δ (DMSO-de): 1.78-1.90 (1H, m), 2.12-2.19 (1H, m), 2.38-2.47 (1H, m), 2.77-2.83 (1H, m), 3.30-3.38 (2H, m), 4.20-4.24 (1H, m), 4.48-4.55 (2H, m), 5.36-5.48 (2H, m), 7.01-7.04 (1H, m), 7.40-7.50 (2H, m), 7.60-7.68 (3H, m), 7.91-7.97 (2H, m), 8.85 (1H, s), 9.07 (1H, s), 11.6 (1H, s).

Example 2
3-1-[(5-(2-Chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl]-4-piperidinyl]-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one (E2)

[5-(2-Chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetic acid (D₄, 85 mg, 0.295 mmol), 3-(4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one (80 mg, 0.325 mmol), (2-(7-aza-1H-benzotriazole-1-yl)-1,3,3-tetramethyluronium hexafluorophosphate) (124 mg, 0.325 mmol) and N,N'-diisopropylethylamine (0.057 mL, 0.325 mmol) were added together in N,N-dimethylformamide (2 mL) and the resulting mixture was stirred at room temperature under argon for 1 hour. The solvent was removed under reduced pressure and the residue was purified by MDAP. Product containing fractions were combined and evaporated under reduced pressure. The resulting solid was dried under high vacuum at 50°C overnight to give the title compound as a white solid. LC/MS (ES+ve): [M+H]⁺ at m/z 515, 517 (C₂₈H₂₇ClN₆O₂ requires [M+H]⁺ at m/z 515, 517).

¹H NMR δ (DMSO-d₆): 1.54-1.90 (4H, m), 2.67-2.73 (1H, m), 2.90-2.93 (2H, m), 3.22-3.43 (3H, m), 4.13-4.16 (1H, m), 4.31-4.44 (2H, m), 5.31-5.41 (2H, m), 6.78-6.85 (1H, m), 7.03-7.07 (3H, m), 7.39-7.50 (2H, m), 7.63-7.87 (2H, m), 7.87 (1H, m), 8.55 (1H, s), 8.85 (1H, s), 9.01 (1H, s).
Example 3

\[ 1-(\text{5-(2-Chlorophenyl)-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl})\text{acetyl}-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-fe]pyridin-2-one \text{ (E3)} \]

\[
\text{[5-(2-Chlorophenyl)-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetic acid (D9, 86 mg, 0.241 mmol), (2-(7-aza-1 H-benzotriazole-1-yl)-1,3,3-tetramethyluronium hexafluorophosphate) (101 mg, 0.265 mmol) and N,N'-diisopropylethylamine (0.046 ml, 0.265 mmol) were added together in N,N-dimethylformamide (2 ml.) at room temperature under argon and the resulting mixture was stirred for 2 hours. The solvent was removed under reduced pressure and the residue was purified by column chromatography eluting with 2M ammonia/methanol and dichloromethane (5:95). Product containing fractions were combined and evaporated under reduced pressure. The resulting solid was dried under high vacuum at 50°C for 2 hours to give the title compound as a white solid.} \\
\text{LC/MS (ES+ve): [M+H] at m/z 557, 559 (C_{29}H_{29}ClN_{8}O_{2} requires [M+H] at m/z 557, 559).} \\
\text{^1H NMR } \delta \text{ (DMSO-}d_{6}) \text{: 1.64 (3H, br s), 1.76-1.86 (2H, m), 2.06-2.14 (1H, m), 2.32-2.40 (1H, m), 2.75-2.81 (1H, m), 3.12-3.17 (1H, m), 3.27-3.33 (5H, m), 4.18-4.21 (1H, m), 4.47-4.53 (2H, m), 5.22 (2H, br m), 6.99-7.02 (1H, m), 7.19 (1H, s), 7.37-7.47 (3H, m), 7.51-7.59 (2H, m), 7.91-7.92 (1H, m), 8.17 (1H, s), 11.59 (1H, m).} \\

Example 4

\[ 3-(\text{5-(2-Chlorophenyl)-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl})\text{acetyl}-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one \text{ (E4)} \]

\[
\text{[5-(2-Chlorophenyl)-4-(1-pyrrolidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetic acid (D9, 86 mg, 0.241 mmol), 3-(4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one (65.0 mg, 0.265 mmol), (2-(7-aza-1 H-benzotriazole-1-yl)-1,3,3-tetramethyluronium hexafluorophosphate) (101 mg, 0.265 mmol) and N,N'-diisopropylethylamine (0.046 ml, 0.265 mmol) were added together in N,N-dimethylformamide (2 ml.) and the} \\
\text{...}
resulting mixture was stirred at room temperature under argon for 2 hours. The solvent was removed under reduced pressure and the residue was purified by MDAP. Product containing fractions were combined and evaporated under reduced pressure. The resulting solid was dried under high vacuum at 50°C for 2 hours to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]⁺ at m/z 584, 586 (C₃₂H₅₄ClN₇O₂ requires [M+H]⁺ at m/z 584, 586).

¹H NMR δ (DMSO-de): 1.55-1.82 (8H, m), 2.66-2.60 (1H, m), 2.89-2.92 (2H, m), 3.17-3.39 (7H, br m), 4.00-4.04 (1H, m), 4.31-4.44 (2H, m), 5.24 (2H, br m), 6.79-6.83 (1H, m), 7.02-7.08 (3H, m), 7.28 (1H, br s), 7.42-7.48 (3H, m), 7.54-7.57 (1H, m), 8.24 (1H, s), S,SS (1H, S).

Example 5


To a solution of [5-(2-chlorophenyl)-4-phenyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetic acid (D14, 120 mg, 0.330 mmol), 1-(4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (72 mg, 0.330 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbo diimide hydrochloride (76 mg, 0.396 mmol) and 1-hydroxybenzotriazole (55.6 mg, 0.363 mmol) in N,N-dimethylformamide (3.5 ml), N-methylmorpholine (0.073 ml, 0.660 mmol) was added. The reaction mixture was stirred for 3 hours at room temperature under an atmosphere of argon. It was then concentrated under reduced pressure to form a brown oil. The product was partitioned between dichloromethane (15 ml) and water (7 ml). The aqueous layer was washed with dichloromethane (10 ml). The combined organic extracts were washed with 5 % citric acid (7 ml), sodium bicarbonate solution (7 ml) and brine (7 ml). The combined organic extracts were dried over magnesium sulfate, filtered, concentrated under reduced pressure and dried under vacuum overnight at 50°C. The residue was purified by column chromatography (Biotage SP4, eluting with a gradient of 0 - 5 % 2M ammonia in methanol / dichloromethane). The fractions containing product were combined and evaporated under reduced pressure. The residue was further purified by MDAP.

Product containing fractions were combined and evaporated under reduced pressure to give 1-(1-{[5-(2-chlorophenyl)-4-phenyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one as a white solid.

¹H NMR δ (DMSO-d₆): 1.79-1.91 (2H, m), 2.08-2.20 (1H, m), 2.39-2.48 (1H, m), 2.67-2.85 (1H, m), 3.33-3.39 (1H, m), 4.23-4.26 (1H, m), 4.50-4.56 (2H, m), 5.39-5.50 (2H, m), 7.01-7.10 (3H, m), 7.21-7.34 (7H, m), 7.61-7.63 (1H, dd), 7.74 (1H, s), 7.92-7.97
1-(1-{[5-(2-Chlorophenyl)-4-phenyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl}-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (72 mg, 0.128 mmol) was dissolved in methanol (1.5 ml) and dichloromethane (1.5 ml), treated with 1M hydrochloric acid in ether (0.268 ml, 0.268 mmol) and stirred at room temperature for 10 minutes. The solvent was removed under reduced pressure and the resulting solid was dried at 50°C under high vacuum overnight to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]+ at m/z 564, 566 (C31H26ClN7O2 requires [M+H]+ at m/z 564, 566).

Example 6-see Table of Examples

Example 7
1,1-Dimethylethyl 4-[[5-(2-chlorophenyl)-7-(2-oxo-2-[4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-fe]pyridin-1-yl)-1-piperidinyl]ethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-1-piperazinecarboxylate (E7)

[5-(2-Chlorophenyl)-4-[[1,1-dimethylethyl]oxy]carbonyl]-1-piperazinyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetic acid sodium salt (D18, 175 mg, 0.371 mmol), 1-(4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (81 mg, 0.371 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride salt (85 mg, 0.445 mmol), 1-hydroxybenzotriazole (62.5 mg, 0.408 mmol) and N-methylmorpholine (0.082 ml, 0.742 mmol) were added together in N,N-dimethylformamide (3 ml) and the resulting mixture was stirred at room temperature under argon for 18 hours. The solvent was removed under reduced pressure and the residue diluted with water and extracted with dichloromethane (x 2). The dichloromethane layers were combined, washed with saturated sodium bicarbonate and brine, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography eluting with a gradient of 0-10 % 2M ammonia/methanol and dichloromethane. Product containing fractions were combined and evaporated under reduced pressure to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]+ at m/z 672, 674 (C34H38ClN9O4 requires [M+H]+ at m/z 672, 674).

1H NMR δ (DMSO-de): 1.36 (9H, s), 1.77-1.87 (2H, m), 2.06-2.17 (1H, m), 2.32-2.41 (1H, m), 2.76-2.82 (1H, m), 3.02 (4H, br s), 3.14 (4H, br s), 3.29-3.33 (1H, m), 4.18-
4.21 (1H, m), 4.48-4.54 (2H, m), 5.23-5.35 (2H, m), 6.97-7.02 (1H, m), 7.40-7.50 (4H, m), 7.57-7.63 (2H, m), 7.89-7.92 (1H, m), 8.36 (1H, s), 11.60 (1H, s).

Example 8

1,1-Dimethylethyl 4-(5-(2-chlorophenyl)-7-{2-oxo-2-[4-(2-oxo-1,2,4,5-tetrahydro-3H-1,3-benzodiazepin-3-yl)-1-piperidinyl]ethyl}-7H-pyrrolo[2,3-rflpyrimidin-4-yl]-1-piperazinecarboxylate (E8)

[5-(2-Chlorophenyl)-4-(4-{{(1,1-dimethylethyl)oxy} carbonyl}-1-piperazinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetic acid sodium salt (D18, 175 mg, 0.371 mmol), 3-(4-piperidinyl)-1,3,4,5-tetrahydro-2H-1 ,3-benzodiazepin-2-one (91 mg, 0.371 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (85 mg, 0.445 mmol) and N-methylmorpholine (0.082 mL, 0.742 mmol) were added together in N,N-dimethylformamide (3 mL) and the resulting mixture was stirred at room temperature under argon for 18 hours. The solvent was removed under reduced pressure and the residue diluted with water and extracted with dichloromethane (x 2). The dichloromethane layers were combined, washed with saturated sodium bicarbonate and brine, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography eluting with a gradient of 0-10 % 2M ammonia/methanol and dichloromethane. Product containing fractions were combined and evaporated under reduced pressure to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]+ at m/z 699, 701 (C37H43ClN8O4 requires [M+H]+ at m/z 699, 701).

1H NMR δ (DMSOδ6): 1.36 (9H, s), 1.48-1.85 (4H, m), 2.66-2.68 (1H, m), 2.86-2.91 (2H, m), 3.01 (4H, br s), 3.13 (4H, br s), 3.19-3.25 (1H, m), 3.39-3.41 (2H, m), 4.10-4.13 (1H, m), 4.25-4.44 (2H, m), 5.19-5.29 (2H, m), 6.78-6.84 (1H, m), 7.02-7.07 (3H, m), 7.40-7.49 (4H, m), 7.61-7.63 (1H, d), 8.37 (1H, s), 8.55 (1H, s).
Example 9

1-(1-{[5-(2-Chlorophenyl)-4-(1-piperazinyl)-7H-pyrrolo[2,3-c]pyrimidin-7-y]acetyl}-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-f-e]pyridin-2-one dihydrochloride (E9)

\[ \text{Product} \]

1,1-Dimethylethyl 4-(5-(2-chlorophenyl)-7-{2-oxo-2-[4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)-1-piperidinyl]ethyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1-piperazinecarboxylate (E7, 123 mg, 0.183 mmol) was dissolved in 1,4-dioxane (2 mL), treated with 4M hydrochloric acid in dioxane (0.229 mL, 0.915 mmol) and stirred at room temperature under argon for 2 hours. A further quantity of 4M hydrochloric acid in dioxane (0.229 mL, 0.915 mmol) was added and the resulting mixture heated at 70°C under argon for 1 hour. The reaction mixture was allowed to cool to room temperature and stirred for 18 hours. The reaction mixture was heated under reflux for 1 hour allowed to cool to room temperature and treated with methanol (5 mL) to aid solubility. A further quantity of 4M hydrochloric acid in dioxane (0.229 mL, 0.915 mmol) was added and the resulting mixture was stirred at room temperature for 4 hours. The solvent was removed under reduced pressure and the residue dried at 50°C under high vacuum overnight. The solid was dissolved in methanol and passed down an SCX cartridge (2 g) eluting with methanol, followed by 2M ammonia/methanol. Product containing fractions were combined and evaporated under reduced pressure. The residue was purified by MDAP. Product containing fractions were combined and evaporated under reduced pressure. The residue was taken up in methanol and passed down an SCX cartridge (2 g) eluting with methanol, followed by 2M ammonia/methanol. Product containing fractions were combined and evaporated under reduced pressure to give 1-(1-{[5-(2-chlorophenyl)-4-(1-piperazinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-y]acetyl}-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one as a white solid.

\(^1\text{H NMR} \delta (\text{DMSO})_{d_6}: 1.77-1.87 (2H, m), 2.07-2.17 (1H, m), 2.32-2.39 (5H, m), 2.76-2.81 (1H, m), 3.10 (4H, br s), 3.28-3.33 (1H, m), 4.18-4.21 (1H, m), 4.48-4.54 (2H, m), 5.21-5.33 (2H, m), 6.99-7.03 (1H, m), 7.37-7.43 (4H, m), 7.57-7.59 (2H, m), 7.91-7.93 (1H, m), 8.31 (1H, s).

1-(1-{[5-(2-Chlorophenyl)-4-(1-piperazinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-y]acetyl}-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (66 mg, 0.115 mmol) was dissolved in methanol (1 mL) and dichloromethane (1 mL), treated with 1M hydrochloric acid in ether (0.242 mL, 0.242 mmol) and stirred at room temperature for 10 minutes. The solvent was removed under reduced pressure and the resulting solid was dried at 50°C under high vacuum overnight to give the title compound as a
white solid.

LC/MS (ES+ve): [M+H]+ at m/z 572, 574 (C_{29}H_{30}ClN_{9}O_{2} requires [M+H]+ at m/z 572, 574).

Example 10
3-(1-[[5-(2-Chlorophenyl)-4-(1^iperazinyl)-7H^yrrolo[2,3-c^pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one hydrochloride (E10)

1,1-Dimethylethyl 4-(5-(2-chlorophenyl)-7-(2-oxo-2-[4-(2-oxo-1,2,4,5-tetrahydro-3H-1,3-benzodiazepin-3-yl)-1-piperidinyl]ethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1-piperazinecarboxylate (E8, 128 mg, 0.183 mmol) was dissolved in dichloromethane (2 ml), treated with trifluoroacetic acid (1 ml, 12.98 mmol) and stirred at room temperature for 30 minutes. The solvent was removed under reduced pressure and the residue passed down an SCX column (2 g) eluting with methanol, followed by 2M ammonia/methanol. Basic fractions were combined and evaporated under reduced pressure. The residue was purified by column chromatography eluting with a gradient of 0-5 % 2M ammonia/methanol and dichloromethane. Product containing fractions were combined and evaporated under reduced pressure to give 3-(1-[[5-(2-chlorophenyl)-4-(1-piperazinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one as a white solid.

^1H NMR δ (DMSO$_d$$_6$): 1.53-1.81 (4H, m), 2.38-2.40 (4H, m), 2.65-2.71 (1H, m), 2.89-2.91 (2H, m), 3.10-3.24 (5H, m), 3.38-3.42 (2H, m), 4.10-4.05 (1H, m), 4.31-4.44 (2H, m), 5.17-5.26 (2H, m), 6.78-6.83 (1H, m), 7.02-7.07 (3H, m), 7.37-7.46 (4H, m), 7.55-7.59 (1H, m), 8.30 (1H, s), 8.55 (1H, s).

3-(1-[[5-(2-Chlorophenyl)-4-(1-piperazinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one (86 mg, 0.144 mmol) was dissolved in methanol (1 ml) and dichloromethane (1 ml), treated with 1M hydrochloric acid in ether (0.158 ml, 0.158 mmol) and stirred at room temperature for 10 minutes. The solvent was removed under reduced pressure and the resulting solid was dried at 50°C under high vacuum overnight to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]+ at m/z 599, 601 (C_{32}H_{35}ClN_{8}O_{2} requires [M+H]+ at m/z 599, 601).
Example 11
3-(1-[[5-(2-Chlorophenyl)-4-(phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one hydrochloride (E11)

![Chemical structure](attachment:structure.png)

[5-(2-Chlorophenyl)-4-(phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetic acid (D19, 138 mg, 0.364 mmol), 3-(4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one (89 mg, 0.364 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (84 mg, 0.437 mmol), 1-hydroxybenzotriazole (61.4 mg, 0.401 mmol) and N-methylmorpholine (0.080 ml, 0.729 mmol) were added together in N,N-dimethylformamide (3 ml.) and the resulting mixture was stirred at room temperature under argon for 18 hours. The solvent was removed under reduced pressure and the residue diluted with water and extracted with dichloromethane (x 2). The dichloromethane layers were combined, washed with saturated sodium bicarbonate and brine, dried under magnesium sulfate and evaporated under reduced pressure. The residue was purified by MDAP. Product containing fractions were combined and evaporated under reduced pressure to give 3-(1-[[5-(2-chlorophenyl)-4-(phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one as a white solid.

1H NMR δ (DMSO-d6): 1.55-1.85 (4H, m), 2.67-2.73 (1H, m), 2.90-2.92 (2H, m), 3.20-3.26 (1H, m), 3.40-3.42 (2H, m), 4.08-4.15 (1H, m), 4.32-4.39 (1H, m), 4.43-4.46 (1H, m), 5.21-5.31 (2H, m), 6.78-6.84 (1H, m), 6.97-7.05 (4H, m), 7.11 (1H, s), 7.26-7.30 (2H, t), 7.44-7.51 (5H, m), 7.54-7.57 (1H, m), 7.65-7.69 (1H, m), 8.38 (1H, s), 8.55 (1H, s).

3-(1-[[5-(2-Chlorophenyl)-4-(phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one (102 mg, 0.168 mmol) was dissolved in methanol (1.5 ml.) and dichloromethane (1.5 ml.), treated with 1M hydrochloric acid in ether (0.353 ml, 0.353 mmol) and stirred at room temperature for 10 minutes. The solvent was removed under reduced pressure and the resulting solid was dried at 50°C under high vacuum overnight to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]+ at m/z 606, 608 (C34H32ClN7O2 requires [M+H]+ at m/z 606, 608).
Example 12
3-(1-([5-(2,3-Difluorophenyl)-7H-pyrrolo[2,3-cGpyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one (E12)

To a solution of [5-(2,3-difluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetic acid (140 mg, 0.484 mmol), 3-(4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one (119 mg, 0.484 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (111 mg, 0.581 mmol) and 1-hydroxybenzotriazole (82 mg, 0.532 mmol) in N,N-dimethylformamide (2.5 ml.) was added N-methylmorpholine (0.106 ml, 0.968 mmol). The reaction mixture was stirred at room temperature for 3 hours under an atmosphere of argon. The reaction mixture was concentrated under reduced pressure to form a pale yellow oil. The product was partitioned between dichloromethane (15 ml.) and water (15 ml). The aqueous layer was washed with dichloromethane (10 ml_). The combined organic extracts were washed with 5% citric acid (10 ml_), sodium bicarbonate solution (10 ml_) and brine (10 ml_). The combined organic extracts were dried over magnesium sulfate, filtered, concentrated under reduced pressure and dried under vacuum at 50°C overnight. The residue was purified by column chromatography eluting with 0 - 5% 2M ammonia in methanol / dichloromethane. The fractions containing product were combined and evaporated under reduced pressure to give the title compound as a white powder.

LC/MS (ES+ve): [M+H]⁺ at m/z 517 (C_{28}H_{26}F_{2}N_{6}O_{2} requires [M+H]⁺ at m/z 517).

¹H NMR δ (DMSO_d₆): 1.52-1.93 (4H, overlapping m), 2.64-2.78 (1H, m, partially obscured by residual N,N-dimethylformamide), 2.83-2.97 (2H, m, partially obscured by residual N,N-dimethylformamide), 3.23 (1H, app t, partially obscured by water signal), 3.42 (2H, m, partially obscured by water signal), 4.14 (1H, app d), 4.29-4.47 (2H, m), 5.30-5.45 (2H, m), 6.76-6.87 (1H, m), 6.99-7.11 (3H, m), 7.29-7.46 (2H, m), 7.68 (1H, t), 8.01 (1H, finely coupled d), 8.55 (1H, s), 8.88 (1H, s), 8.26 (1H, finely coupled d).

Examples 13-24 - see Table of Examples
Example 25

1-(1-[(5-(2-Chlorophenyl)-4-ethyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetyl]-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (E25)

[5-(2-Chlorophenyl)-4-ethyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetic acid lithium salt (D27, 52.0 mg, 0.161 mmol) was dissolved in N,N-dimethylformamide (2 ml.) and N-methylmorpholine (0.035 mL, 0.322 mmol) added followed by 1-hydroxybenzotriazole (27.1 mg, 0.177 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (37.0 mg, 0.193 mmol). The mixture was stirred at room temperature under argon for 5 minutes then 1-(4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (52.7 mg, 0.242 mmol) added. The reaction was stirred for 17 hours, then at 50°C for 10 hours, concentrated under reduced pressure then partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was washed with brine, dried and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with 0-5% 2M ammonia/methanol in dichloromethane to give a white solid. Further purification by MDAP gave the title compound as a white solid.

LC/MS (ES+ve): [M+H]⁺ at m/z 516, 518 (C₂₇H₂₈ClN₇O₂ requires [M+H]⁺ at m/z 516, 518).

¹H NMR δ (DMSO₆): 1.04 (3H, t), 1.74-1.92 (2H, m), 2.05-2.19 (1H, m), 2.31-2.43 (2H, m), 2.57-2.66 (2H, m), 2.74-2.85 (1H, m), 4.22 (1H, d), 4.43-4.57 (2H, m), 5.35 (2H, q), 6.98-7.04 (1H, m), 7.45-7.52 (3H, m), 7.55 (1H, s), 7.58-7.65 (2H, m), 7.90-7.94 (1H, m), 8.73 (1H, s), 11.33-1.72 (1H, br s).

Examples 26-71 - see Table of Examples
Example 72
1-(1-[(5-(2-Chlorophenyl)-4-(3-pyrrolidinyl oxy)-7/y-pyrrolo[2,3-o]pyrimidin-7-yl]acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-fe]pyridin-2-one formic acid salt (E72)

1,1-Dimethylethyl 3-[(5-(2-chlorophenyl)-7-{2-oxo-2-[4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)-1-piperidinyl]ethyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy]-1-pyrrolidinecarboxylate (345 mg, 0.513 mmol) [derived from D57 by methods similar to those described herein] was dissolved in dichloromethane (5 ml), treated with trifluoroacetic acid (1 ml, 12.98 mmol) and stirred at room temperature for 30 minutes. The solvent was removed under reduced pressure and the residue passed down an SCX column (5 g) eluting with methanol, followed by 2M ammonia/methanol. Basic fractions were combined and evaporated under reduced pressure. The residue was purified by MDAP and product containing fractions were combined and evaporated under reduced pressure to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]^+ at m/z 573, 575 (C_{29}H_{29}CIN_{8}O_{3} requires [M+H]^+ at m/z 573, 575 for the free base).

^1H NMR δ (DMSO_d6) 1.78-1.88 (3H, m), 2.04-2.19 (2H, m), 2.33-2.44 (1H, m), 2.76-2.90 (2H, m), 3.06-3.13 (2H, m), 3.30-3.44 (2H, m), 4.18-4.22 (1H, m), 4.48-4.55 (2H, m), 5.28-5.42 (2H, m), 5.62-5.65 (1H, m), 7.00-7.04 (1H, m), 7.34-7.41 (2H, m), 7.55-7.61 (4H, m), 7.91-7.93 (1H, m), 8.29 (1H, s), 8.45 (1H, s).

Example 73 - see Table of Examples

Example 74
1-(1-[(5-(2-Chlorophenyl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-cf]pyrimidin-7-yl]acetyl)-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-fe]pyridin-2-one (E74)
[5-(2-Chlorophenyl)-4-(3-hydroxy-1-azetidinyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetic acid lithium salt (D39, 2.267 g, 6.2 mmol) was dissolved in N,N-dimethylformamide (5 ml.) and N-methylmorpholine (0.682 ml, 6.20 mmol), 1-hydroxybenzotriazole hydrochloride (1.044 g, 6.82 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide added. After stirring for 10 minutes, 1-(4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one dihydrochloride (1.986 g, 6.82 mmol) was added and the reaction stirred at room temperature under argon for 18 hours. The N,N-dimethylformamide was evaporated and the residue partitioned between ethyl acetate and saturated sodium bicarbonate solution. An insoluble material remained, so this and the aqueous layer were re-extracted with dichloromethane. There was still some insoluble material present which was removed by filtration. The two organic extracts were separately washed with water and brine and dried over magnesium sulfate then evaporated. The residues and insoluble material were combined and stirred with 10% methanol in dichloromethane. The resulting off-white solid was filtered, washed with dichloromethane and dried to give the title compound. The filtrate was purified by flash chromatography, eluting with 0-10% 2M ammonia/methanol in dichloromethane to give more product as a cream solid.

LC/MS (ES+ve): [M+H]^+ at m/z 559, 561 (C_{28}H_{27}ClIN_{8}O_{3} requires [M+H]^+ at m/z 559, 561).

\(^1\)H NMR \(\delta (\text{DMSO-d}_6)\): 1.77-1.99 (2H, m), 2.06-2.15 (1H, m), 2.33-2.41 (1H, m), 2.75-2.86 (1H, m), 3.27-3.38 (3H + water signal, overlapping m), 3.68-3.87 (2H, br s), 4.18-4.21 (1H, m), 4.25-4.32 (1H, m), 4.47-4.53 (2H, m), 5.11-5.36 (2H, m), 5.50 (1H, d), 6.99-7.01 (1H, m), 7.23 (1H, s), 7.42-7.45 (3H, m), 7.56-7.60 (2H, m), 7.91-7.94 (1H, m), 8.22 (1H, s), 11.60 (1H, s).

Examples 75 to 97 - see Table of Examples

Example 98

1-Methyl-4-[2-(7-[2-oxo-2-[4-(2-oxo-1,2,4,5-tetrahydro-3H-1,3-benzoazepin-3-yl)-1-piperidinyl]ethyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]phenyl]piperazin-1-ium formate (E98)

\[
\begin{align*}
\text{HCO}_2\text{H} & \\
\end{align*}
\]

\{5-[2-(4-Methyl-1-piperazinyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl\}acetic acid lithium salt (D64, 86.5 mg, 0.241 mmol) was dissolved in N,N-dimethylformamide (3
ml) and N-methylmorpholine (0.053 ml, 0.483 mmol) added followed by 1-hydroxybenzotriazole hydrate (40.7 mg, 0.266 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (55.5 mg, 0.290 mmol). The mixture was stirred at room temperature under argon for 5 minutes then 3-(4-piperidinyl)-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one (65.1 mg, 0.266 mmol) added. The reaction was stirred for 17 hours, evaporated, partitioned between saturated sodium bicarbonate solution and dichloromethane, separated by hydrophobic frit, evaporated then purified by MDAP to give the product as an off-white solid.

LC/MS (ES+ve): [M+H]+ at m/z 579 (C_{32}H_{39}N_{8}O_{2} requires [M+H]+ at m/z 579 for free base)

1H NMR δ (DMSO-de): 1.55-1.91 (4H, m), 2.06 (3H, m), 2.06-2.24 (3H, m), 2.67-2.69 (1H, m), 2.71-2.86 (4H, m), 2.90-2.93 (2H, m), 3.11-3.16 (4H + water signal, overlapping m), 4.13-4.16 (1H, m), 4.32-4.44 (2H, m), 5.27-5.37 (2H, m), 6.79-6.83 (1H, m), 7.03-7.06 (2H, m), 7.08-7.12 (1H, m), 7.15-7.17 (1H, m), 7.29-7.34 (1H, m), 7.37-7.39 (1H, m), 7.79 (1H, s), 8.16 (1H, s), 8.55 (1H, s), 8.80 (1H, s), 9.05 (1H, s).

Example 99
i-II-KS^-ChlorophenyO^-^-hydroxyethyOoxyl-ZW-pyrroloP.S-cflpyrimidin-Zy|acetyl)-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-fe]pyridin-2-one (E99)

1-(1-[[5-(2-Chlorophenyl)-4-((2-[(phenylmethyl)oxy]ethyl)oxy)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (173 mg, 0.271 mmol) prepared by procedures disclosed herein starting from 5-bromo-4-((2-[(phenylmethyl)oxy]ethyl)oxy)-7H-pyrrolo[2,3-d]pyrimidine itself prepared from 2-[(phenylmethyl)oxy]ethanol and D5 by the method of Description 29 was dissolved in a mixture of ethanol (3 ml), methanol (3 ml) and dichloromethane (3 ml), treated with 10% palladium on carbon (paste) (10 mg) and hydrogenated at room temperature for 18 hours. A further quantity of 10% palladium on carbon (paste) (20 mg) was added and the mixture hydrogenated at room temperature for a further 18 hours. The reaction mixture was filtered through celite and the solvent was removed under reduced pressure. The residue was purified using MDAP. Product containing fractions were combined and evaporated under reduced pressure. The resulting solid was dried under high vacuum at 50°C overnight to give the title compound as a white solid.

LC/MS (ES+ve): [M+H]+ at m/z 548, 550 (C_{27}H_{26}ClN_{7}O_{4} requires [M+H]+ at m/z 548, 550).

1H NMR δ (DMSO-de): 1.77-1.88 (2H, m), 2.07-2.17 (1H, m), 2.33-2.44 (1H, m), 2.76-2.82 (1H, m), 3.29-3.35 (1H, m, under water signal), 3.61-3.65 (2H, m), 4.18-4.22
Examples 100 to 103 - see Table of Examples

Example 104

1-(1-[(5-(2-Chlorophenyl)-4-[3-(methyloxy)-1-azetidinyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl)-4-piperidinyl]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (E104)

\[
\text{O} \quad \text{N}
\]

\[
\begin{align*}
&\text{Cl} \\
&\text{O} \\
&\text{N}
\end{align*}
\]

{[5-(2-Chlorophenyl)-4-[3-(methyloxy)-1-azetidinyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetic acid lithium salt (81 mg, 0.212 mmol) was dissolved in N,N-dimethylformamide (2 ml.) and N-methylmorpholine (0.023 mL, 0.212 mmol), 1-hydroxybenzotriazole (35.7 mg, 0.233 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (48.8 mg, 0.254 mmol) added. After stirring for 10 minutes, 1-(4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one dihydrochloride (67.9 mg, 0.233 mmol) was added and the reaction stirred at room temperature under argon for 18 hours. The N,N-dimethylformamide was evaporated and the residue partitioned between dichloromethane and saturated sodium bicarbonate. The layers were separated on a hydrophobic frit and the organic layer evaporated. The residue was purified by MDAP to give the title compound as a cream solid.

LC/MS (ES+ve): [M+H]⁺ at m/z 573, 575 (C_{29}H_{29}ClN_{8}O_{3} requires [M+H]⁺ at m/z 573, 575).

\(^{1}\text{H} \text{NMR} \delta (\text{DMSO}_d\_6): 1.77-1.87 (2H, m), 2.06-2.15 (1H, m), 2.33-2.41 (1H, m), 2.75-2.87 (1H, m), 3.05 (3H, s), 3.23-3.37 (3H + water signal, overlapping m), 3.72-3.86 (2H, br s), 4.01-4.06 (1H, m), 4.18-4.21 (1H, m), 4.47-4.53 (2H, m), 5.1 1-5.36 (2H, m), 6.99-7.03 (1H, m), 7.25 (1H, s), 7.42-7.45 (3H, m), 7.57-7.60 (2H, m), 7.91-7.92 (1H, m), 8.23 (1H, s), 11.60 (1H, s).

Examples 105 to 144 - see Table of Examples
Example 145
1-(1-[(4-Amino-5-(2,3-dichlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (E145)

![Chemical Structure](image)

1-(1-[(4-Chloro-5-(2,3-dichlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (D76, 250 mg, 0.449 mmol) was suspended in ammonia (2M in methanol) (8.979 ml, 17.96 mmol) and heated at 150 °C for 4 hours in the microwave (high absorbance). The solvent was evaporated and the residue triturated with dichloromethane to remove inorganic material. The resulting filtrate was purified by column chromatography (Biotage, 5-10% methanol/dichloromethane) to give the title compound as a white solid after crystallisation of the cleanest fractions from methanol.

LC/MS (ES+ve): [M+H]+ at m/z 537, 539, 541 (C_{25}H_{22}Cl_{2}N_{8}O_{2} requires [M+H]+ at m/z 537, 541).

^1H NMR δ (DMSOδ6): 1.77-1.87 (2H, m), 2.06-2.15 (1H, m), 2.33-2.41 (1H, m), 2.75-2.80 (1H, m), 3.27-3.28 (1H + water signal, overlapping m), 4.08-4.12 (1H, m), 4.49-4.50 (2H, m), 5.15-5.32 (2H, m), 6.03 (2H, broad s) 6.99-7.02 (1H, m), 7.30 (1H, s), 7.36-7.49 (2H, m), 7.56-7.58 (1H, m), 7.64-7.67 (1H, m), 7.91 (1H, d), 8.14 (1H, s), 11.60 (1H, s)

Examples 146 to 160 - see Table of Examples
Example 161
N-(5-(2,3-Dichlorophenyl)-7-(2-oxo-2-[4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)-1-piperidinyl]ethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)acetamide (D161)

A solution of 1-(1-[[4-amino-5-(2,3-dichlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetyl]-4-piperidinyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (E145, 100 mg, 0.186 mmol), acetic anhydride (0.053 ml, 0.558 mmol) and 4-dimethylaminopyridine (6.82 mg, 0.056 mmol) in pyridine (3 ml) was stirred at room temperature under an atmosphere of argon for 2 hours. The reaction mixture was then concentrated under reduced pressure and the residue was purified by column chromatography (Biotage SP425+M column, 0-10% 2M ammonia in methanol/dichloromethane). The product containing fractions were combined and concentrated under reduced pressure to give an off-white solid. NMR showed the presence of ammonium acetate and so the product was dissolved in dichloromethane and then washed with water. The aqueous layer was washed with dichloromethane and the combined organics were dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the title compound as an off-white solid which was dried at 50°C under vacuum overnight.

LC/MS (ES+ve): [M+H]+ at m/z 579, 581, 583 (C27H24Cl2N8O3 requires [M+H]+ at m/z 579, 581, 583).

1H NMR δ (DMSO-d6): 1.65 (3H, s), 1.72-1.92 (2H, overlapping app d), 2.13 (1H, m), 2.42 (1H, m, partially overlapping with dmso signal), 2.80 (1H, app t), 3.26-3.52 (1H, m, overlapped by water signal), 4.21 (1H, app d), 4.43-4.60 (2H, m), 5.33 (1H, d), 5.41 (1H, d), 7.02 (1H, m), 7.27 (1H, m), 7.37 (1H, t), 7.54-7.63 (2H, m), 7.69 (1H, s), 7.92 (1H, m), 8.63 (1H, s), 10.36 (1H, s), 11.59 (1H, s).

Examples 162 to 163 - see Table of Examples

Table of Examples

In the Table, the following general methods of synthesis are referred to:
Method A - as Examples 1-4
Method B - as Examples 5 and 11
Method C - as Examples 7 and 8
Method D - as Example 9
Method E - as Examples 10 and 72
Method F - as Example 12
Method G - as Examples 25 and 98
Method H - as Example 99
Method I - as Examples 74 and 104*
Method J - as Example 145
Method K - as Example 161

* The starting material used in Method I can be a free acid or a salt. By way of example only, E74 and E104 describe the use of a lithium salt.

Conversions of free base to hydrochloride are carried out for example as described in Example 5, 9, 10 or 11.

Starting materials are prepared using the methods described hereinabove in the Descriptions.

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Biological Assay

The activity of the compounds of the Examples was investigated using the following assay.

Generation of CALCRL and Rampi stable cell line

Human calcitonin receptor like receptor (CALCRL) (Genbank U17473) and Rampi (Genbank AJ001014) were cloned into bicistronic mammalian expression vectors (BioTechniques, 1996, 20:102-110) pCIN3 and pCIH5.

Human embryonic kidney 293 cells (HEK293) were maintained in DMEM containing 2mM glutamine (Gibco 41966-029) with 10% Heat inactivated FCS (Gibco 10100-147).

Both of the plasmids were transfected into a 50% confluent T75 flask of HEK293 cells using Lipofectamine according to the manufacturers guidelines (Invitrogen 18324-012).

48 hours following transfection, the cells were dilution cloned into 96-well plates using selection media containing DMEM containing 2mM glutamine (Gibco 41966-029), 10% Heat inactivated FCS (Gibco 10100-147), 500 µg/ml Geneticin (Gibco 10131-027) and 200 µg/ml of hygromycin B (Gibco 10687-010). 10 to 14 days post dilution cloning, antibiotic resistant clones were grown on and expanded.

The clones were screened for increases in cAMP production on addition of human β-CGRP using cAMP SPA screening Biotrack assay (GE healthcare RPA556) according to the manufacturers instructions. A positive clone from this screening was then chosen and used for all subsequent assay work.

CRLR-RAMP1 cAMP TR-FRET assay

Calcitonin Receptor Like Receptor (CRLR) and Receptor Activity Modifying Protein (RAMP1) is a 7-transmembrane G protein coupled receptor that is positively coupled to adenylate cyclase by Ga. Stimulation of CRLR-RAMP1 with the agonist Calcitonin Gene Related Peptide (CGRP) produces an increase in the intracellular secondary
messenger cAMP. Receptor activity can therefore be measured using a cAMP accumulation immunoassay. This assay is based on competition between a europium labelled cAMP complex and cellular cAMP for binding sites on anti-cAMP antibodies labelled with Alexa Fluor 647 (Trade Mark). Time Resolved Fluorescence Resonance Energy Transfer (TR-FRET) occurs when the europium labelled cAMP tracer complex is bound by an Alexa Fluor 647 labelled anti-cAMP antibody. Light at 340nm excites the europium-cAMP which transfers energy to the Alexa647 which in turns emits at 665nm. The fluorescence intensity measured at 665nm is inversely proportional to the cAMP concentration of the sample.

Assay plates containing 100nl test compounds (dissolved in 100% DMSO and serially diluted with DMSO), positive and negative controls wells, were thawed. Frozen recombinant cells expressing CRLR-RAMP1 are thawed and diluted in stimulation buffer. 5μl of this is added to all wells and the plates are incubated for 15 minutes at room temperature. 5μl of stimulation buffer containing an EC₅₀ concentration of CGRP and europium-cAMP is added to all wells and the plates are incubated for a further 45 minutes at room temperature. Finally 10μl of detection mix containing Alexa Fluor 647 anti-cAMP antibody is added to all wells, plates are incubated (lidded) for a minimum of 4 hours before reading the TR-FRET signal on the ViewLux (Trade Mark) imager. The raw data (acceptor counts) is processed using ActivityBase software and % inhibition values determined. These values are then plotted to provide dose response curves giving pIC50 and fpKi values.

The compounds of the Examples were tested in this assay and exhibited fpKi values greater than or equal to 6.5.
CLAIMS

1. A compound of formula (I) or (IA) or a pharmaceutically acceptable salt thereof:

   \[ R_1 = \text{hydrogen, acetyl, amino, cyano, ethoxycarbonyl, or acetamido; or } R_1 \text{ is selected from the group consisting of aryl, heterocyclyl, alkyl, alkyloxy, alkylamino, dialkylamino, and arylamino, any of which is optionally substituted;} \]

   \[ R_2 \text{ is an optionally substituted aryl group;} \]

   \[ n = 0, 1 \text{ or } 2; \text{ and} \]

   \[ R_3 \text{ and } R_4 \text{ together form a fused six-membered aromatic ring which is optionally substituted and contains } 0, 1 \text{ or } 2 \text{ nitrogen atoms.} \]

2. A compound according to claim 1, wherein \( R_1 \) is selected from the group consisting of hydrogen; optionally substituted 1-piperazinyl, 1-azetidinyl, 1-piperidinyl, 4-morpholinyl, 3-pyridinyl, or 1-pyrrolidinyl; optionally substituted phenyl; optionally substituted phenylamino; methyl; ethyl; methoxy; methylamino; dimethylamino; dimethylaminoethyloxy; 2-(1-pyrrolidinyl)ethyloxy; and methoxyethylamino;

3. A compound according to claim 1 or 2, wherein \( R_2 \) is phenyl optionally substituted by up to three substituents independently selected from the group consisting of chloro, fluoro and methyl;
4. A compound according to any one of the preceding claims, wherein \( n \) is 0 and \( R_3 \) and \( R_4 \) together form a fused pyridyl, or \( n \) is 1 or 2 and \( R_3 \) and \( R_4 \) together form a fused phenyl.

5. A compound selected from either of Lists 1 and 2 hereinabove or a pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition which comprises a compound as defined in any one of the preceding claims and a pharmaceutically acceptable carrier or excipient.

7. A compound as defined in any one of claims 1 to 5 for use in the treatment of migraine, headache, or cluster headache.

8. Use of a compound as defined in any one of claims 1 to 5 in the manufacture of a medicament for the treatment of migraine, headache, or cluster headache.

9. A method of treatment of migraine, headache, or cluster headache which comprises administering to a host in need thereof an effective amount of a compound as defined in any one of claims 1 to 5.

10. A process for the preparation of a compound according to any one of claims 1 to 5, which process comprises:

   (a) reacting a compound of formula (II) or a salt or protected derivative thereof:

   ![Formula (II)](image)

   with a compound of formula (III) or (NIA):

   ![Formula (III)](image)
and/or

(b) converting a compound of formula (I) or (IA) to a different compound of formula (I) or (IA); and/or

(c) removing any protecting group; and/or

(d) as appropriate, separating diastereomeric or enantiomeric mixtures of compounds of formula (I) or (IA).
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 C07D519/00 A61K31/519 A61K31/5365 A61K31/551
A61P25/06

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

B. RELDS 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 database consulted during the international search (name of database and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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D 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
'E' earlier document but published on or after the international filing date
'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
'O' document referring to an oral disclosure, use, exhibition or other means
'P' document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search

13 March 2009

Date of mailing of the international search report

23/03/2009

Name and mailing address of the ISA/
European Patent Office, P B 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Fax (+31-70) 340-3016

Authorized officer

Mates Valdi viel so, J
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